27 June 2019
EMA/CHMP/644912/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0047

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
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CIT	chemoimmunotherapy
Clb	chlorambucil
CLL	chronic lymphocytic leukemia
CrCl	creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
CR, CRi	complete response, complete response with incomplete blood count recovery
del11q	deletion of the long arm of chromosome 11
del17p	deletion of chromosome 17p
DOR	duration of response
ECOG	European Cooperative Group
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
HR	hazard ratio
IGHV	immunoglobulin heavy-chain variable
IRC	Independent Review Committee
ILD	interstitial lung disease
IRR	infusion-related reaction
ISS	Integrated Summary of Safety
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LTS	long term safety
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	non-melanoma skin cancer
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NE	not estimable
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PR	partial response
PBRER	Periodic Benefit Risk Evaluation Report
PMR	Postmarketing Requirement
PT	preferred term
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
WM	Waldenström's macroglobulinemia

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 combination use with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Imbruvica based on data from the phase 3 study PCYC-1130-CA; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) is also submitted.

Imbruvica was designated as an orphan medicinal product EU/3/12/984 on 26 April 2012. Imbruvica was designated as an orphan medicinal product in the following indication: "Treatment of chronic lymphocytic leukaemia". 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 an EMA Decision P/0398/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0398/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

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	30 January 2019
PRAC Rapporteur Assessment Report	4 February 2019
Updated PRAC Rapporteur Assessment Report	6 February 2019
PRAC Outcome	14 February 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 February 2019
Request for supplementary information (RSI)	28 February 2019
PRAC Rapporteur Assessment Report	3 June 2019
CHMP Rapporteur Assessment Report	13 June 2019
PRAC Outcome	13 June 2019
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	27 June 2019

2. Scientific discussion

2.1. Introduction

Ibrutinib is a potent small molecule BTK for oral use.

In patients with chronic lymphocytic leukemia (CLL), ibrutinib is presently approved for the treatment of adult patients with previously untreated CLL and as a single agent or combination therapy with bendamustine and rituximab for the treatment of adult patients with CLL who received at least one prior therapy.

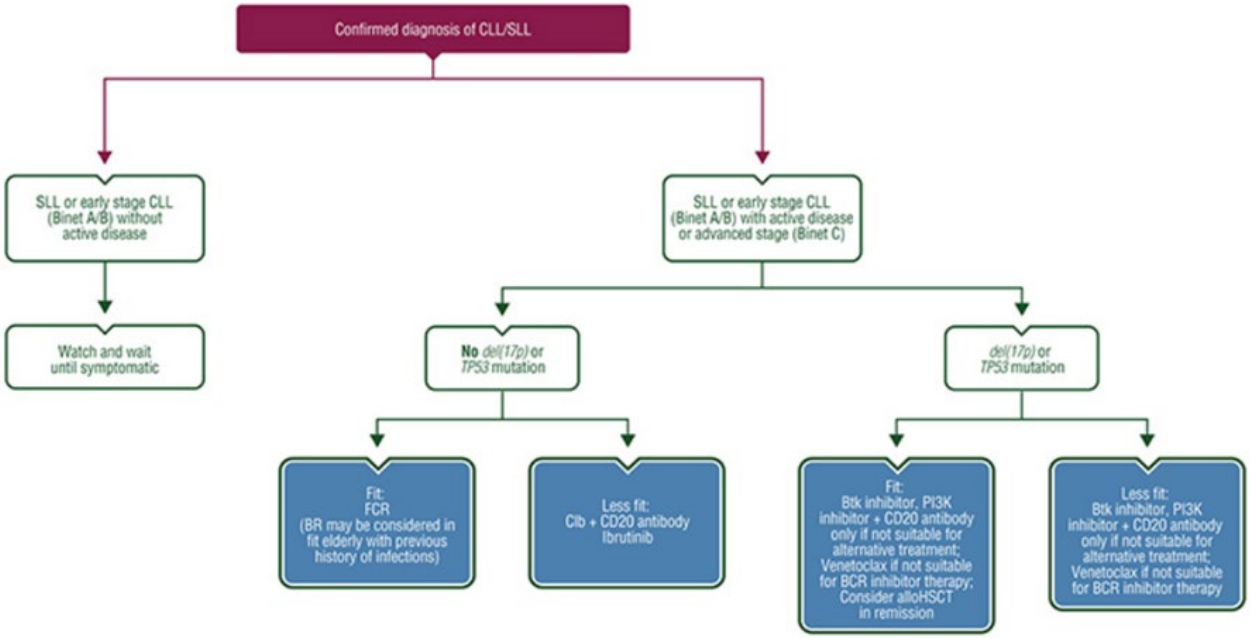
The target indication, which is the subject of this Type II variation, is to extend the indications for ibrutinib in CLL, as follows:

- IMBRUVICA as a single agent *or in combination with obinutuzumab* is indicated for the treatment of adult patients with previously untreated CLL.

Background on the Target Indication and Current Treatments

Treatment guidelines from the European Society of Medical Oncology (ESMO) indicate the choice of treatment for previously untreated patients with CLL is based on stage of disease, whether a patient is considered "fit" and presence or absence of del17p or mutated TP53 (Eichhorst 2015; ESMO 2017).

Figure 1: ESMO (2018) treatment algorithm for front-line treatment of CLL



The benefit of FCR is strongly correlated to the presence of high-risk features other than del 17p/TP53 mutation, with a reported 10-year PFS of ~55% and a plateau thereafter in subjects with mutated IGHV vs ~10% in subjects with unmutated IGHV (*MDACC group, 2016*). The group of young fit patients with no TP53 aberration and mutated IGHV disease constitutes approximately one-third of the young fit patients and around 8-10% of all patients of all age groups requiring frontline therapy (*Jain, Hematology Am Soc Hematol Edu Program; 2018, p242*). The Clb+CD20 antibody combination is not recommended in subjects with del 17p/TP53 mutated disease

Table 1: Summary of first-line treatments for patients with CLL

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
Ibrutinib 2016	Previously untreated CLL	Monotherapy	Phase 3 /chlorambucil	269	PFS, ORR, OS
Ibrutinib 2014	CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT	Monotherapy	Phase 3/ ofatumumab	391	PFS, OS, ORR
Venetoclax 2016	CLL with 17p deletion or *TP53* mutation in patients unsuitable for a B-cell receptor pathway inhibitor (BCR)	Monotherapy	Phase 2/none	107	ORR, DOR, PFS
Idelalisib + rituximab 2014	In combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT	Combination	Phase3/rituximab	220	PFS, OS
Ofatumumab with chlorambucil or bendamustine 2014	In combination with chlorambucil for the treatment of patients with CLL who have not received prior therapy and who are not eligible for	Combination	Phase 3/ chlorambucil	444	PFS, ORR, DOR

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
	fludarabine-based therapy				
Obinutuzumab with chlorambucil 2014	In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy.	Combination	Phase 3/ chlorambucil	356	PFS, DOR, OS
Rituximab[a] 2010	CLL (in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia)	Combination	Phase 3/FC	817	PFS
Bendamustine[a, b] 2008	CLL in patients for whom fludarabine combination chemotherapy is not appropriate).	Monotherapy	Phase 3/ chlorambucil	301	ORR, PFS
Cyclophosphamide[a] 1959	CLL (unspecified)	Monotherapy	Unknown	Unknown	Unknown
Chlorambucil[a] 1957	CLL (unspecified)	Monotherapy	Unknown	Unknown	Unknown

CLL: chronic lymphocytic leukemia; DOR: duration of response; EU: European Union; FC: fludarabine + cyclophosphamide; N/A: not available; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

[a] Efficacy in CLL relative to first-line therapies other than chlorambucil has not been established.

[b] Used for first- and second-line treatment of CLL

Chemoimmunotherapies (chemotherapy and anti-CD20 agents) are a mainstay of treatment for frontline CLL (Eichhorst 2015; ESMO 2017; NCCN 2018). The most effective CIT regimen, fludarabine, cyclophosphamide, and rituximab (FCR), is however also associated with increased hematologic toxicities, and therefore its use is limited to younger, fitter patients without comorbidities (ESMO 2017; NCCN 2018; Hallek 2010; Keating 2005; Robak 2017). By contrast, of the recommended multi-agent CIT regimens, the alkylating-agent based regimens, bendamustine plus rituximab (BR) and chlorambucil plus obinutuzumab (Clb+Ob), are recommended for broader groups of patients based on their improved safety profiles but are seemingly less efficacious than the FCR combination (Eichhorst 2015; ESMO 2017; NCCN 2018).

When treated with CIT, patients with high-risk CLL characterized by del 17p, del 11q, or unmutated IGHV had shorter PFS and OS compared with those without these high-risk features (Thompson 2016; Byrd 2006). In CLL patients with high-risk genomic features (eg, del 17p or del 11q), mutated TP53, or unmutated IGHV, there are few frontline treatment options available (ESMO 2017; NCCN 2018), and the guidelines note it is important to fully explore the potential of ibrutinib-based therapy in these high-risk CLL patients. Phase 3 data from Study 1112 demonstrated a significant PFS and OS benefit in patients with previously treated CLL, including patients with del 17p CLL treated with ibrutinib (Byrd 2014). Data from Study 1112 ultimately led to the regulatory approval of ibrutinib in previously treated patients with CLL in the US, European Union, and globally (IMBRUVICA USPI, IMBRUVICA Summary of Product Characteristics [SmPC]) as well as the approval in the EU of ibrutinib in the first-line treatment of CLL in patients with del17 p/mutated TP53 who are not suited for CIT (IMBRUVICA® SmPC). Subsequently,

Phase 3 data from Study 1115 led to approvals in the US, EU, and globally in patients with previously untreated CLL (IMBRUVICA USPI, IMBRUVICA SmPC).

The recently updated 2018 iwCLL guidelines (Hallek 2018) and National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2018), emphasize the importance of obtaining prognostic information using molecular genetic testing with fluorescence *in situ* hybridization (FISH) to identify common high-risk genomic features such as del 11q and del 17p and sequencing to detect TP53 mutations and IGHV mutational status to inform treatment decisions in clinical practice. Progression-free survival and OS are similar in patients with CLL carrying del 17p and patients carrying a TP53 mutation in the absence of del 17p (Zenz 2010). The presence of adverse genomic features del 17p and del 11q, along with TP53 mutations and unmutated IGHV clones identified by DNA sequencing, typically confer unfavorable outcomes (eg, shorter PFS and OS) with conventional CIT regimens used in CLL including alkylating drugs or purine analogues (Thompson 2016; Fink 2013; Byrd 2006). However, when historically poor prognostic genomic factors were examined in ibrutinib-treated patients, these factors did not confer adverse prognosis for PFS (Kipps 2017). Assessment of CLL patients for del 17p, del 11q, mutated TP53, and IGHV mutational status has prognostic value and should be performed prior to treatment as well as guide therapeutic decisions in clinical practice (Hallek 2018; NCCN 2018). Providing patients who have these high-risk genomic features with effective therapy options remains an urgent, unmet need.

Ibrutinib has previously been used in combination with 2 anti-CD20 antibodies, ofatumumab and rituximab, in 2 Phase 1/2 CLL studies (Jaglowski 2014; Burger 2014; Burger 2017). Ibrutinib use in this setting was shown to be well tolerated and produced high rates of overall response (83% to 95%) with minimal treatment-related lymphocytosis, suggesting that an ibrutinib plus anti-CD20 antibody strategy was likely to be administered safely and potentially produce improved quality of responses in CLL.

Phase 3 data from the CLL11 trial has established the efficacy and safety of the anti-CD20 antibody, obinutuzumab, in combination with chlorambucil in treatment-naive CLL (Goede 2014; Goede 2015). The addition of obinutuzumab to chlorambucil demonstrated significant improvement in efficacy over both single-agent chlorambucil and chlorambucil combined with rituximab. The addition of obinutuzumab to ibrutinib was expected to result in a further significant improvement in disease control, including in patients with high-risk CLL, due to the targeting of distinct mechanisms of action important in attenuating aberrant B-cell activity in frontline CLL. Treatment with ibrutinib in combination with obinutuzumab may provide an important treatment benefit for all patients with CLL and previously untreated patients with CLL with del 17p/ mutated TP53, del 11q, or unmutated IGHV - a patient population with poor prognosis for which fewer treatment options are available. A need exists for novel therapies in this hard-to-treat population, the importance of which was further underscored by the updated iwCLL guidelines (Hallek 2018). Obinutuzmab was therefore considered to be an appropriate agent with which to combine ibrutinib in Study 1130.

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 clinical data have been submitted in this application, which is considered acceptable.

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, and the conclusion remains: The clinical use of ibrutinib is not expected to be a risk for the environment.

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.

- **Table 2: Tabular overview of clinical studies**

Study ID EudraCT No. First Patient First Visit/ Completion Date Study Status	Country(ies) Number of Centers	Phase Study Description/Design Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	No. of Subjects Treated (by Treatment Group)	Type of Study Report Approved Date CTD Location of Report
PCYC-1112-CA 2012-000694-23 22 Jun 2012/06 Nov 2013 Ongoing [a]	AUS, AUT, BEL, FRA, IRL, ITA, POL, ESP, UK, USA: 76 Centers	Phase 3, randomized, multicenter, open-label; Subjects with CLL/SLL who have failed at least 1 prior line of therapy; Assess PFS by IRC.	Planned: 350 Enrolled: 391	Ibrutinib (oral) Ofatumumab (intravenous) Treatment Arm A: Ofatumumab: 12 doses total: Week 1: 300 mg IV once, Weeks 2 to 8: 2000 mg IV weekly, Weeks 12 to 24: 2000 mg IV (every 4 weeks) Arm B: Ibrutinib capsule (oral): 420 mg po daily Until PD or unacceptable toxicity.	195 ibrutinib 192 ofatumumab	CSR Date: 25 Mar 2014 Module 5.3.5.1
PCYC-1115-CA 2012-003967-23 21 March 2013/ 28 May 2015 Completed (Eligible subjects could enroll into Extension Study 1116)	Australia, Belgium, Canada, China, Czech Republic, Ireland, Israel, Italy, New Zealand, Poland, Russia, Spain, Turkey, Ukraine, United Kingdom, USA 88 Centers	Phase: 3; Randomized, open-label, multicenter; Subjects ≥65 years with treatment-naive CLL/SLL Assess efficacy of Ibrutinib compared with Chlorambucil based on PFS by IRC.	Planned: 272 Enrolled: 273	Ibrutinib (oral) Chlorabmucil (oral) Subject randomized to 1 of 2 treatment arms in a 1:1 ratio Treatment arm - Ibrutinib capsule (oral): 420 mg daily until PD or unacceptable toxicity Treatment arm - Chlorambucil tablet (oral): starting dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle up to maximum of 12 cycles, with an allowance for intra-patient dose increases of up to 0.8 mg/kg based on tolerability, in the absence of PD or unacceptable toxicity.	Ibrutinib: 136 Chlorambucil: 133	CSR 04 August 2015 Module 5.3.5.1

Type of Study	Study ID	Population	Number of Subjects [a]	Dose (mg)	Status
Phase 3 Safety and Efficacy	PCYC-1130-CA (Study 1130)	Subjects previously untreated CLL/SLL	103	420	Completed

CLL=chronic lymphocytic leukemia; PK=pharmacokinetic; SLL=small lymphocytic lymphoma.
a Refers only to subjects who were included in the PK analysis.

2.3.2. Pharmacokinetics

Methods

Study drug administration

Subjects were randomized in a 1:1 ratio to 1 of 2 treatment arms and received the following regimens:

- Arm A: Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity plus intravenous obinutuzumab given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 1000 mg on Days 8 and 15 of Cycle 1 and 1000 mg on Day 1 of each cycle up to 6 cycles.
- Arm B: Chlorambucil given orally at a dose of 0.5 mg/kg body weight on Days 1 and 15 of each cycle plus intravenous obinutuzumab per instructions shown for Arm A up to a total of 6 cycles.

Bioanalytical methods

The bioanalytical method (BTM-1792-R0) used for the measurement of ibrutinib and its metabolite PCI-452227 in study 1130 was previously assessed in application EMEA/H/C/3791/X/37. No changes were made to the method reported in previous submissions for ibrutinib. 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 1130, was conducted and met the acceptance criteria. Interference from co-medicine obinutuzumab on ibrutinib and PCI-45227 was evaluated. Results showed the mean concentrations for the test samples were within ± 15.0% of the Low QC nominal values and that there was no interference from the co-medicine on the ibrutinib and PCI-45227 samples.

Sampling

Sparse PK samples were collected in all subjects randomized to receive ibrutinib. On Cycle 1, Day 15, samples were collected pre-dose, at 1 hour (window: 45–75 minutes), 2 hours (window: 1.5–2.5 hours) and 4 hours (window: 3.5–4.5 hours). On Cycle 2, Day 1 a pre-dose sample was collected.

Pharmacokinetic analysis

A previously developed model (*Population Pharmacokinetic Analysis of Ibrutinib, EDMS-ERI-112451527: 1.0, 1 October 2015*, EMEA/H/C/003791/II/0020) was used in the analysis of the data from study PCYC-1130-CA. The previously developed model to describe ibrutinib was a 2-compartment PK model with sequential zero to first order absorption and first order elimination. It included an effect of meal on relative bioavailability and duration of zero order input, as well as an effect of the co-administration of CYP3A4 inhibitors and age on F1. The between subject variability and the residual variability was high (56.0 – 155% and 48.8 – 81.3% respectively). Between-subject variability was included on relative bioavailability (F1, instead of on oral clearance (CL/F)), apparent central volume of distribution (V2/F), apparent inter-compartmental clearance (Q/F), apparent peripheral volume of distribution (V3/F) and lag-time (ALAG1). Calculation of posthoc the PK parameters CL/F, V2/F, V3/F and Q/F need to account for the separate estimate of F1.

Pharmacokinetic parameters including the mean oral clearance (CL/F), distribution volume (Vss/F), and metrics of systemic exposure (e.g., the area under the plasma concentration-time curve from 0 to 24 hours [AUC0-24h], plasma concentration at 24 hours after dosing [C24h] of ibrutinib) were estimated using a Bayesian feedback analysis based on a previously developed population PK model (The NONMEM maximum a posteriori approach using the First Order Conditional Estimation method (FOCE) and the feature MAXEVAL equal to 0 applied to the data of Study PCYC-1130-CA). Analyses of ibrutinib plasma concentration-time data were conducted using non-linear mixed effects modelling (NONMEM) software (v. 7.1).

The individual empirical Bayesian estimates (EBE) of PK parameters were used to obtain the individual model-derived estimates of the ibrutinib exposure. Exposure metrics, AUCtau and Ctrough were calculated by means of predictions i.e. predicting individual PK profiles at steady state over the dosing interval (24 hours) using individual EBE of PK parameters with the residual variability fixed to zero.

The model was fitted to the data using the log transform both sides approach and the first-order conditional estimation method.

Results

Demographics

Table 3 Demographic Characteristics (Intent-to-Treat Population)

	Ibr+Ob N=113	Clb+Ob N=116	Total N=229
Age (years)			
Mean (SD)	70.3 (7.56)	71.2 (8.47)	70.8 (8.03)
Median	70.0	72.0	71.0
Min, Max	47, 87	40, 86	40, 87
Age groups, n (%)			
<65 years	22 (19.5)	24 (20.7)	46 (20.1)
≥65 years	91 (80.5)	92 (79.3)	183 (79.9)
Gender, n (%)			
Male	67 (59.3)	79 (68.1)	146 (63.8)
Female	46 (40.7)	37 (31.9)	83 (36.2)
Race, n (%)			
Asian	1 (0.9)	2 (1.7)	3 (1.3)
Black or African American	2 (1.8)	2 (1.7)	4 (1.7)
Native Hawaiian or Other Pacific Islander	1 (0.9)	1 (0.9)	2 (0.9)
White	109 (96.5)	111 (95.7)	220 (96.1)
Ethnicity, n (%)			
Hispanic or Latino	4 (3.5)	6 (5.2)	10 (4.4)
Not Hispanic or Latino	109 (96.5)	110 (94.8)	219 (95.6)

Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; SD: standard deviation
N=number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.

Pharmacokinetic analysis

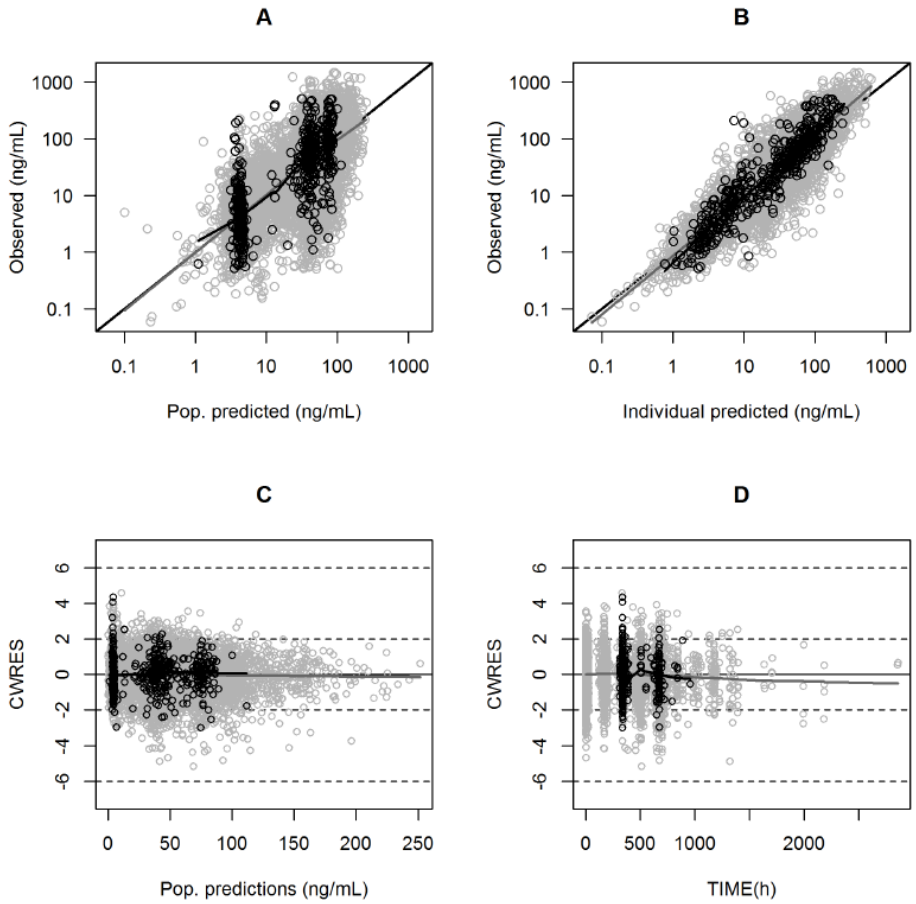
The NONMEM maximum a posteriori approach using the First Order Conditional Estimation method (FOCE) and the feature MAXEVAL equal to 0 applied to the data of Study PCYC-1130-CA was successful. The model was able to describe the data well, as can be appreciated from the GOF and residual plots shown in Figure 1.

The distributions of the EBE of ETAs for the individual parameters had median near zero, consistent with the expectations. This indicated an absence of bias in the PK parameters obtained from these analyses. The shrinkage (η_{sh}) was higher for ALAG1 (58%), Q (60%) as well as for V2 (44%) and V3 (63%). The Ibrutinib population pharmacokinetics are described with between-subject variability of bioavailability (F1) rather than on oral clearance (CL/F). This suggests that CL/F was well estimated (shrinkage on F1 of 18%), while some parameters tended more to regress toward the mean (e.g., ALAG1, Q, V2, V3), consistent with the sparse sampling approach used in this study.

Table 4. Summary Statistics of PK-Exposure

	AUC_{tau} (ng.h/mL)	C_{max} (ng/mL)	C_{trough} (ng/mL)
N	97	97	97
Mean	517	101	5.48
Median	481	92.9	4.53
SD	268	57.1	3.74
CV%	51.7	56.8	68.3
Max	1358	280	26.7
Min	67.0	10.1	1.01

Figure 2. Standard Goodness of Fit (GOF) for Ibrutinib PK: NONMEM Maximum a Posteriori Approach

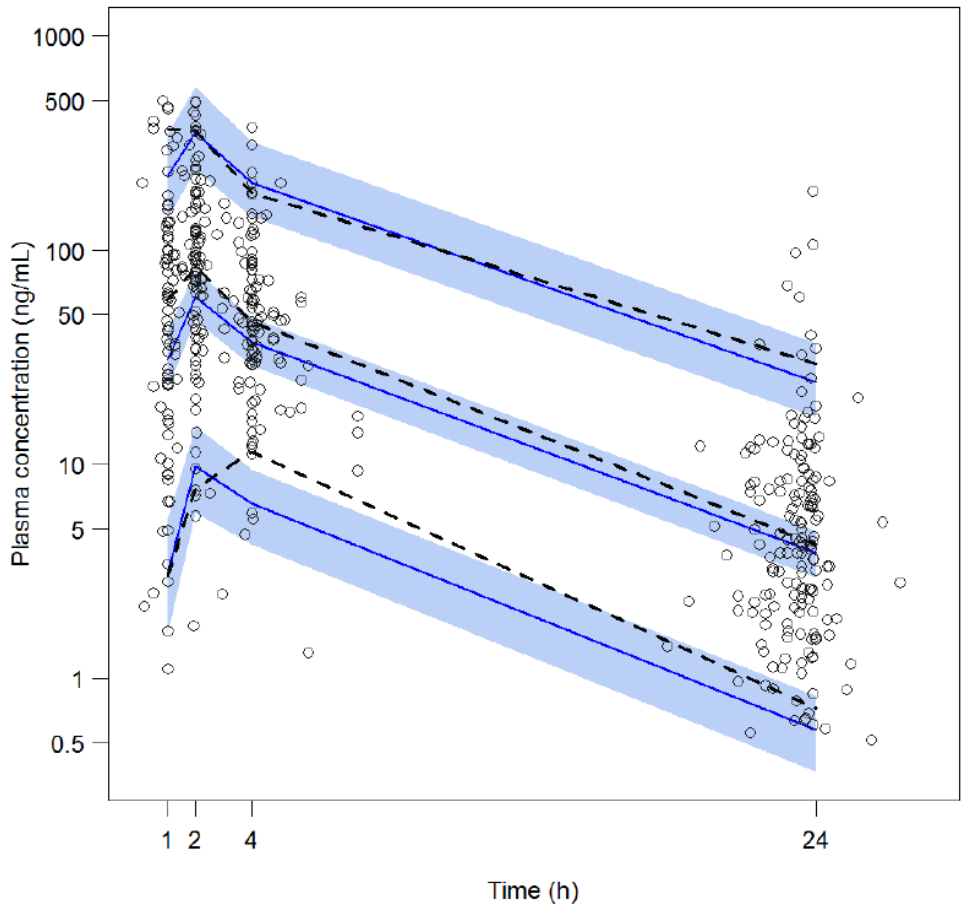


Gray symbols: previous PK assessment; black symbols: Study PCYC-1130-CA data. Gray and black lines: smoothers (Lowess).
A: observations [DV] vs population predictions [PRED]; B: observations [DV] vs individual predictions [IPRED]; C: conditional weighted residuals [CWRES] vs population predictions [PRED]; D: conditional weighted residuals [CWRES] vs time since first dose.

When ibrutinib is administered in combination with obinutuzumab, the PK profile of ibrutinib is in alignment with historical data with ibrutinib for ibrutinib as monotherapy, and there was no evidence of effect of obinutuzumab on ibrutinib exposure. The mean CL/F and Vss/F were 1114 L/h and 9501 L, respectively. The goodness-of-fit plots, the graphical exploration of the empirical Bayesian estimates, and

the visual predictive check plots indicated the absence of bias in the individual predictions. Figure 3 represents the ibrutinib concentration-time data overlaying model-based simulations derived from a previously developed PK model for ibrutinib. There was a substantial overlap of observed and predicted values based on the previous nonlinear mixed-effects model, thereby indicating that the PK behaviour observed in this study was consistent with previous assessments. In addition, the previously developed PK model for ibrutinib monotherapy allowed for description of the data obtained in subjects with CLL/SLL when treated with Ibr+Ob. Mean steady-state AUC0-24h and C24h or trough concentration (standard deviation [SD]) were 517 (268) ngxh/mL and 5.48 (3.74) ng/mL, respectively.

Figure 3. Observed Ibrutinib Plasma Concentration after 420 mg Ibrutinib Daily Overlaid to the 90% Prediction Intervals Based on a Previously Developed Pharmacokinetic Model (Study 1130).



Blue solid lines: median, 5th and 95th percentiles of the simulated data with its 95% confidence interval (blue shaded area); black dashed lines: median, 5th and 95th percentiles of the observed data for ibrutinib. The dots are the observed data from PCYC-1130-CA.

2.3.3. Discussion on clinical pharmacology

The MAH has conducted a clinical trial (study 1130) where subjects were randomized in a 1:1 ratio to 1 of 2 treatment arms and received wither ibrutinib 420 mg/day plus intravenous obinutuzumab (Arm A) or chlorambucil 0.5 mg/kg body weight plus intravenous obinutuzumab (Arm B), up to a total of 6 cycles for each treatment arm.

Obinutuzumab concentrations were not determined and therefore no assessment can be made of the effect of ibrutinib on obinutuzumab. Mechanistically, an interaction between ibrutinib and obinutuzumab is not expected.

A previously developed population pharmacokinetic model was used to derive the individual exposure metrics (EMEA/H/C/003791/II/0020). The PPK model used in this analysis (based on 8697 observations from 1202 subjects) was generally similar to the model presented in the NDA with the exception that effects of body weight on V/F and of antacids on duration of zero order input (D1) were no longer included as they were considered not clinically significant. The conclusion was that the population pharmacokinetic model performed sufficiently well for its purpose.

The approach for deriving individual exposure is considered acceptable.

Sparse sampling was employed and a previously developed population pharmacokinetic model was used to derive the individual ibrutinib exposure. The applicant has presented goodness-of-fit plots, ETA-distributions and the shrinkage as well as a visual predictive check-plot. The shrinkage is high for all parameters but F1 (44-63%), indicating that the sparse sampling resulted in less informative data. The shrinkage on F1 is acceptable. The maximum concentration is somewhat under-predicted; however the model is considered to predict the data adequately.

2.3.4. Conclusions on clinical pharmacology

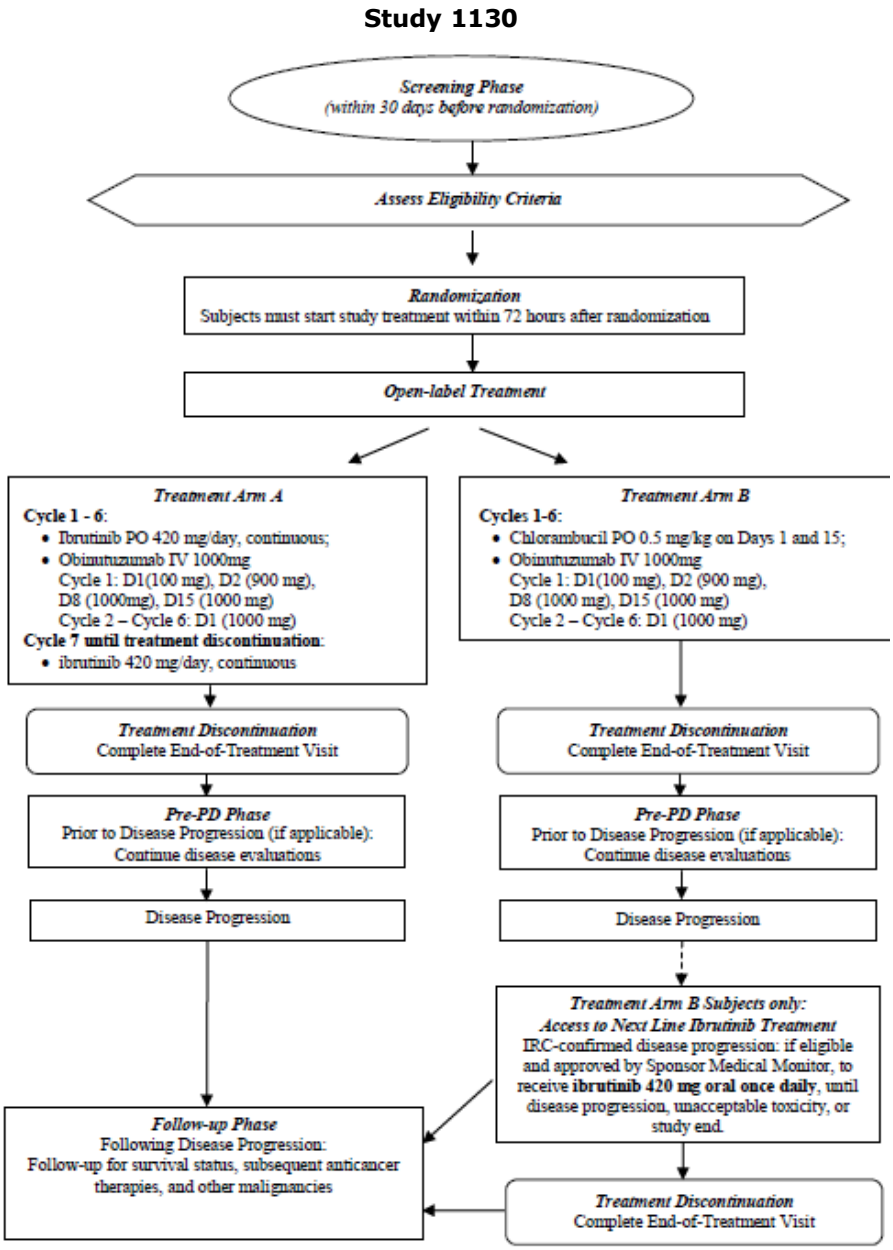
The clinical trial performed, and the method of analysing the data is considered acceptable. The pharmacokinetics profile is not considered to differ between this population and the previous populations.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Study PCYC-1130-CA (hereafter abbreviated 1130): A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.

Figure 4: Study design



Methods

Study participants

Key inclusion criteria

1. Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008).
2. Age 65 yrs and older OR if less than 65 years old, must have at least one of the following criteria:
   a. Cumulative Illness Rating Score (CIRS) >6.
   b. Creatinine clearance estimated <70 mL/min using the Cockcroft-Gault equation.
   c. Del 17p by FISH or TP53 mutation by PCR or Next Generation Sequencing (NGS).
3. Active disease meeting at least 1 of the following IWCLL criteria (Hallek 2008) for requiring treatment:

In addition, all subjects were required to have measurable nodal disease (defined as at least 1 lymph node with > 1.5 cm in the longest diameter in a site not previously irradiated) per CT scan.

Key exclusion criteria

Any previous CLL/SLL treatment, known lymphoma or leukemia of the central nervous system, and history or current evidence of Richter's transformation.

Treatments

- Treatment Arm A (ibrutinib+Ob, n=113): Ibrutinib given orally at a dose of 420 mg/day until progressive disease or unacceptable toxicity plus IV Ob at a fixed dose of 1,000 mg given on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), Days 8 and 15 of Cycle 1, and on Day 1 of each remaining cycle for up to 6 cycles.
- Treatment Arm B (Clb+Ob, n=116): Chlorambucil given orally at a dose of 0.5 mg/kg up to a period of 6 cycles on Days 1 and 15 of each cycle plus IV Ob according to the schedule described for Treatment Arm A.

Upon IRC-confirmed disease progression, subjects randomized to Arm B were eligible to receive ibrutinib monotherapy as next-line treatment with the approval of a medical monitor.

Outcomes/endpoints

Table 5: Outcomes and definitions

Endpoint	Definition	Analysis Method
Primary Endpoint		
PFS assessed by IRC	Time from the date of randomization to the date of IRC-assessed disease progression or date of death from any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented disease progression or death. For subjects with baseline and post-baseline response assessments but without IRC-assessed disease progression and were not known to have died at the time of the analysis, PFS was censored at the date of the last evidence of no progression as assessed by the IRC. For subjects without baseline or post-baseline assessments, PFS was censored on the date of randomization.	Primary Treatment effect of ibrutinib plus obinutuzumab compared to chlorambucil plus obinutuzumab was tested with a unstratified log-rank test. The HR and its 95% CI based on an unstratified Cox regression model. PFS distribution is estimated by Kaplan-Meier method: median PFS and landmark estimates with 2-sided 95% CIs were to be provided for each treatment arm. Sensitivity Analyzing PFS assessed by investigator using the same method as PFS assessed by IRC. Use of stratified log-rank test Subgroup HR and its 95% CI based on unstratified Cox regression model for each subgroup.

Endpoint	Definition	Analysis Method
Secondary Endpoints – Efficacy		
PFS assessed by IRC in high-risk subpopulation and high-risk population	Defined the same as the primary endpoint.	Primary Analyzed the same as primary endpoint in del17p/TP53 mutation/del11q high-risk subpopulation Additional analysis Same as primary plus unmutated IGHV (ie, del17p/TP53 mutation/del11q/unmutated IGHV high-risk population)
Rate of sustained hemoglobin improvement	Proportion of subjects with hemoglobin increase ≥50% over baseline continuously for ≥56 days without blood transfusions or growth factors.	Primary Chi-square test. Subgroup Same analysis in subjects with baseline anemia (hemoglobin ≤110 g/L)
Rate of MRD-negative response	Proportion of subjects who achieved MRD-negative response defined as <1 CLL cell per 10,000 leukocytes as assessed by flow cytometry of a bone marrow aspirate or peripheral blood sample per central laboratory.	Primary Chi-square test for MRD-negative response rate by bone marrow. Supportive MRD-negative response rate in peripheral blood and overall.
ORR assessed by IRC	The proportion of subjects achieving a best overall response of CR, CRi, nPR, or PR per IRC assessment at or prior to initiation of subsequent antineoplastic therapy.	Primary Chi-square test Sensitivity Investigator assessed ORR by chi-square test. Supportive Descriptive summary on duration of response.
OS	Time from the date of randomization to the date of death from any cause. All deaths observed at the time of the analysis were considered as events. For subjects who were not known to have died at the time of the analysis, OS data was censored at the date when the subjects were last known to be alive.	Primary Analyzed the same as PFS primary analysis.
Rate of IRRs	Proportion of subjects experiencing IRRs that started on the day of an obinutuzumab infusion and are assessed as related or possibly related to obinutuzumab.	Primary Fisher's exact test for the between-arm comparison of the rates of Grade ≥ 3 or SAEs based on the PT (infusion-related reactions). Supportive Descriptive summary for any grade IRRs.
Rate of sustained platelet improvement	Proportion of subjects with platelet increase ≥ 50% over baseline continuously for ≥56 days without blood transfusions or growth factors.	Primary Chi-square test. Subgroup Same analysis in subjects with baseline thrombocytopenia (platelets $\leq 100\times10^9$/L)

Endpoint	Definition	Analysis Method
Rate of clinically meaningful improvement in EQ-5D-5L	Proportion of subjects with utility score increase ≥ 0.08 points over baseline at or prior to initiation of subsequent antineoplastic therapy.	Primary Chi-square test. Sensitivity Same analysis for clinically meaningful improvement in visual analogue scale (increase ≥ 7 points over baseline at or prior to initiation of subsequent antineoplastic therapy).

CI=confidence interval; CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with incomplete marrow recovery; del11q= deletion of the long arm of chromosome 11; del17p=deletion of the short arm of chromosome 17; EQ-5D-5L=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EuroQol Five-Dimension; HR: hazard ratio; IGHV=immunoglobulin heavy-chain variable; IRC=Independent Review Committee; IRR=infusion-related reaction; MRD=minimum residual disease; PR=partial response; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; PT=preferred term; SAE=serious adverse event

Analysis of the primary and key efficacy endpoints (ie, PFS and ORR) was based on assessment by an IRC. Assessment of response and progression was conducted in accordance with the 2008 IWCLL criteria with recent clarifications (Hallek et al, 2013; Cheson et al, 2014; Hallek et al, 2012; Hallek et al, 2008).

The main disease evaluations included the following assessments:

- Physical examination with focus on the presence/absence of size increase/decrease in lymph nodes, liver, and spleen).
- Hematologic parameters by complete blood count performed at a central laboratory.
- Radiographic evaluation (CT or magnetic resonance imaging scan of the neck, chest, abdomen, and pelvis).
- Flow cytometric evaluation of MRD, which is defined as < 1 CLL cell per 10,000 leukocytes; key time points in this evaluation are as follows:
    - A peripheral blood and bone marrow aspirate and/or biopsy with MRD at Cycle 9 and as appropriate if there was evidence of CR in the other response parameters.
    - Responders with MRD-negative status in the bone marrow were followed with peripheral blood MRD assessments every 4 cycles until Cycle 33 and then every 6 cycles starting at Cycle 39.
    - Responders with MRD-positive status in the bone marrow or peripheral blood were followed with peripheral blood MRD assessments every 4 cycles until Cycle 33 and then every 6 cycles starting Cycle 39. Upon MRD negativity in peripheral blood, this result was subsequently confirmed with a bone marrow MRD assessment.

If study treatment was held before a scheduled response assessment, the response assessment could be delayed up to 4 weeks to allow re-initiation of study treatment for 2 weeks (or as long as possible) prior to performing the scheduled response assessment. For the purposes of the study result analyses, efficacy assessments were performed by an IRC (whose members were blinded to each subject's study treatment assignment) and were independent of investigators and personnel who were involved in the conduct of the study.

Sample size

This study was designed to evaluate the effect of treatment on PFS and was powered for this endpoint. The sample size for the study was calculated based on the following considerations:

- Randomization ratio of 1:1.
- Median PFS of 27 months for Arm B (chlorambucil in combination with obinutuzumab).
- Target HR of 0.55, which corresponds to median PFS of 49.1 months for Arm A (ibrutinib combined with obinutuzumab).
- Enrollment rate of 18 subjects per month.
- A minimum of 94 PFS events provides at least an 80% power to detect the target HR of 0.55 based on a log-rank test and a 2-sided overall significance level of 0.05.

On this basis, 94 PFS events provide 80% power to achieve a statistical significance level of 5% (2-sided) under exponential distribution. With an estimated accrual rate of 18 subjects per month, approximately 212 eligible subjects were to be enrolled to observe 94 PFS events in approximately 36 months from the first subject randomized.

Randomisation

Approximately 212 subjects were planned for randomization. Two randomization schemes were generated: 1 for each geographic region (North America vs. ROW). Under each scheme, randomization was stratified according to the following factors:

- Eastern Cooperative Oncology Group performance status of 0-1 vs. 2.
- Cytogenetics were to be stratified into 1 of 3 categories:
  - Del 17p.
  - Del 11q without del 17p.
  - Others (neither del 17p nor del 11q).

The randomization code was controlled through a centralized procedure. The primary efficacy evaluation was performed by an IRC that was blinded to study treatment information.

Blinding (masking)

This was an open-label study; no blinding was performed.

Statistical methods

The analysis of PFS will be performed in the ITT population to compare PFS (as assessed by the IRC) for the two treatment arms using a log-rank test. Distribution of PFS including median and its corresponding 95% confidence interval (CI) will be summarized for each treatment arm using the Kaplan-Meier estimate. The estimate of the hazard ratio and its corresponding 95% CI will be computed using a Cox proportional hazards model.

The following two randomization stratification factors will be used for the stratified analysis/test: ECOG performance status (0, 1 versus 2) and Cytogenetics (del 17p, del 11q without del 17p, others). To reflect the randomization process and maintain the integrity of randomization, all stratified tests will be based on randomization stratification factors as recorded in the IWRS.

Tests of primary and secondary efficacy endpoints were performed at the 2-sided significance level of 0.05 based on a serial gatekeeping testing procedure in the following sequential hierarchical manner: PFS by IRC, PFS by IRC in the high-risk subpopulation, rate of sustained Hgb improvement, rate of MRD-negative response, ORR by IRC, OS, rate of IRRs, rate of sustained platelet improvement, and rate of clinically meaningful improvement of EQ-5D-5L utility score.

Table 6: Summary of analysis populations

Analysis Population	Definition
ITT population	All randomized subjects.
PK-evaluable population	All subjects who received at least 1 dose of ibrutinib and had at least 1 post-treatment sample obtained
Safety population	All randomized subjects who received at least 1 dose of study treatment
High-risk subpopulation	Randomized subjects with del 17p/TP53 mutation, or del 11q at baseline per central laboratory results.
High-risk population	Randomized subjects with del 17p/TP53 mutation, or del 11q or unmutated IGHV at baseline per central laboratory results.

The recently released IWCLL guidelines (Hallek et al, 2018) have placed new emphasis on the importance of testing for IGHV mutational status and are now recommending this testing in clinical practice. Given the guidelines from Hallek et al, 2018 on the importance of IGHV, an analysis for PFS was conducted in the high-risk population, which additionally includes subjects with unmutated IGHV (ie, del 17p/TP53 mutation/del 11q/unmutated IGHV). The IGHV mutational status subgroups were already selected as independent subgroups for analysis in addition to the high-risk subpopulation.

Results

Participant flow

Table 7: Participant flow

	Ibr+Ob N=113		Clb+Ob N=116	
	Ibrutinib n (%)	Obinutuzumab n (%)	Chlorambucil n (%)	Obinutuzumab n (%)
Treatment status				
Did not receive any study treatment	0	0	1 (0.9)	1 (0.9)
Ongoing	79 (69.9)	0	0	0
Completed	NA	100 (88.5)	103 (88.8)	100 (86.2)
Discontinued	34 (30.1)	13 (11.5)	12 (10.3)	15 (12.9)
Primary reason for discontinuation of study treatment[a]				
Disease progression	4 (3.5)	1 (0.9)	0	0
Intercurrent illness or adverse event[b]	18 (15.9)	10 (8.8)	11 (9.5)	15 (12.9)
Death	2 (1.8)	0	0	0
Withdrawal of consent	4 (3.5)	1 (0.9)	0	0
Investigator decision	3 (2.7)	0	1 (0.9)	0
Other[c]	3 (2.7)	1 (0.9)	0	0

Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; NA: not applicable.

N=: number of subjects in the specified population. n=: number of subjects in each category. % = 100*n/N.

[a] Note: The primary reason for discontinuation of each study drug (ie, ibrutinib, chlorambucil, or obinutuzumab) were collected separately. If a subject discontinued study drugs in a treatment arm due to the same primary reason, then the event is counted in both columns (Attachment 1-Listing 14.1.1.5).

[b] Otherwise known as unacceptable toxicity/adverse event.

[c] Other reasons in Ibr+Ob arm include treatment discontinuation due to planned operation that did not occur (1 subject), unwillingness to continue treatment (2 subjects), and dispensing of last dose on Cycle 1 Day 2 (Clb+Ob). Additional information on these reasons is provided in Attachment 1-Listing 14.1.1.5.

Recruitment

Study Period: 06 October 2014 (first informed consent signed) to 26 March 2018 (date of database lock).

The study was conducted at a total of 9 sites in the United States (US) and 80 sites in rest-of-world (ROW).

Conduct of the study

There were 3 amendments to the original protocol, which was dated 12 May 2014. Key changes (as selected by the assessor) in the amendments included

1. 18 Aug 2014 Included interim analysis to be conducted at approximately 66 PFS events.

   Clarified that progressive disease could be assessed based on ≥ 50% increase from nadir rather than baseline count if the ALC is ≥ 30,000/μL and lymphocyte doubling time is rapid.

2. 10 May 2016 Removed the 36-month timepoint from interim analysis.

3. 17 Feb 2017 Removed the planned interim analysis and updated plans for primary analysis to ensure maturity of PFS outcome data per FDA feedback.

Important changes in the planned analyses

- The randomization strata were based on available FISH results at randomization from either the central or local laboratory. Post-randomization, the central laboratory continued FISH tests and reported results based on samples drawn at baseline for all randomized subjects prior to database lock. According to the final central FISH results, there were 10% more subjects in the Clb+Ob arm with either del 17p or del 11q. In order to use the most complete information, the unstratified analysis was used for the primary analysis of the primary endpoint (PFS by IRC) and all secondary endpoints. In addition, the original planned stratified analysis for primary endpoint (PFS by IRC) was maintained as a sensitivity analysis.
- Based on updated IWCLL guidelines (Hallek et al, 2018), in which there is new emphasis on the importance of testing for IGHV mutational status, an additional analysis for PFS was conducted inclusive of this high-risk population.

Table 8: Important protocol violations

Category	Ibr+Ob N=113 n (%)	Clb+Ob N=116 n (%)	Total N=229 n (%)
Informed consent not properly administered	3 (2.7)	6 (5.1)	9 (3.9)
Investigational product compliance	3 (2.7)	1 (0.8)	4 (1.7)
Administration of prohibited concomitant medication	0	1 (0.8)	1 (0.4)

One of the deviations resulted in a major hemorrhagic event (continuation of ibrutinib dosing prior to a surgical procedure to remove a central catheter, where the subject subsequently developed a hematoma requiring surgical evacuation).

Baseline data

Table 9: Demographic characteristics (ITT)

	Ibr+Ob N=113	Clb+Ob N=116	Total N=229
Age (years)			
Mean (SD)	70.3 (7.56)	71.2 (8.47)	70.8 (8.03)
Median	70.0	72.0	71.0
Min, Max	47, 87	40, 86	40, 87
Age groups, n (%)			
<65 years	22 (19.5)	24 (20.7)	46 (20.1)
≥65 years	91 (80.5)	92 (79.3)	183 (79.9)
Gender, n (%)			
Male	67 (59.3)	79 (68.1)	146 (63.8)
Female	46 (40.7)	37 (31.9)	83 (36.2)
Race, n (%)			
Asian	1 (0.9)	2 (1.7)	3 (1.3)
Black or African American	2 (1.8)	2 (1.7)	4 (1.7)
Native Hawaiian or Other Pacific Islander	1 (0.9)	1 (0.9)	2 (0.9)
White	109 (96.5)	111 (95.7)	220 (96.1)
Ethnicity, n (%)			
Hispanic or Latino	4 (3.5)	6 (5.2)	10 (4.4)
Not Hispanic or Latino	109 (96.5)	110 (94.8)	219 (95.6)

Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; SD: standard deviation
N=number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.

Table 10: Baseline Characteristics (ITT)

	Ibr+Ob N=113	Clb+Ob N=116	Total N=229
Time from initial diagnosis to randomization (months)			
Mean (SD)	41.4 (41.94)	53.9 (65.99)	47.7 (55.68)
Median	29.6	36.5	32.6
Min, Max	0, 192	0, 480	0, 480
Histology, n (%)			
CLL	107 (94.7)	107 (92.2)	214 (93.4)
SLL	6 (5.3)	9 (7.8)	15 (6.6)
Rai stage, n (%)			
Stage 0/I/II	53 (46.9)	57 (49.1)	110 (48.0)
Stage III/IV	60 (53.1)	59 (50.9)	119 (52.0)
Bulky disease[a], n (%)			
≥10 cm	2 (1.8)	2 (1.7)	4 (1.7)
≥5 cm	30 (26.5)	44 (37.9)	74 (32.3)
Cytopenia, n (%)			
Hemoglobin ≤110 g/L	51 (45.1)	50 (43.1)	101 (44.1)
Platelets ≤100x10^9/L	28 (24.8)	22 (19.0)	50 (21.8)
Absolute neutrophil count ≤1.5x10^9/L	7 (6.2)	4 (3.4)	11 (4.8)
Any of the above	63 (55.8)	62 (53.4)	125 (54.6)

[a] Bulky disease is based on the largest longest diameter of target lymph node at screening per the IRC assessment.

Table 11: Baseline Genomic characteristics by central laboratory (ITT)

	Ibr+Ob N=113 n (%)	Clb+Ob N=116 n (%)	Total N=229 n (%)
High-risk (del17p/TP53 mut/del11q/unmut IGHV)[a]			
Yes	73 (64.6)	75 (64.7)	148 (64.6)
No	40 (35.4)	41 (35.3)	81 (35.4)
Del17p/TP53 mut or del11q[b]			
Yes	30 (26.5)	45 (38.8)	75 (32.8)
No	83 (73.5)	71 (61.2)	154 (67.2)
TP53			
Mutated	13 (11.5)	16 (13.8)	29 (12.7)
Not mutated	99 (87.6)	94 (81.0)	193 (84.3)
Missing	1 (0.9)	6 (5.2)	7 (3.1)
IGHV			
Unmutated	66 (58.4)	57 (49.1)	123 (53.7)
Mutated	41 (36.3)	50 (43.1)	91 (39.7)
Missing	6 (5.3)	9 (7.8)	15 (6.6)
Hierarchical Classification[c]			
del 17p	14 (12.4)	18 (15.5)	32 (14.0)
del 11q	13 (11.5)	22 (19.0)	35 (15.3)
Trisomy 12	25 (22.1)	21 (18.1)	46 (20.1)
del 13q	43 (38.1)	37 (31.9)	80 (34.9)

[a] del 17p/TP53 mutated or del 11q or IGHV unmutated according to central laboratory results. High-risk population consists of subject with any of these genomic characteristics.
[b] del 17p/TP53 mutated or del 11q according to central laboratory results. High-risk subpopulation consists of subjects with any of these genomic characteristics.
[c] The high-risk factors was identified per the hierarchical order del 17p>del 11q>trisomy 12>del 13q.

Numbers analysed

Data from Study 1130 (N=229) are presented individually and in a side-by-side format with the previously submitted data from Study 1115 (N=269, data cutoff of 28 May 2015). Efficacy analyses were performed using the intent-to-treat (ITT) population.

Outcomes and estimation

- **Primary endpoint: PFS by IRC**

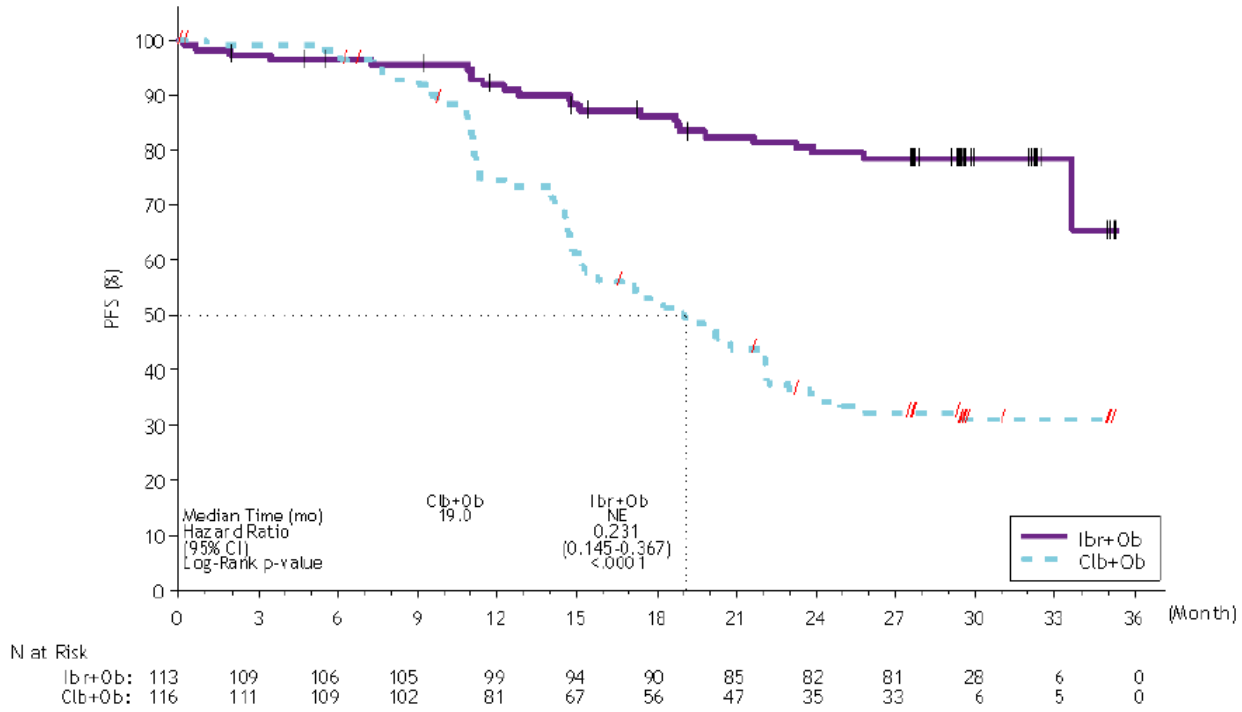
Overall median follow-up was 31.3 months.

Table 12: Progression-free survival based on IRC Assessment (ITT)

Progression-free Survival	Ibr+Ob N=113	Clb+Ob N=116	Comparison/ Difference Ibr+Ob vs. Clb+Ob
Events - n (%)	24 (21.2)	74 (63.8)	
Disease progression- n	11	64	
Death - n	13	10	
Censored - n (%)	89 (78.8)	42 (36.2)	
PFS (Months)			
Median (95% CI)[a]	NE (33.6, NE)	19.0 (15.1, 22.1)	
Min, Max	0.16, 35.32+	0.03+, 35.22+	
P value[b]			<0.0001
Hazard ratio (95% CI)[c]			0.231 (0.145, 0.367)
Landmark Estimates - % (95% CI)[a]			
6 Months	96.5 (90.8, 98.7)	97.3 (91.9, 99.1)	-0.9 (-5.4, 3.7)
12 Months	91.9 (84.9, 95.7)	74.4 (65.2, 81.6)	17.4 (7.8, 27.1)
18 Months	86.3 (78.2, 91.5)	52.3 (42.6, 61.2)	33.9 (22.5, 45.3)
24 Months	79.5 (70.5, 86.0)	34.3 (25.5, 43.3)	45.2 (33.4, 57.0)
30 Months	78.5 (69.5, 85.2)	31.1 (22.5, 40.0)	47.5 (35.7, 59.3)

CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; IRC: Independent Review Committee; NE: not estimable; PFS: progression-free survival
N: number of subjects in the specified population. n: number of subjects with PFS events. %=100*n/N.
+ Indicates censored observation.
[a] Estimated by Kaplan-Meier method.
[b] P value is from unstratified log-rank test.
[c] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.

Figure 5: Kaplan-Meier Curves of Progression-free Survival Based on IRC Assessment (Intent-To-Treat Population)

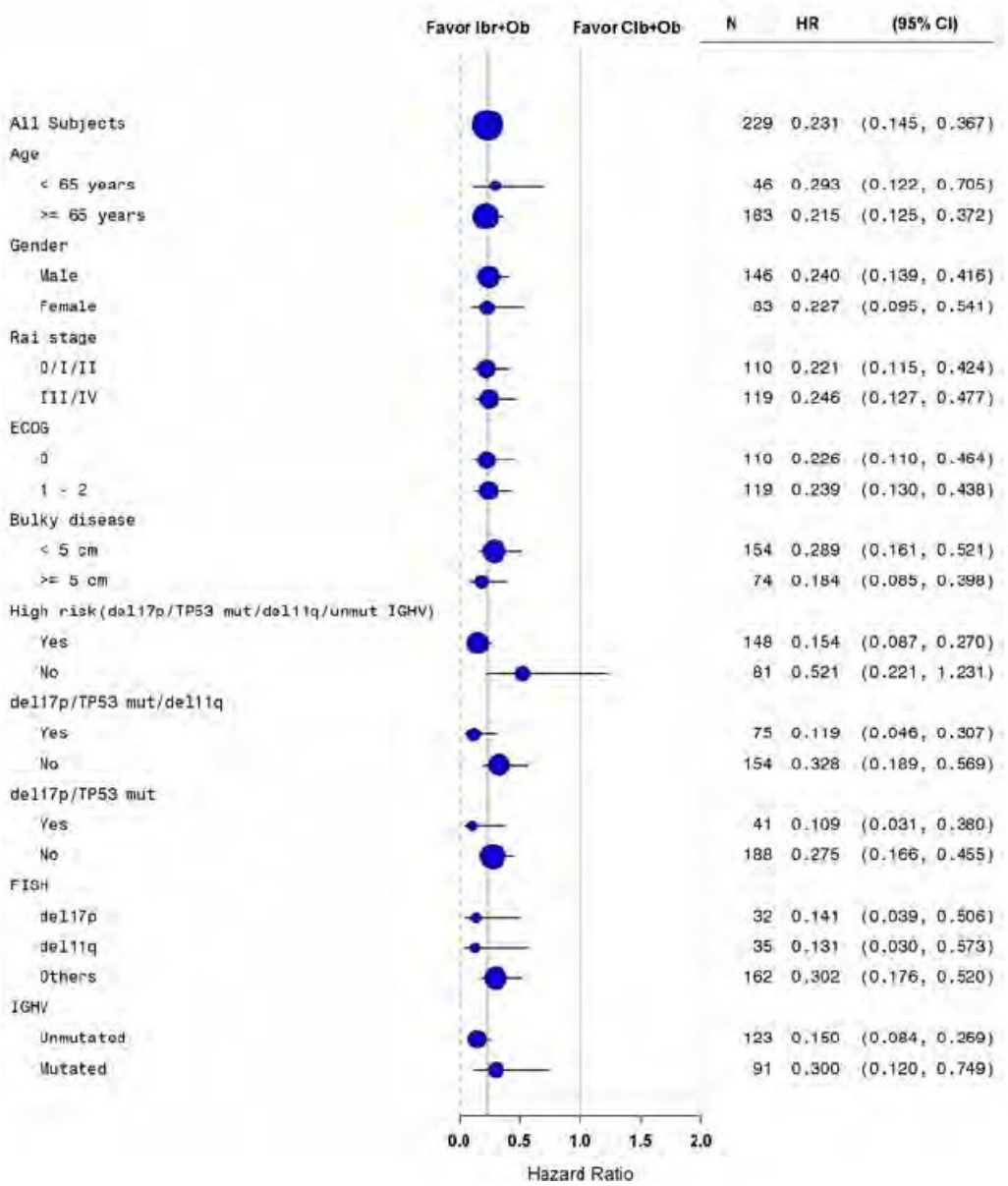


CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; IRC: Independent Review Committee; NE: not estimable; PFS: progression-free survival.
P value is from unstratified long-rank test.
Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.

Table 13: sensitivity analyses for PFS (ITT population)

	Ibr+Ob vs. Clb+Ob	
Analysis	**Hazard Ratio (95% CI)**	**P-value**
IRC assessment - use of stratified Cox regression model	0.229 (0.144, 0.366)	< 0.0001
Investigator assessment – unstratified analysis	0.260 (0.163, 0.415)	< 0.0001

Figure 6: Forest Plot of Hazard ratios for PFS (ITT population)



No cases of Richter's transformation were reported in the Ibr+Ob arm. Two cases of Richter's transformation in the Clb+Ob arm were reported.

Updated analyses (cut off 28.02.2019)

For the ITT population, at an event rate of 23% in the experimental arm and 63% in the control arm, the risk of disease progression or death per investigator assessment was reduced by 74.9% for Ibr+Ob vs. Clb+Ob (HR = 0.251, 95% CI: 0.160, 0.395). The median PFS was not estimable for the Ibr+Ob arm and was 21.9 months for the Clb+Ob arm. The Kaplan-Meier point estimates of the PFS rate per investigator assessment at 36 months were 76.3% for the Ibr+Ob arm and 32.6% for the Clb+Ob arm.

For the high-risk population, at an event rate of 26% in the experimental arm and 83% in the control arm,the risk of disease progression or death per investigator assessment was reduced by 83.8% for Ibr+Ob vs. Clb+Ob (HR = 0.162, 95% CI: 0.096, 0.275). The median PFS was not reached for the Ibr+Ob arm and was 18.0 months for the Clb+Ob arm. The Kaplan-Meier point estimates of the PFS rate

per investigator assessment at 36 months were 72.4% for the Ibr+Ob arm and 12.0% for the Clb+Ob arm.

Given the higher proportion of discontinuation of study treatment in the experimental arm, mostly related to adverse events and unacceptable toxicity, a sensitivity analysis was requested, imputing an event at the time of discontinuation of treatment, instead of censoring, if a PFS event was not determined at a later time. Not unexpectedly, considering the longer time on treatment in the Ibr+Ob arm, the imputation of treatment discontinuation due to reasons other than progressive disease (PD) as a progressive event increases the hazard of progression. The HR between the Ibr+Ob arm and the Clb+Ob arm is increased from 0.231 (95% CI: 0.145, 0.367) in the CSR submitted to 0.327 (95% CI: 0.219, 0.486) for the unstratified analysis, and from 0.229 (95% CI: 0.144, 0.366) in the CSR submitted to 0.316 (95% CI: 0.211, 0.473) for the stratified analysis. Nevertheless, the difference between the 2 treatment arms remains statistically significant.

Secondary endpoints

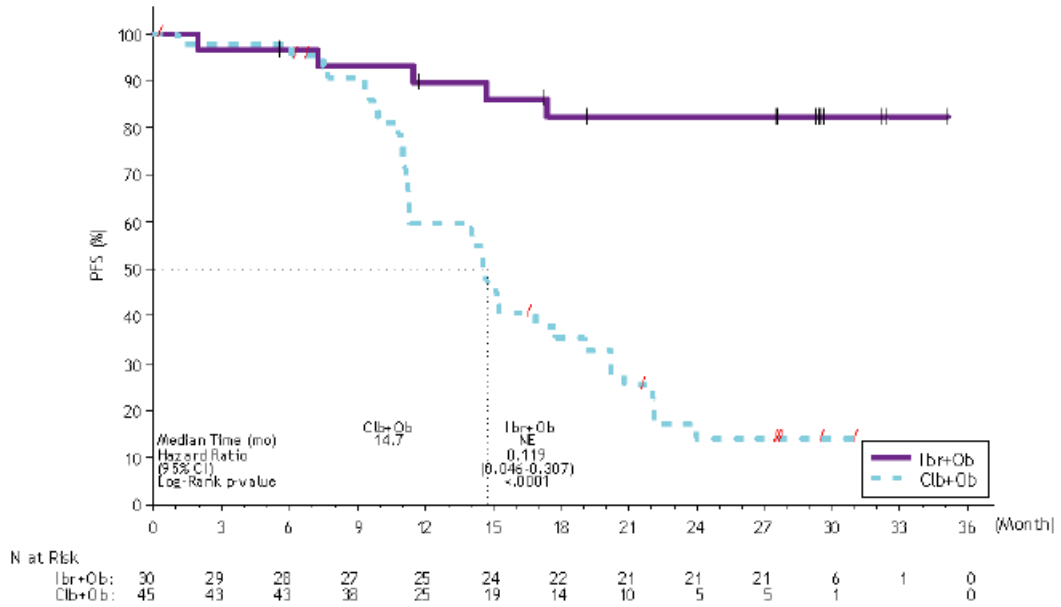
Note: Secondary efficacy endpoints were tested with a closed testing procedure at the 2-sided significance level of 0.05. The first endpoint in the testing order (PFS in del 17p/TP53 mutation/del 11q high-risk subpopulation) met statistical significance. The next endpoint in the testing order (ie, rate of sustained hemoglobin improvement) did not meet statistical significance. As a result, all p-values for subsequent endpoints (ie, rate of MRDnegative response, ORR by IRC, OS, rate of sustained platelet improvement, rate of IRRs, and rate of clinically meaningful improvement in EQ-5D-5L utility score) are presented nominally.

Table 14: Progression-free Survival – del 17p/TP53 mutation/del 11q High-risk Subpopulation

Progression-free Survival	Ibr+Ob N=30	Clb+Ob N=45	Comparison/ Difference Ibr+Ob vs. Clb+Ob
Events - n (%)	5 (16.7)	35 (77.8)	
Disease progression- n	2	32	
Death – n	3	3	
Censored - n (%)	25 (83.3)	10 (22.2)	
PFS (Months)			
Median (95% CI)[a]	NE (NE, NE)	14.7 (11.3, 17.8)	
Min, Max	1.94, 35.12+	0.30+, 31.08+	
P value[b]			< 0.0001
Hazard ratio (95% CI)[c]			0.119 (0.046, 0.307)
Landmark Estimates - % (95% CI)[a]			
6 Months	96.7 (78.6, 99.5)	97.7 (84.9, 99.7)	-1.1 (-8.8, 6.7)
12 Months	89.8 (71.5, 96.6)	59.7 (43.4, 72.7)	30.1 (11.7, 48.6)
18 Months	82.4 (62.7, 92.3)	35.5 (21.5, 49.8)	46.9 (26.7, 67.2)
24 Months	82.4 (62.7, 92.3)	14.1 (5.3, 26.9)	68.3 (50.5, 86.2)
30 Months	82.4 (62.7, 92.3)	14.1 (5.3, 26.9)	68.3 (50.5, 86.2)

CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; del11q: deletion of the long arm of chromosome 11; del17p: deletion of the short arm of chromosome 17; Ibr+Ob: ibrutinib+obinutuzumab; IRC: Independent Review Committee; NE: not estimable; PFS: progression-free survival;
N: number of subjects in the specified population. n: number of subjects with PFS events. %=100*n/N.
+ Indicates censored observation.
[a] Estimated by Kaplan-Meier method.
[b] P value is from unstratified log-rank test.
[c] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.
High-risk subpopulation defined as randomized subjects with del17p or TP53 mutation or del11q at baseline per central laboratory results.

Figure 7 Kaplan-Meier Curves for PFS based on IRC del 17p/TP53 mutation/del 11q High-risk Subpopulation



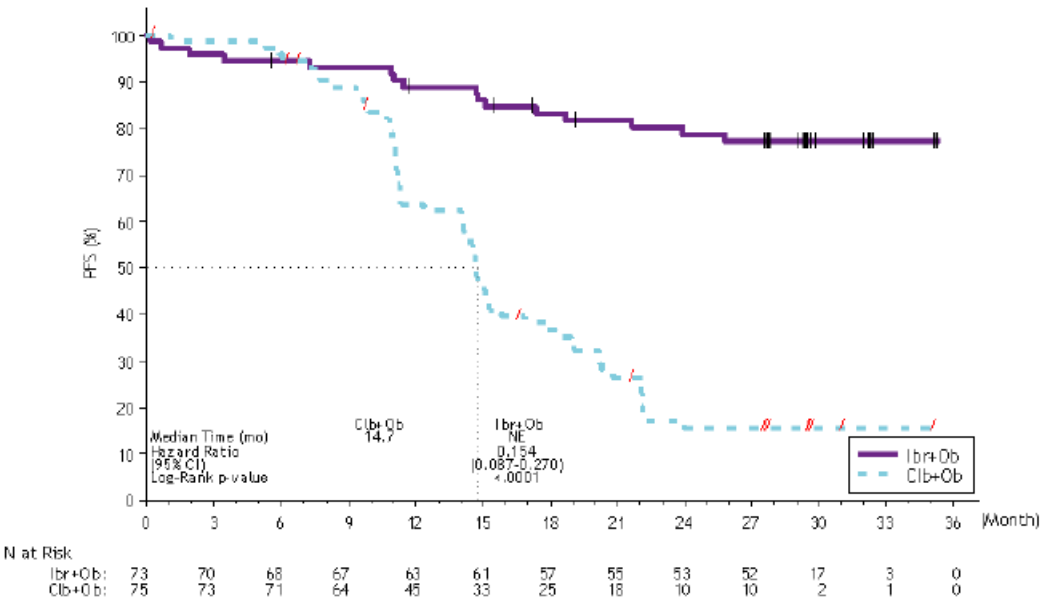
PFS by IRC in the high-risk population (including unmutated IGHV)

Table 15: PFS based on IRC del 17p/TP53 mutation/del 11q / del11q unmutated IGHV High-risk Subpopulation

Progression-free Survival	Ibr+Ob N=73	Clb+Ob N=75	Comparison/ Difference Ibr+Ob vs. Clb+Ob
Events - n (%)	16 (21.9)	59 (78.7)	
Disease progression- n	9	54	
Death - n	7	5	
Censored - n (%)	57 (78.1)	16 (21.3)	
PFS (Months)			
Median (95% CI)[a]	NE (NE, NE)	14.7 (12.4, 16.9)	
Min, Max	0.16, 35.32+	0.30+, 35.09+	
P value[b]			< 0.0001
Hazard ratio (95% CI)[c]			0.154 (0.087, 0.270)
Landmark Estimates - % (95% CI)[a]			
6 Months	94.5 (86.1, 97.9)	95.9 (88.0, 98.7)	-1.4 (-8.3, 5.5)
12 Months	89.0 (79.1, 94.3)	63.6 (51.4, 73.6)	25.3 (12.0, 38.6)
18 Months	83.3 (72.4, 90.1)	36.7 (25.6, 47.8)	46.6 (32.4, 60.8)
24 Months	78.8 (67.3, 86.7)	15.5 (8.1, 25.2)	63.3 (50.4, 76.2)
30 Months	77.3 (65.7, 85.5)	15.5 (8.1, 25.2)	61.8 (48.7, 74.9)

CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; del11q: deletion of the long arm of chromosome 11; del17p: deletion of the short arm of chromosome 17; Ibr+Ob: ibrutinib+obinutuzumab; IGHV: immunoglobulin heavy chain variable region; IRC: Independent Review Committee; NE: not estimable; PFS: progression-free survival
N: number of subjects in the specified population. n: number of subjects with PFS events. %=100*n/N. + Indicates censored observation.
[a] Estimated by Kaplan-Meier method.
[b] P value is from unstratified log-rank test.
[c] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.
High-risk population defined as randomized subjects with del17p/TP53 mutation or del11q or IGHV unmutated at baseline per central laboratory results.

Figure 8 Kaplan-Meier Curves for Progression-free Survival Based on IRC Assessment (del17p/TP53 mutation/del11q/unmutated IGHV High-risk Population



Rate of Sustained Hemoglobin Improvement

Table 16 Proportion of Sustained Hemoglobin Improvement (Intent-to-Treat Population)

	Ibr+Ob	Clb+Ob	Chi-Square Test P-value
ITT subjects - N	113	116	
Achieved sustained improvement – n (%)	45 (39.8)	51 (44.0)	0.5253
ITT subjects with anemia at baseline[a] – N	51	50	
Achieved sustained improvement – n (%)	34 (66.7)	31 (62.0)	0.6244

Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; ITT: intent-to-treat
N: Number of subjects in the specified population, n: number of subjects with sustained hemoglobin improvement before initiation of subsequent antineoplastic treatment.
Sustained hemoglobin improvement is defined as hemoglobin increase ≥20 g/L over baseline continuously for ≥56 days without blood transfusion or growth factors.
[a] Hemoglobin ≤110 g/L at baseline.

Rate of Minimal Residual Disease-Negative Response

Subjects were evaluated for MRD assessment per central laboratory in both the bone marrow and peripheral blood every 4 cycles after Cycle 9 until Cycle 33, then every 6 cycles starting at Cycle 39.

Treatment with Ibr+Ob resulted in a MRD negativity rate in the bone marrow of 20.4% vs. 17.2% in the Clb+Ob arm (nominal pvalue = 0.5465).

The MRD negativity rate in the peripheral blood or bone marrow was 34.5% for the Ibr+Ob arm and 25.0% for the Clb+Ob arm (nominal pvalue = 0.1152).

Overall Response Rate

Table 17 Overall Response Rate Based on IRC Assessment (Intent-to-Treat Population)

	Ibr+Ob N=113 n (%)	Clb+Ob N=116 n (%)	Ibr+Ob vs. Clb+Ob P-value [a]
Overall Response Rate (CR, CRi, nPR, or PR)	100 (88.5)	85 (73.3)	
Rate ratio (95% CI)[a]			1.208 (1.062, 1.373)
P-value[a]			0.0035
Complete Response Rate (CR, CRi)	22 (19.5)	9 (7.8)	
Rate ratio (95% CI)[a]			2.509 (1.208, 5.212)
P-value[a]			0.0096
Best overall response			
Complete response (CR)	21 (18.6)	9 (7.8)	
CR with incomplete blood count recovery (CRi)	1 (0.9)	0	
Nodular partial response (nPR)+partial response (PR)	78 (69.0)	76 (65.5)	
Stable disease (SD)	7 (6.2)	24 (20.7)	
Non-progressive disease	3 (2.7)	4 (3.4)	
Progressive disease	0	0	
Unknown/Missing	3 (2.7)	3 (2.6)	

CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; IRC: Independent Review Committee; ORR: overall response rate; PRL: partial response with lymphocytosis
N: number of subjects in the specified population. n: number of subjects in each category. %: 100*n/N.
CR, CRi, nPR, and PR require confirmation with 2 consecutive assessments that are at least 56 days apart and no use of blood supportive product and/or growth factor during this period.
[a] Rate ratio and p-values for ORR are based on chi-square test.

Time to normalization of absolute lymphocyte count (ALC) was assessed as an indicator of response:

107 subjects in the Ibr+Ob arm and 105 subjects in the Clb+Ob arm had a baseline ALC of ≥ 4 x 109/L.

For the Ibr+Ob arm, the percentage of subjects whose ALC had normalized to < 4 x 109/L was 98.1%, and the median time to normalization was 8.3 weeks.

For the Clb+Ob arm, the percentage of subjects whose ALC had normalized to < 4 x 109/L was 93.3%, and the median time to normalization was 1.4 weeks.

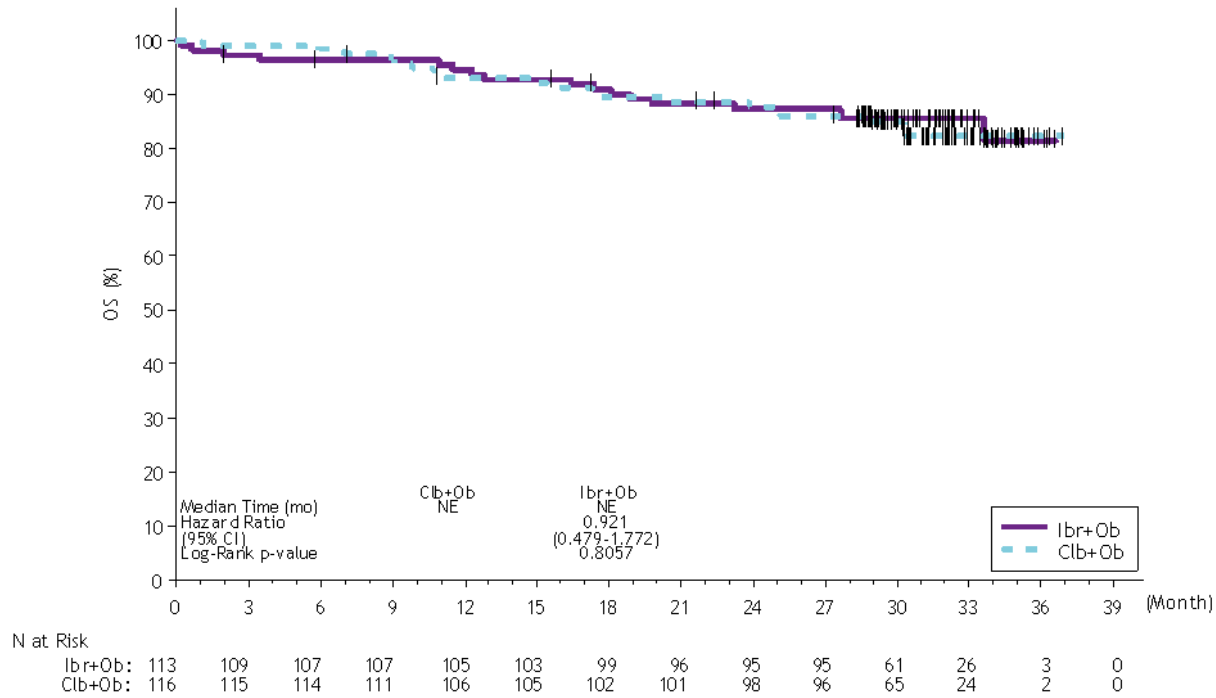
Overall survival

Table 18 Overall Survival (Intent-toTreat Population)

Overall Survival	Ibr+Ob N=113	Clb+Ob N=116	Comparison/ Difference Ibr+Ob vs. Clb+Ob
Deaths - n (%)	17 (15.0)	19 (16.4)	
Censored - n (%)	96 (85.0)	97 (83.6)	
Overall survival (months)			
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.16, 36.60+	1.08, 36.90+	
P value[b]			0.8057
Hazard ratio (95% CI)[c]			0.921 (0.479, 1.772)
Landmark Estimates - % (95% CI)[a]			
6 Months	96.5 (90.8, 98.7)	98.3 (93.3, 99.6)	-1.8 (-6.0, 2.3)
12 Months	94.6 (88.5, 97.6)	93.1 (86.6, 96.5)	1.6 (-4.6, 7.8)
18 Months	91.0 (83.9, 95.1)	89.6 (82.3, 93.9)	1.5 (-6.3, 9.2)
24 Months	87.3 (79.6, 92.3)	87.8 (80.2, 92.6)	-0.4 (-9.1, 8.2)
30 Months	85.5 (77.4, 90.9)	84.9 (76.8, 90.4)	0.6 (-8.7, 9.9)

CI: confidence interval; Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; NE: not estimable
N: number of subjects in the specified population. + Indicates censored observation.
[a] Estimated by Kaplan-Meier method.
[b] P-value is from unstratified log-rank test.
[c] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.

Figure 9: Kaplan-Meier curves for OS (ITT)



Updated analyses (28.02.2019 cut-off)

Updated analyses for overall survival [OS; ITT population]) are provided based on a 28 February 2019 data extraction date. This is not a formal database lock, but rather a data snapshot, and the results

should be interpreted accordingly. At an event rate of 18% in both study arms, the median OS was not reached for either treatment arm; the OS for both arms was similar (HR = 0.969, 95% CI: 0.525, 1.789). The Kaplan-Meier point estimate for the OS rate at 36 months was 82.7% for the Ibr+Ob arm and 82.3% for the Clb+Ob arm.

Rate of Infusion-related Reactions

The rate of serious or ≥ Grade 3 IRRs identified by MedDRA PT was 2.7% for the Ibr+Ob arm and 8.6% for the Clb+Ob arm (nominal pvalue= 0.0835).

The rate of IRRs of any grade identified by MedDRA PT was 24.8% for the Ibr+Ob arm and 57.8% for the Clb+Ob arm (nominal p-value< 0.0001).

Rate of Sustained Platelet Improvement

Table 19 Proportion of Sustained Platelet Improvement (Intent-toTreat Population)

	Ibr+Ob	Clb+Ob	Chi-Square Test P-value
ITT population – N	113	116	
Achieved sustained improvement – n(%)	33 (29.2)	16 (13.8)	0.0045
ITT subjects with thrombocytopenia at baseline[a] - N	28	22	
Achieved sustained improvement – n(%)	16 (57.1)	10 (45.5)	0.4115

Clb+Ob: chlorambucil+obinutuzumab; Ibr+Ob: ibrutinib+obinutuzumab; ITT: intent-to-treat
N: Number of subjects in the specified population. n: number of subjects with sustained platelet improvement before initiation of subsequent antineoplastic treatment.
Sustained platelet improvement is defined as platelet counts increase ≥50% over baseline continuously for ≥56 days without blood transfusion or growth factors.
[a] Platelet counts ≤ $100x10^9$/L at baseline.

Exploratory/other analyses

Time to Next Treatment

The percentages of subjects who started their next treatment were 3.5% for the Ibr+Ob arm and 44.0% for the Clb+Ob arm.

There was a 93.7% reduction in the risk of the requirement for next treatment observed for the Ibr+Ob arm relative to the Clb+Ob arm (HR = 0.063, 95% CI: 0.023, 0.175; p < 0.0001).

The median time to next treatment was not reached for either treatment arm. At the 30-month landmark time point, an estimated 96.2% of subjects in the Ibr+Ob arm and 51.3% for the Clb+Ob arm had not received subsequent treatment.

Medical Resource Utilization

Medical resource utilization was evaluated during the first 9 months of study treatment.

In the Ibr+Ob arm, 44 subjects were hospitalized, and the median number of hospitalizations was 1.0 (with a median of 6.5 days of hospitalization). Seventeen subjects had emergency room visits, and the median number of emergency room visits was 1.0. During the first 9 months, 14 subjects (12.4%) received blood supportive products, while 24 subjects (21.2%) received growth factors.

In the Clb+Ob arm, 35 subjects were hospitalized, and the median number of hospitalizations was 1.0 (with a median of 7.0 days of hospitalization). Fifteen subjects had emergency room visits, and the

median number of emergency room visits was 1.0. During the first 9 months, 24 subjects (20.7%) received blood supportive products, while 47 subjects (40.5%) received growth factors.

Lymphocytosis

Lymphocytosis was defined as an elevation in ALC of ≥ 50% compared to baseline and to ≥ 5,000/μL at a post-baseline assessment. For subjects with lymphocytosis, resolution of lymphocytosis was defined as a decrease of ALC value to the baseline level or lower, or an ALC value that was below 5,000/μL, whichever occurred first.

Treatment-emergent lymphocytosis occurred in 8 subjects (7.2%) in the Ibr+Ob arm and 1 subject (0.9%) in the Clb+Ob arm. For subjects who developed lymphocytosis, the median time to lymphocytosis was 1.1 weeks (range: 1.0 to 2.1 weeks) for the Ibr+Ob arm and 2.1 weeks for the 1 subject in the Clb+Ob arm. The median time to resolution was 3.1 weeks (95% CI: 1.3 to 7.0 weeks) in the Ibr+Ob arm and 6.3 weeks for the 1 subject in the Clb+Ob arm. These events resolved in all subjects in both treatment arms.

Sensitivity analyses

Sensitivity analyses have been performed using both unstratified and stratified methods.

Table 20: Progression Free Survival (PFS) Based on IRC Assessment with Treatment Discontinuation without PD/Death as an Event (Unstratified); ITT Analysis Set (Study PCYC-1130-CA)

	Ibr+Ob	Clb+Ob	Comparison Ibr+Ob vs. Clb+Ob
Analysis set: ITT	113	116	
Subjects randomized, n (%)	113 (100.0)	116 (100.0)	
PFS Events	36 (31.9%)	79 (68.1%)	
Disease Progression	11 (9.7%)	64 (55.2%)	
Death	13 (11.5%)	10 (8.6%)	
Disc. treatment without PD or Death	12 (10.6%)	5 (4.3%)	
Censored	77 (68.1%)	37 (31.9%)	
25th percentile (months) (95% CI)	21.4 (14.8, NE)	11.2 (10.8, 14.2)	
Median (months) (95% CI)	NE (33.6, NE)	17.8 (14.8, 22.1)	
75th percentile (months) (95% CI)	NE (NE, NE)	NE (23.8, NE)	
Range (months)	(0.16, 35.32+)	(0.03+, 35.22+)	
Hazard ratio (95% CI)[a]			0.327 (0.219, 0.486)
p-value[b]			<0.0001
Progression Free Survival			
12-month PFS rate (95% CI)	0.88 (0.80, 0.92)	0.71 (0.62, 0.78)	
18-month PFS rate (95% CI)	0.80 (0.71, 0.86)	0.50 (0.40, 0.58)	
24-month PFS rate (95% CI)	0.72 (0.62, 0.79)	0.32 (0.24, 0.41)	
30-month PFS rate (95% CI)	0.69 (0.60, 0.77)	0.29 (0.21, 0.38)	

CI= confidence interval. + Indicates censored observation. NE= not estimable.
[a] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate
[b] P value is from unstratified log-rank test

Table 21: Progression Free Survival (PFS) Based on IRC Assessment with Treatment Discontinuation without PD/Death as an Event (Stratified); ITT Analysis Set (Study PCYC-1130-CA)

	Ibr+Ob	Clb+Ob	Comparison Ibr+Ob vs. Clb+Ob
Analysis set: ITT	113	116	
Subjects randomized, n (%)	113 (100.0)	116 (100.0)	
PFS Events	36 (31.9%)	79 (68.1%)	
Disease Progression	11 (9.7%)	64 (55.2%)	
Death	13 (11.5%)	10 (8.6%)	
Disc. treatment without PD or Death	12 (10.6%)	5 (4.3%)	
Censored	77 (68.1%)	37 (31.9%)	
25th percentile (months) (95% CI)	21.4 (14.8, NE)	11.2 (10.8, 14.2)	
Median (months) (95% CI)	NE (33.6, NE)	17.8 (14.8, 22.1)	
75th percentile (months) (95% CI)	NE (NE, NE)	NE (23.8, NE)	
Range (months)	(0.16, 35.32+)	(0.03+, 35.22+)	
Hazard ratio (95% CI)[a]			0.316 (0.211, 0.473)
p-value[b]			<0.0001
Progression Free Survival			
12-month PFS rate (95% CI)	0.88 (0.80, 0.92)	0.71 (0.62, 0.78)	
18-month PFS rate (95% CI)	0.80 (0.71, 0.86)	0.50 (0.40, 0.58)	
24-month PFS rate (95% CI)	0.72 (0.62, 0.79)	0.32 (0.24, 0.41)	
30-month PFS rate (95% CI)	0.69 (0.60, 0.77)	0.29 (0.21, 0.38)	

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 ECOG performance status ('0-1' vs '2') and cytogenic status as reported in IWRS.

Summary of main study

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

Table 22: Summary of Efficacy for trial 1130

	Previously Untreated CLL	
	Study 1130	
	ibrutinib+Ob N=113	**Clb+Ob N=116**
Median Follow-up	31.3 months	
Progression-free Survival (months) by IRC		
Median	NE	19.0
Min, Max	0.16, 35.32+	0.03+, 35.22+
p-value	<0.0001	
Hazard Ratio (95% CI)	0.231 (0.145, 0.367)	
Progression-free survival (months) in high-risk subpopulation (del17p/mutated TP53/del11q) by IRC	N=30	N=45
Median	NE	14.7
Min, Max	1.94, 35.12+	0.30+, 31.08+
p-value	< 0.0001	

	Previously Untreated CLL	
	Study 1130	
	ibrutinib+Ob N=113	Clb+Ob N=116
Hazard Ratio (95% CI)	0.119 (0.046, 0.307)	
Progression-free survival (months) in high-risk population (del17p/mutated TP53/del11q/unmutated IGHV) by IRC	N=73	N=75
Median	NE	14.7
Min, Max	0.16, 35.32+	0.30+, 35.09+
p-value	<0.0001	
Hazard Ratio (95% CI)	0.154 (0.087, 0.270)	
Overall Response Rate (CR, CRi, nPR, or PR) by IRC	88.5%	73.3%
p-value	0.0035	
CR rate	18.6%	7.8%
CRi rate	0.9%	0%
Overall Survival (months)[a]		
Median	NE	NE
Min, Max	0.16, 36.60+	1.08, 36.90+
p-value	0.8057	
Hazard Ratio (95% CI)	0.921 (0.479, 1.772)	

CI: confidence interval; Clb: chlorambucil; Clb+Ob: chlorambucil plus obinutuzumab; CR: complete response; CRi: complete response with incomplete blood count recovery; Ibr: ibrutinib; ibrutinib+Ob: ibrutinib plus obinutuzumab; IRC independent review committee; NE: not estimable; nPR: nodular partial response; PR: partial response
+ Indicates censored observation.
[a] For subjects who were not known to have died at study closure, the overall survival was right-censored on the date last known alive at study exit or survival follow-up regardless initiation of subsequent antineoplasm therapy.

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

Cross-study comparisons with study 1130 or longer-term efficacy outcomes from ongoing studies of ibrutinib in CLL/SLL were performed

Table 23: Baseline risk factors

Appendix 1: Baseline Biomarker Risk Factors (Studies 1130, 1115, 1112, and CLL3001; Intent-to-Treat Population)

Subgroups	Study 1130 n (%)	Study 1115 [1] n (%)	Study 1112 n (%)	CLL3001 [1] n (%)
All Subjects (N)	229	269	391	578
High Risk (del17p/TP53 mut/del11q/unmut IGHV)				
Yes	148 (64.6%)	143 (53.2%)	322 (82.4%)	439 (76.0%)
No	81 (35.4%)	126 (46.8%)	69 (17.6%)	139 (24.0%)
del17p/TP53 mut/del11q				
Yes	75 (32.8%)	65 (24.2%)	275 (70.3%)	154 (26.6%)
No	154 (67.2%)	204 (75.8%)	116 (29.7%)	424 (73.4%)
del17p/TP53 mut				
Yes	41 (17.9%)	16 (5.9%)	196 (50.1%)	2 (0.3%)
No	188 (82.1%)	253 (94.1%)	195 (49.9%)	576 (99.7%)
FISH				
del17p	32 (14.0%)	1 (0.4%)	127 (32.5%)	2 (0.3%)
del11q	35 (15.3%)	53 (19.7%)	95 (24.3%)	152 (26.3%)
Others	162 (70.7%)	215 (79.9%)	169 (43.2%)	424 (73.4%)
IGHV				
Unmutated	123 (53.7%)	118 (43.9%)	182 (46.5%)	418 (72.3%)
Mutated	91 (39.7%)	82 (30.5%)	84 (21.5%)	101 (17.5%)

Percentage is calculated as n/N*100.
TP53 mut = TP53 mutation. Unmut IGHV = unmutated immunoglobulin heavy-chain variable region. FISH = fluorescence in situ hybridization and classified as del17p, del11q (excluding del17p) and others (neither del17p nor del11q).
[1] Studies 1115 and CLL3001 excluded subjects with del17p. However, in Study 1115, 1 subject was enrolled with del17p per local lab (TP53 mutation status unknown) and was randomized to the control arm. In Study CLL3001, 2 subjects were enrolled with del17p in the Ibr + BR arm. TP53 mutation status was not evaluated in Study CLL3001.
Note: The 'No' or 'Others' category for the combined subgroup (del17p/TP53 mut/del11q/unmut IGHV), (del17p/TP53 mut/del11q), del17p/TP53 mut or FISH include all randomized subjects who were not identified any of the specified high risk component factor.

Comparison with study 1115

The Applicant has also provided a comparison of efficacy data between study 1115 (ibrutinib monotherapy *vs* chlorambucil monotherapy, n=269, data cutoff of 28 May 2015) and study 1130, both recruiting previously untreated patients with CLL/SLL. The median subject age was 71.0 years in Study 1130 and 73.0 years in Study 1115, with the majority of subjects being white (96.1% and 91.1%, respectively) and male (range: 63.8% and 62.8%, respectively). Greater than 90% of subjects across both studies had CLL and an ECOG performance status score of 0 or 1. Baseline Rai Stage of III or IV was reported for 52.0% of subjects in Study 1130 and 45.4% of subjects in Study 1115.

Study 1115 excluded subjects with a chromosome 17p deletion; whereas 14.0% of subjects in Study 1130 had a del17p at baseline. In Study 1115, data for IGHV mutational status and TP53 mutational testing were not included in the original analysis and clinical study report. Testing results for IGHV mutational status and TP53 mutations were subsequently updated. In Study 1115, 53.2% of subjects had high-risk genomic features (mutated TP53/del11q/unmutated IGHV). In Study 1130, 64.6% of subjects had high-risk genomic features (ie, del17p/mutated TP53/del11q/unmutated IGHV)".

Table 24: Comparison of efficacy outcomes 1130 vs 1115

Table 5: Efficacy Results – Studies PCYC-1130-CA and PCYC-1115-CA				
	PCYC-1130-CA		PCYC-1115-CA	
	Ibr+Ob	Clb+Ob	Ibr	Clb
Analysis set: ITT	113	116	136	133
Events	24 (21.2%)	74 (63.8%)	15 (11.0%)	64 (48.1%)
Disease Progression	11 (9.7%)	64 (55.2%)	12 (8.8%)	57 (42.9%)
Death	13 (11.5%)	10 (8.6%)	3 (2.2%)	7 (5.3%)
Censored at cutoff	89 (78.8%)	42 (36.2%)	121 (89.0%)	69 (51.9%)
PFS (Months) per IRC				
Median (95% CI)	NE (33.6, NE)	19.0 (15.1, 22.1)	NE (NE, NE)	18.9 (14.1, 22.0)
Min, Max	(0.16, 35.32+)	(0.03+, 35.22+)	(0.03+, 24.71+)	(0.03+, 23.98+)
P-value		<0.0001		<0.0001
Hazard Ratio (95% CI)		0.231 (0.145, 0.367)		0.161 (0.091, 0.283)
Kaplan-Meier point estimate for PFS rate at				
6-months	0.965 (0.908, 0.987)	0.973 (0.919, 0.991)	0.978 (0.932, 0.993)	0.767 (0.684, 0.831)
12-months	0.919 (0.849, 0.957)	0.744 (0.652, 0.816)	0.932 (0.873, 0.964)	0.617 (0.526, 0.696)
18-months	0.863 (0.782, 0.915)	0.523 (0.426, 0.612)	0.899 (0.832, 0.940)	0.515 (0.419, 0.603)
24-months	0.795 (0.705, 0.860)	0.343 (0.255, 0.433)	0.839 (0.711, 0.914)	NE (NE, NE)
30-months	0.785 (0.695, 0.852)	0.311 (0.225, 0.400)	NE (NE, NE)	NE (NE, NE)
Overall Survival (Months)				
Deaths, n (%)	17 (15.0%)	19 (16.4%)	3 (2.2%)	17 (12.8%)
Censored, n (%)	96 (85.0%)	97 (83.6%)	133 (97.8%)	116 (87.2%)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	(0.16, 36.60+)	(1.08, 36.90+)	(0.10+, 24.84+)	(0.10+, 24.25+)
P-value		0.8057		0.0010
Hazard Ratio (95% CI)		0.921 (0.479, 1.772)		0.163 (0.048, 0.558)
Kaplan-Meier point estimate for OS rate at				
6-months	0.965 (0.908, 0.987)	0.983 (0.933, 0.996)	0.978 (0.933, 0.993)	0.962 (0.910, 0.984)
12-months	0.946 (0.885, 0.976)	0.931 (0.866, 0.965)	0.978 (0.933, 0.993)	0.915 (0.852, 0.952)
18-months	0.910 (0.839, 0.951)	0.896 (0.823, 0.939)	0.978 (0.933, 0.993)	0.872 (0.799, 0.920)
24-months	0.873 (0.796, 0.923)	0.878 (0.802, 0.926)	0.978 (0.933, 0.993)	0.853 (0.769, 0.909)
30-months	0.855 (0.774, 0.909)	0.849 (0.768, 0.904)	NE (NE, NE)	NE (NE, NE)
36-months	0.814 (0.688, 0.893)	0.822 (0.733, 0.884)	NE (NE, NE)	NE (NE, NE)
ORR (CR, CRi, nPR, PR), per IRC	100 (88.5%)	85 (73.3%)	112 (82.4%)	47 (35.3%)
Relative risk (95% CI)		1.21 (1.06, 1.37)		2.33 (1.83, 2.97)
p-value		0.0035		< 0.0001
CR (CR, CRi)	22 (19.5%)	9 (7.8%)	6 (4.4%)	2 (1.5%)
Relative risk (95% CI)		2.51 (1.21, 5.21)		2.93 (0.60, 14.28)
p-value		0.0098		0.1612
Best Response, per IRC				
Complete Response (CR)	21 (18.6%)	9 (7.8%)	5 (3.7%)	2 (1.5%)
CR with Incomplete Marrow Recovery (CRi)	1 (0.9%)	0	1 (0.7%)	0
Nodular Partial Response (nPR)	5 (4.4%)	0	1 (0.7%)	0
Partial Response (PR)	73 (64.6%)	76 (65.5%)	105 (77.2%)	45 (33.8%)
PR with Lymphocytosis (PRL)	0	0	5 (3.7%)	0
Stable Disease (SD)	7 (6.2%)	24 (20.7%)	13 (9.6%)	61 (45.9%)
Progressive Disease (PD)	0	0	0	17 (12.8%)
No Evidence of Disease (NED)	0	0	0	1 (0.8%)
Not Evaluable (NE)	0	0	1 (0.7%)	0
Non-PD	3 (2.7%)	4 (3.4%)	0	0
Unknown/Missing	3 (2.7%)	3 (2.6%)	5 (3.7%)	7 (5.3%)

Long-term efficacy: Studies 1112 and 1115/1116

Study 1112

Study 1112 is an ongoing, Phase 3, randomized, multicenter, open-label, comparator-controlled study in subjects with previously treated CLL/SLL. The study compared the efficacy and safety of orally administered ibrutinib 420 mg/day with that of ofatumumab administered IV at an initial dose of 300 mg followed by 11 doses of 2,000 mg over a 24-week period. Randomization of subjects into both treatment arms was 1:1, and subjects received ibrutinib until progressive disease or unacceptable toxicity was observed, whichever occurred first. Baseline disease characteristics indicate that high-risk genomic features were consistent across the treatment groups (ibrutinib vs ofatumumab). Genomic analyses of high-risk features indicate that 32.5% of subjects had del17p, 24.3% had del11q, and 46.5% had unmutated IGHV; subjects with these high-risk genomic features comprised 82.4% of the study population.

The updated efficacy results are based on a median time on study of 56 months in Study 1112; 133 of the 196 subjects (67.9%) originally randomized to the ofatumumab treatment arm crossed over to ibrutinib treatment, with 63 (47.4%) of those 133 subjects still on ibrutinib treatment.

Table 25: PFS (ITT) in study 1112

	Long-term Results[d] by Investigator	
	Ibrutinib N=195	Ofatumumab N=196
Median follow-up time[a]	55.9 months	
Progression-free survival		
Events, n (%)	104 (53.3)	179 (91.3)
Disease progression	77	160
Death	27	19
Median (95% CI), months[b]	44.1 (38.54, 56.87)	8.1 (7.79, 8.25)
HR (95% CI)[c]	0.141 (0.106, 0.187)	
P value[c]	< 0.0001	

CI: confidence interval; HR: hazard ratio; IWRS: interactive web response system
Subjects are not censored for initiation of subsequent antineoplastic treatment prior to progressive disease or death.

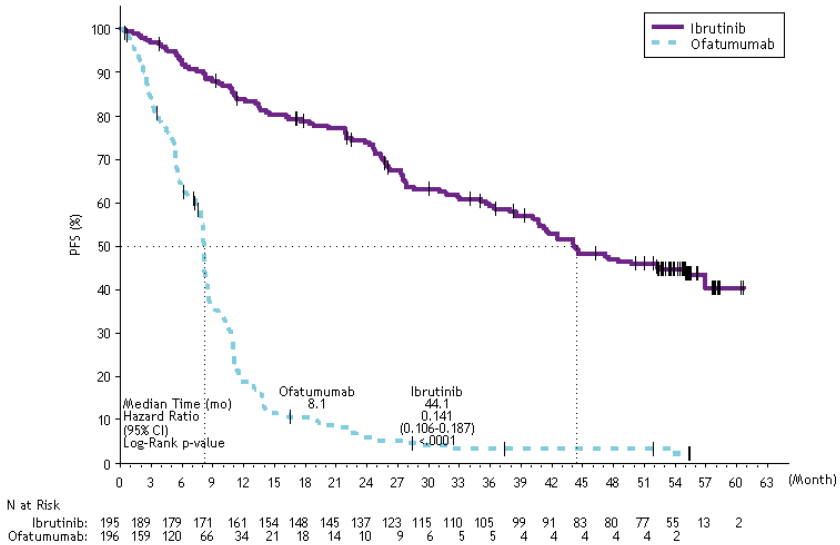
[a] Time on study is based on the follow-up time of overall survival using reverse Kaplan-Meier estimates of overall survival.

[b] Based on Kaplan-Meier estimates.

[c] Hazard ratio is based on Cox regression model (with treatment as the only covariate) stratified by the 2 randomization stratification factors reported in the IWRS at the time of randomization and is relative to ofatumumab with <1 favoring ibrutinib. P value is from stratified log-rank test.

[d] A total of 133 subjects originally randomized to ofatumumab subsequently received ibrutinib as crossover study therapy. All but 4 subjects had documented disease progression prior to crossover.

Figure 10 Kaplan-Meier Curves for Progression-Free Survival per Investigator Assessment with a Median Follow-up of 56 Months ((Intent-to Treat Population, Study 1112)



CI=confidence interval; PFS=progression-free survival.
Hazard ratio and 95% CI estimated using Cox regression model (with treatment as the only covariate) stratified by the 2 randomization stratification factors

ORR: The investigator-assessed ORR (PR or better) was 87.2% for the ibrutinib arm vs. 22.4% for the ofatumumab arm; p<0.0001.

OS: The median OS was not reached in either treatment arm

Table 26: Kaplan-Meier Overall Survival Estimates at Landmark Time Points (Intent-to Treat Population, Study 1112)

	Overall Survival Rate	
Time Point	Ibrutinib N=195	Ofatumumab N=196
12 months	90.2%	79.3%
24 months	83.4%	71.7%
36 months	73.6%	64.9%
48 months	63.4%	59.7%
54 months	62.2%	55.5%
60 months	62.2%	54.8%

Subjects (n=127) with del 17p:

The median investigator-assessed PFS was 40.6 months in the ibrutinib arm vs. 6.2 months in the ofatumumab arm (HR=0.124, 95% CI: 0.074, 0.208);

The investigator-assessed ORR was 88.9% for the ibrutinib arm vs. 18.8% for the ofatumumab arm.

Study 1115/1116

Study 1115 compared the efficacy and safety of ibrutinib with Clb, both administered as single oral agents, in subjects with previously untreated CLL/SLL. Chlorambucil was administered on Days 1 and 15 of each 28-day cycle for a maximum of 12 cycles. Subjects in Study 1115 were transferred to extension Study 1116 after IRC confirmation of disease progression or at study closure, whichever occurred first. Study 1116 was prospectively designed in conjunction with Study 1115 to ensure retention of subjects and allow for collection of long-term safety and efficacy data in all subjects randomized in Study 1115 for at least 5 years following the first subject enrolled in this parent study. Study 1116 was also designed to provide continued treatment for subjects in the ibrutinib arm who had not progressed, and to allow second-line therapy after progressive disease to study subjects. Baseline disease characteristics indicate that high-risk genomic features were consistent across the treatment groups (ibrutinib vs Clb). Genomic analyses indicated that 5.9% had a del17p/TP53 mutation, 20.1% of subjects had a del11q mutation, and 43.9% had unmutated IGHV; subjects with these high-risk genomic features comprised 53.2% of the study population.

In Study 1116, disease progression and response were assessed by the investigator; there was no IRC assessment. After disease progression, second-line therapy, when clinically indicated, could include ibrutinib for subjects randomized to the Clb arm. All subjects were followed for progression and survival.

The updated efficacy results provided in this report are based on a median time on study of 48 months in Studies 1115/1116. One hundred thirty-six subjects received ibrutinib and 133 subjects received Clb. At the time of the long-term efficacy update, 73 (54.9%) of the 133 subjects originally randomized to the Clb treatment arm crossed over to ibrutinib treatment, with 44 (60.3%) of those 73 crossover subjects still on ibrutinib treatment.

Table 27: Progression-free Survival (Intent-to-Treat Population, Studies 1115/1116)

	Long-term Results by Investigator	
	Ibrutinib N=136	Chlorambucil N=133
Median follow-up time[a]	48.1 months	
Progression-free survival		
Events, n (%)	31 (22.8)	101 (75.9)
Disease progression	18	92
Death	13	9
Median (95% CI), months[b]	NE ---	15.0 (10.22, 19.35)
HR (95% CI)[c]	0.137 (0.090, 0.210)	
P value[c]	< 0.0001	

CI=confidence interval; HR=hazard ratio; NE=not evaluable
Subjects are not censored for initiation of subsequent antineoplastic treatment prior to progressive disease or death.
[a] Time on study is based on the follow-up time of overall survival using reverse Kaplan-Meier estimates of overall survival.
[b] Based on Kaplan-Meier estimates.
[c] Hazard ratio is estimated using stratified Cox regression model with treatment as the only covariate. P value is from stratified log-rank test.

The HR for the subjects with the high-risk features (mutated TP53/del11q/unmutated IGHV) was 0.068; 95% CI: 0.037, 0.127, consistent with the intent-to-treat population at a median follow-up of 48 months.

ORR: The investigator-assessed ORR (PR or better) was 91.2% in the ibrutinib arm vs. 36.8% in the Clb arm. Compared to the primary analysis, the ORR increased with further ibrutinib treatment as subjects with stable disease or PR with lymphocytosis in Study 1115 achieved PR or better with further follow-up. Notably, improvement in investigator-assessed CR rates continued to increase with ongoing ibrutinib treatment.

Twenty-six subjects were confirmed as complete responders by the Sponsor based on IWCLL response criteria (Hallek 2008). Sponsor-confirmed CRs were observed in 22 subjects (16.2%) in the ibrutinib arm and 4 subjects (3.0%) in the Clb arm.

OS: The median OS was not reached in either arm.

Table 28: Kaplan-Meier Overall Survival Estimates at Landmark Time Points (Intent-to-Treat Population, Studies 1115/1116)

	Overall Survival Rate	
Time Point	Ibrutinib N=136	Chlorambucil N=133
12 months	97.8%	91.5%
24 months	94.6%	84.3%
36 months	88.4%	80.0%
48 months	85.5%	75.6%

Clinical studies in special populations

See subgroup analyses above.

Supportive study(ies)

See section "Analyses across studies"

2.4.2. Discussion on clinical efficacy

This application is based on one pivotal study, 1130: "A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma".

Design and conduct of clinical studies

The study enrolled patients who were 65 years of age or older or <65 years of age with coexisting medical conditions, reduced renal function as measured by creatinine clearance <70 mL/min, or presence of del17p/TP53 mutation. Notably, the study only enrolled patients ≥65 years, or younger with comorbidities or 17p del/TP53 mutation, with previously untreated measurable nodal CLL/SLL requiring treatment. Patients were randomized 1:1 to receive either IMBRUVICA 420 mg daily until disease progression or unacceptable toxicity or chlorambucil at a dose of 0.5 mg/kg on Days 1 and 15 of each 28-day cycle for 6 cycles. In both arms, patients received 1000 mg of obinutuzumab on Days 1, 8 and 15 of the first cycle, followed by treatment on the first day of 5 subsequent cycles (total of 6 cycles, 28 days each). The first dose of obinutuzumab was divided between day 1 (100 mg) and day 2 (900 mg). Standard dose and regimen were used for all study drugs. The control arm corresponds to the regimen used in the pivotal study supporting the approval for "Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy". In that study, similar to study 1130, subjects had to present a comorbidity score (CIRS) of greater than 6 and/or reduced renal function as measured by CrCl <70 mL/min, but age was not considered for inclusion. Subjects on the control arm were eligible to receive ibrutinib monotherapy as next-line treatment.

The amendments, changes in planned analyses and protocol violations are not considered likely to impact on the interpretation of the study results. Based on external information in terms of updated IWCLL guidelines during the study, emphasizing the importance of IGHV status, a high-risk population including this marker was defined. Final central FISH results, prior to database lock, revealed an imbalance for del 17p/del 11q between the study arms, with 10% higher prevalence in the control arm (the MAH considers that this numerical imbalance between treatment arms may have been due to multifactorial reasons (eg, hierarchical stratification input and multiple genomic factors)). This was addressed by using the unstratified analysis for the primary analysis of the primary endpoint and all secondary endpoints; the high-risk population, including IGHV status, was balanced between study arms. The originally planned stratified analysis for the primary endpoint was kept as a sensitivity analysis. The chosen analyses are generally considered acceptable. The rationale for using a non-stratified log-rank test for the primary outcome is understood with reference to new guidance on IGHV status during study conduct – without this marker the high-risk population could be unbalanced.

The control regimen in high-risk disease, which corresponds to the regimen used in the pivotal study supporting the approval for "Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy"is deemed appropriate. In that study, similar to study 1130, subjects had to present a comorbidity score (CIRS) of greater than 6 and/or reduced renal function as measured by CrCl <70 mL/min, but age was not considered for inclusion. In study 1130 also fit subjects with high-risk disease, including del 17p, were enrolled, which would today be

considered obsolete. However, as the study was planned before the first approval of B cell receptor inhibitors, and considering the known inferior results obtained with FCR in this group, the control regimen must be deemed acceptable also for subjects with high-risk disease.

The prospected median PFS for the control arm corresponds to the observed outcome in the obinutuzumab+chlorambucil arm in the BO21004/CLL11 registration study. No stratification for IGHV status was performed. Outcome per IGHV status was a predefined subgroup analysis. The results of the unstratified tests are presented as the primary results. The stratified analysis results are presented as a sensitivity analysis. The results are very similar. It is preferred that the statistical analysis model reflects the randomisation procedure however in this study were an imbalance occurred it is accepted to use the unstratified analysis as primary. Statistical methods and the method for controlling type I error rate are otherwise considered acceptable.

The design of the pivotal study, ibr+obi *vs* chl+obi, does not allow isolation of the contribution of each of the drug components to the effect. Specifically, it is not known to what extent obinutuzumab adds to the efficacy of ibrutinib. Indeed, in a recently published study, the combination of ibrutinib with another anti-CD20 antibody, rituximab, was in terms of PFS not superior to ibrutinib monotherapy in subjects ≥65 years with previously untreated CLL (*Woyach et al, NEJM, 2018: Dec 1*). However, as ibrutinib could be viewed as a substitution of chlorambucil in the approved combination with obinutuzumab, the strategy is considered acceptable from a regulatory perspective. The MAH is encouraged to further investigate the efficacy of ibrutinib + obinutuzumab *vs* ibrutinib monotherapy.

Efficacy data and additional analyses

Study PCYC-1130-CA randomized 229 patients. The median age was 71 years (range, 40 to 87 years), 64% were male, and 96% were Caucasian. All patients had a baseline ECOG performance status of 0 (48%) or 1-2 (52%). At baseline, 52% had advanced clinical stage (Rai Stage III or IV), 32% of patients had bulky disease (≥5 cm), 44% with baseline anemia, 22% with baseline thrombocytopenia, 28% had a CrCL <60 mL/min, and the median Cumulative Illness Rating Score for Geriatrics (CIRS-G) was 4 (range, 0 to 12). At baseline, 65% of patients presented with CLL/SLL with high risk factors (del17p/TP53 mutation [18%], del11q [15%], or unmutated IGHV [54%]).

Progression-free survival (PFS) was assessed by IRC according to IWCLL criteria indicated a 77% statistically significant reduction in the risk of death or progression in the IMBRUVICA arm.

Given the higher proportion of discontinuation of study treatment in the experimental arm, a sensitivity analysis was requested, imputing an event at the time of discontinuation of treatment, instead of censoring, if a PFS event was not determined at a later time. Not unexpectedly, considering the longer time on treatment in the Ibr+Ob arm, the imputation of treatment discontinuation due to reasons other than progressive disease (PD) as a progressive event increases the hazard of progression. The HR between the Ibr+Ob arm and the Clb+Ob arm is increased from 0.231 (95% CI: 0.145, 0.367) in the CSR submitted to 0.327 (95% CI: 0.219, 0.486) for the unstratified analysis, and from 0.229 (95% CI: 0.144, 0.366) in the CSR submitted to 0.316 (95% CI: 0.211, 0.473) for the stratified analysis. Nevertheless, the difference between the 2 treatment arms remains statistically significant.

The treatment effect of ibrutinib was consistent across the high-risk CLL/SLL population (del 17p/TP53 mutation, del 11q, or unmutated IGHV), with a PFS HR of 0.15 [95% CI (0.09, 0.27)]. The 2-year PFS rate estimates for the high-risk CLL/SLL population were 78.8% [95% CI (67.3, 86.7)] and 15.5% [95% CI (8.1, 25.2)] in the IMBRUVICA+obinutuzumab and chlorambucil+obinutuzumab arms, respectively.

With a median follow-up time on study of 31 months, the median PFS was not reached in the IMBRUVICA+obinutuzumab arm and was 19 months in the chlorambucil+obinutuzumab arm.

The external validity of the study is not challenged in relation to the intended study population with a mean age of 71 years and 20% of subjects younger than 65 years. An overall median follow-up of 31 months, an event rate of 64% in the control arm, and consistent sensitivity analyses all support a robust estimate of the primary outcome measure (unstratified PFS according to IRC), and pre-planned subgroup analyses show internal consistency with favourable efficacy for the experimental arm in subjects with high-risk features as well as in the complementary group.

Note that OS data, as expected in first-line treatment of CLL, was immature at the data cut-off of March 2018 with an event rate of 16% in the control arm.

Long-term efficacy is supported by reported data from the 1112 and 1115/1116 studies. With a median follow-up time on study of 56 months in Study PCYC-1112-CA, an 86% reduction in the risk of death or progression by investigator assessment was observed for patients in the IMBRUVICA arm. The median investigator-assessed PFS according to IWCLL criteria was 44.1 months [95% CI (38.54, 56.87)] in the IMBRUVICA arm and 8.1 months [95% CI (7.79, 8.25)] in the ofatumumab arm, respectively; HR=0.14 [95% CI (0.11, 0.19)]. The investigator-assessed ORR in the IMBRUVICA arm was 87.2% versus 22.4% in the ofatumumab arm. At the time of long-term follow-up, 133 (67.9%) of the 196 subjects originally randomized to the ofatumumab treatment arm had crossed over to ibrutinib treatment. The Kaplan-Meier landmark estimate for OS at 60-months was 62.2% in the IMBRUVICA arm.

The outcomes of the subgroup analyses are generally consistent but HR point estimates associated with high-risk features are generally lower than for the complementary groups.

ORR, based on IRC assessment, was 88% in the experimental arm and 73% in the control arm. The corresponding figures for CR were 20% and 8%, respectively. It is noted that time to normalisation of ALC was faster in the control arm, 1.4 weeks vs 8.3 weeks in the experimental arm. With only 17 (15%) events in the experimental arm and 19 (16%) in the control arm data are immature. The early deaths noted in the experimental arm are discussed in the safety section. Overall, no trend for a worse outcome in the experimental arm is noted.

With almost a year longer follow-up, with 3 additional events in the experimental arm and 2 in the control arm, the median OS was not reached for either treatment arm; the OS for both arms was similar (HR = 0.969, 95% CI: 0.525, 1.789). OS data is still immature. A further update is expected with the final CSR. MRD negativity rates in the bone marrow were similar between study arms, around 20%.

Infusion-related reactions (i.e. obinutuzumab-related) were numerically less frequently noted in the experimental arm and were observed in 25% of patients treated with IMBRUVICA+obinutuzumab and 58% of patients treated with chlorambucil+obinutuzumab. Grade 3 or higher or serious infusion-related reactions were observed in 3% of patients treated with IMBRUVICA+obinutuzumab and 9% of patients treated with chlorambucil+obinutuzumab. Achievement of sustained platelet improvement in subjects with thrombocytopenia at baseline was roughly similar between study arms. New treatment was started for 44% and 3.5% of subjects in the control and experimental arm, respectively; HR 0.063. The median time to next treatment was not reached for either treatment arm.

The MAH applies for an indication in all patients with previously untreated CLL while the studied population is restricted to patients ≥65 years, or younger with comorbidities or 17p del/TP53 mutation. A similar extrapolation was extensively discussed in the II-16 variation, where the pivotal 1115 study investigating ibrutinib monotherapy *vs* chlorambucil monotherapy in subjects ≥65 years with previously untreated CLL ultimately lead to the approval of ibrutinib monotherapy in all previously untreated patients with CLL.

2.4.3. Conclusions on the clinical efficacy

The efficacy results are robust and support clinically relevant benefit of Imbruvica in the sought indication.

The MAH accepted a recommendation from the CHMP to provide post-approval data on PFS2 or corresponding proxy from Study PCYC-1130 (expected in 3Q 2020).

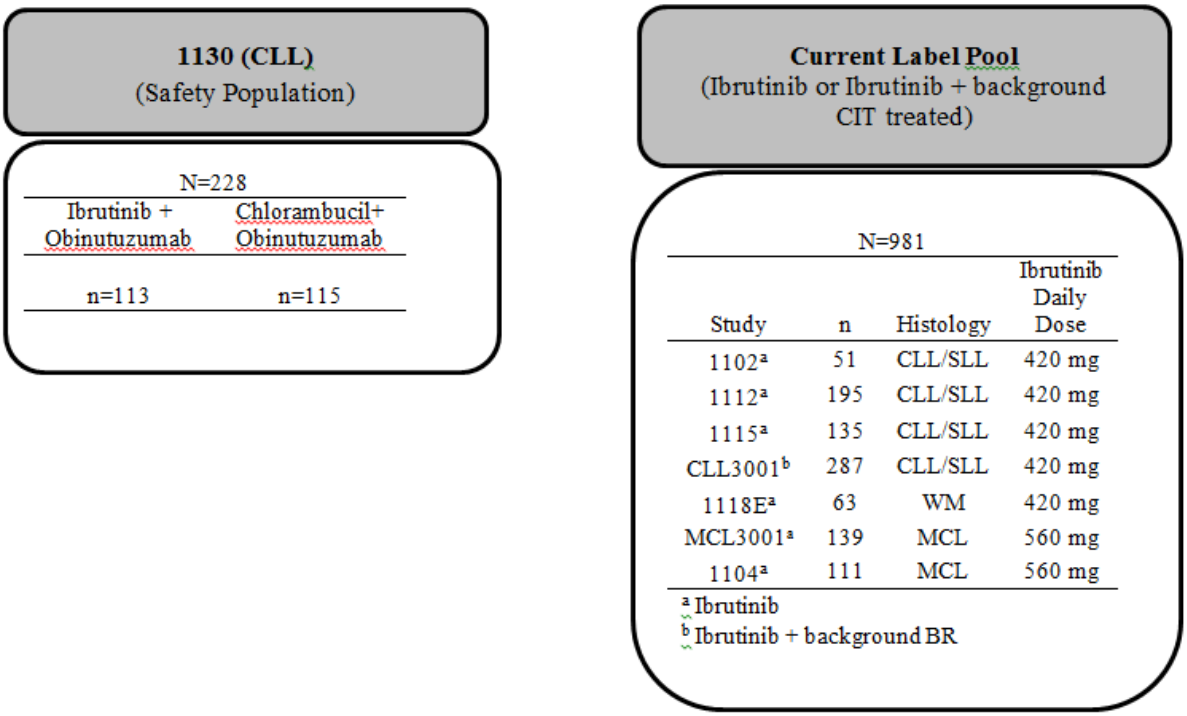
2.5. Clinical safety

Introduction

The 7 studies forming the basis of the authorized indications in the ibrutinib EU SmPC are: Studies PCYC-1102-CA, PCYC-1112-CA, PCYC-1115-CA, and PCI-32765CLL3001 (hereafter referred to as Studies 1102, 1112, 1115, and CLL3001) for CLL; Study PCYC-1118E (hereafter referred to as Study 1118E) for Waldenström's macroglobulinemia (WM); and Studies PCYC-1104-CA and PCI-32765MCL3001 (hereafter referred to as Studies 1104 and MCL3001) for mantle cell lymphoma (MCL). Data for the 981 ibrutinib-treated subjects from these 7 pivotal studies are referred to as the Current Label Pool.

Safety data from Study 1130, both separately and together with safety data from Study 1127, were integrated with those for Current Label Pool, ie, the registrational studies representing the currently approved indications in the ibrutinib SmPC, for determination of the ADR profile for ibrutinib as a single agent or in combination therapy. The integrated population of Study 1130, Study 1127, and the Current Label Pool is referred to as the "Overall Label Pool" and represents data from 1,200 ibrutinib-treated subjects. Relative to the currently approved ADR table for ibrutinib in the IMBRUVICA SmPC, no new ADRs were identified based on the addition of data from Studies 1130 or 1127.

Figure 11 Key Safety Populations Supporting Type II Variation for Extended Indication in CLL



Key: BR=bendamustine and rituximab; CIT=chemoimmunotherapy; CLL=chronic lymphocytic leukemia; MCL=mantle cell lymphoma; SLL=small lymphocytic lymphoma; WM=Waldenström's macroglobulinemia.

Patient exposure

Table 29 Extent of Exposure – Stuady PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+ O	Label Pool
Analysis set: Safety Population	113	115	981
Treatment duration (months)			
Mean (SD)	25.4 (10.16)	4.9 (1.29)	12.9 (6.75)
Median	29.3	5.1	13.0
Range	(0.10; 36.57)	(0.03; 6.74)	(0.03; 28.71)
0 - <3 months	8 (7.1%)	8 (7.0%)	100 (10.2%)
3 - <6 months	2 (1.8%)	102 (88.7%)	73 (7.4%)
6 - <9 months	5 (4.4%)	5 (4.3%)	139 (14.2%)
9 - <12 months	3 (2.7%)	0	126 (12.8%)
12 - <15 months	3 (2.7%)	0	151 (15.4%)
15 - <18 months	4 (3.5%)	0	126 (12.8%)
18 - <24 months	5 (4.4%)	0	231 (23.5%)
≥24 months	83 (73.5%)	0	35 (3.6%)
Average dose level per administration[a] (mg/day)			
CLL/SLL			
N	113	115	668
Mean (SD)	390.2 (48.88)	0.5 (0.04)	392.6 (47.24)
Median	411.3	0.5	413.6
Range	(180.0; 420.2)	(0.4; 0.6)	(140.7; 430.3)
Relative dose intensity (%)			
N	113	115	981
Mean (SD)	92.9 (11.64)	95.8 (7.61)	93.8 (11.06)
Median	97.9	100.0	98.7
Range	(42.9; 100.0)	(72.2; 117.7)	(30.3; 102.4)

CLL=chronic lymphocytic leukemia; N=number; O=obinutuzumab; SD=standard deviation; SLL=small lymphocytic lymphoma

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 CLL/SLL.

At the time of the primary analysis for Study 1130, the median duration of study drug exposure for the ibrutinib+Ob arm was 5.7-fold higher compared with the Clb+Ob arm.

Table 30 Demographics and Baseline Disease Characteristics – Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Age (years)			
Mean (SD)	70.3 (7.56)	71.2 (8.50)	66.3 (9.73)
Median	70.0	72.0	67.0
Min, Max	(47; 87)	(40; 86)	(30; 89)
Time from initial diagnosis to randomization/first dose (months)			
Mean (SD)	41.4 (41.94)	54.3 (66.13)	74.3 (57.60)
Median	29.6	37.0	61.7
Range	(0; 192)	(0; 480)	(1; 334)
Region			
North America	16 (14.2%)	16 (13.9%)	397 (40.5%)
Europe	91 (80.5%)	82 (71.3%)	515 (52.5%)
ROW	6 (5.3%)	17 (14.8%)	69 (7.0%)

Table 31 Subject Disposition and Treatment Withdrawal Information – Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Analysis set: Safety Population	113 (100.0%)	115 (100.0%)	981 (100.0%)
Still on study treatment	79 (69.9%)	0	651 (66.4%)
Completed treatment	0	103 (89.6%)	35 (3.6%)
Discontinued treatment	34 (30.1%)	12 (10.4%)	295 (30.1%)
Reason for discontinuation from study treatment			
Progressive disease or relapse	4 (3.5%)	0	136 (13.9%)
Adverse event	18 (15.9%)	11 (9.6%)	84 (8.6%)
Death	2 (1.8%)	0	31 (3.2%)
Lost to follow-up	0	0	2 (0.2%)
Pregnancy	0	0	0
Investigator or sponsor decision	3 (2.7%)	1 (0.9%)	8 (0.8%)
Subject refuses further treatment	4 (3.5%)	0	29 (3.0%)
Non-compliance	0	0	1 (0.1%)
Other	3 (2.7%)	0	4 (0.4%)
Time on study (months)[a]			
Mean (SD)	28.2 (8.12)	28.5 (7.51)	14.4 (6.11)
Median	30.9	31.3	16.2
Range	(0.2+; 36.6)	(1.1+; 36.8)	(0.2+; 29.0)

Adverse events

Table 32 Overall Summary of Treatment-emergent Adverse Events – Studay PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Analysis set: Safety Population	113	115	981
Any TEAE	112 (99.1%)	112 (97.4%)	968 (98.7%)
Grade ≥3	87 (77.0%)	82[a] (71.3%)	687 (70.0%)
Any ibrutinib/chlorambucil-related TEAE	105 (92.9%)	93 (80.9%)	820 (83.6%)
Grade ≥3	66 (58.4%)	65 (56.5%)	430 (43.8%)
Any serious TEAE	65 (57.5%)	40 (34.8%)	466 (47.5%)
Grade ≥3	54 (47.8%)	32 (27.8%)	412 (42.0%)
Drug-related	30 (26.5%)	21 (18.3%)	212 (21.6%)
TEAE leading to discontinuation of ibrutinib or chlorambucil	19 (16.8%)	11 (9.6%)	112 (11.4%)
TEAE leading to ibrutinib or chlorambucil dose reduction	17 (15.0%)	14 (12.2%)	81 (8.3%)
TEAE with outcome of death	10 (8.8%)	3 (2.6%)	69 (7.0%)

O=obinutuzumab; 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.

[a] One additional subject in the chlorambucil+obinutuzumab arm is identified as having a Grade ≥3 TEAE in the 1130 clinical study report. This is due to the inclusion of an event that was reported after cross-over to ibrutinib therapy and was categorized as related to obinutuzumab therapy by the investigator.

Table 33 Overview of Treatment-emergent Adverse Events (Safety Population)

	Ibr+Ob N=113 n (%)		Clb+Ob N=115 n (%)	
	Overall	First 9 Months	Overall	First 9 months
Subjects with any treatment-emergent AE	112 (99.1)	110 (97.3)	112 (97.4)	112 (97.4)
Grade ≥3	87 (77.0)	71 (62.8)	83 (72.2)	82 (71.3)
Subjects with any ibrutinib/chlorambucil-related AE[a]	105 (92.9)	92 (81.4)	93 (80.9)	93 (80.9)
Grade ≥3	66 (58.4)	50 (44.2)	65 (56.5)	65 (56.5)
Subjects with any obinutuzumab-related AE[a]	85 (75.2)	84 (74.3)	101 (87.8)	100 (87.0)
Grade ≥3	43 (38.1)	42 (37.2)	64 (55.7)	61 (53.0)
Subjects with any AE leading to discontinuation of ibrutinib or chlorambucil	19 (16.8)	11 (9.7)	11 (9.6)	11 (9.6)
Subjects with any AE leading to discontinuation of obinutuzumab	10 (8.8)	10 (8.8)	15 (13.0)	15 (13.0)
Subjects with any AE leading to ibrutinib or chlorambucil dose reduction	17 (15.0)	10 (8.8)	14 (12.2)	14 (12.2)
Subjects with any AE leading to obinutuzumab infusion interruption	42 (37.2)	42 (37.2)	67 (58.3)	67 (58.3)
Subjects with any SAE	65 (57.5)	43 (38.1)	40 (34.8)	39 (33.9)
Grade ≥3	54 (47.8)	35 (31.0)	32 (27.8)	31 (27.0)
Ibrutinib/chlorambucil-related SAEs[a]	30 (26.5)	21 (18.6)	21 (18.3)	20 (17.4)
Obinutuzumab-related SAEs[a]	17 (15.0)	16 (14.2)	27 (23.5)	26 (22.6)
Fatal AE	10 (8.8)	6 (5.3)	3 (2.6)	3 (2.6)
Major hemorrhage[b]	5 (4.4)	1 (0.9)	0	0
Grade ≥3	4 (3.5)	1 (0.9)	0	0
SAE	3 (2.7)	1 (0.9)	0	0

AE: adverse event; Clb+Ob: chlorambucil+obinutuzumab; CNS: central nervous system; Ibr+Ob: ibrutinib+obinutuzumab; SAE: serious adverse event; SMQ: standardized MedDRA Query

N: Number of subjects in specified treatment arm of safety population. n: number of subjects with the specified event. %=100*n/N.

[a] Possibly related or related to study treatment per investigator's judgment.

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

Table 34: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term – Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Analysis set: Safety Population	113	115	981
Subjects with Any TEAE	112 (99.1%)	112 (97.4%)	968 (98.7%)
System Organ Class/ Preferred Term			
Gastrointestinal disorders	81 (71.7%)	60 (52.2%)	707 (72.1%)
Diarrhoea	38 (33.6%)	12 (10.4%)	400 (40.8%)
Nausea	14 (12.4%)	35 (30.4%)	264 (26.9%)
Constipation	18 (15.9%)	14 (12.2%)	160 (16.3%)
Vomiting	11 (9.7%)	14 (12.2%)	141 (14.4%)
Abdominal pain	10 (8.8%)	6 (5.2%)	104 (10.6%)
Infections and infestations	77 (68.1%)	49 (42.6%)	700 (71.4%)
Upper respiratory tract infection	16 (14.2%)	7 (6.1%)	184 (18.8%)
Pneumonia	15 (13.3%)	8 (7.0%)	115 (11.7%)
Urinary tract infection	13 (11.5%)	8 (7.0%)	89 (9.1%)
Nasopharyngitis	13 (11.5%)	4 (3.5%)	72 (7.3%)
Conjunctivitis	12 (10.6%)	2 (1.7%)	56 (5.7%)
General disorders and administration site conditions	60 (53.1%)	63 (54.8%)	569 (58.0%)
Fatigue	20 (17.7%)	19 (16.5%)	264 (26.9%)
Pyrexia	22 (19.5%)	30 (26.1%)	199 (20.3%)
Oedema peripheral	14 (12.4%)	8 (7.0%)	142 (14.5%)
Asthenia	11 (9.7%)	17 (14.8%)	73 (7.4%)
Blood and lymphatic system disorders	81 (71.7%)	86 (74.8%)	522 (53.2%)
Neutropenia	49 (43.4%)	73 (63.5%)	295 (30.1%)
Thrombocytopenia	40 (35.4%)	29 (25.2%)	195 (19.9%)
Anaemia	19 (16.8%)	29 (25.2%)	191 (19.5%)
Skin and subcutaneous tissue disorders	61 (54.0%)	25 (21.7%)	511 (52.1%)
Rash	10 (8.8%)	1 (0.9%)	118 (12.0%)
Rash maculo-papular	17 (15.0%)	2 (1.7%)	52 (5.3%)
Respiratory, thoracic and mediastinal disorders	57 (50.4%)	44 (38.3%)	473 (48.2%)
Cough	30 (26.5%)	14 (12.2%)	192 (19.6%)
Dyspnoea	11 (9.7%)	16 (13.9%)	105 (10.7%)
Musculoskeletal and connective tissue disorders	58 (51.3%)	38 (33.0%)	460 (46.9%)
Muscle spasms	15 (13.3%)	7 (6.1%)	138 (14.1%)
Arthralgia	25 (22.1%)	12 (10.4%)	122 (12.4%)
Back pain	20 (17.7%)	12 (10.4%)	105 (10.7%)
Nervous system disorders	40 (35.4%)	41 (35.7%)	344 (35.1%)
Headache	9 (8.0%)	13 (11.3%)	126 (12.8%)
Metabolism and nutrition disorders	41 (36.3%)	27 (23.5%)	342 (34.9%)
Decreased appetite	7 (6.2%)	5 (4.3%)	121 (12.3%)
Hyperuricaemia	15 (13.3%)	0	70 (7.1%)
Injury, poisoning and procedural complications	52 (46.0%)	74 (64.3%)	286 (29.2%)
Contusion	5 (4.4%)	1 (0.9%)	103 (10.5%)
Infusion related reaction	28 (24.8%)	67 (58.3%)	48 (4.9%)
Vascular disorders	24 (21.2%)	19 (16.5%)	191 (19.5%)
Hypertension	19 (16.8%)	5 (4.3%)	89 (9.1%)

Table 34: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term – Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current Label Pool
	Ibrutinib+O	Chlorambucil+O	
Psychiatric disorders	22 (19.5%)	15 (13.0%)	170 (17.3%)
Insomnia	13 (11.5%)	5 (4.3%)	66 (6.7%)
Cardiac disorders	39 (34.5%)	8 (7.0%)	161 (16.4%)
Atrial fibrillation	14 (12.4%)	0	63 (6.4%)

O=obinutuzumab; 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.

Treatment-emergent Adverse Events Over Time

Study 1130: For the following common TEAEs (≥10% per period), a suggestion of an increase in prevalence was observed with continued ibrutinib treatment (ie, difference of at least 2-fold between Days 1-90 and Days 271-365 [intervals of similar duration]), with consistently higher or stable rates for each subsequent time period compared with Days 1-90): upper respiratory tract infection (1.0% for Days 1-90; 2.4% for Days 271-365), nasopharyngitis (1.0% for Days 1-90; 3.5% for Days 271-365), hypertension (2.9% for Days 1-90; 8.2% for Days 271-365), and atrial fibrillation (0% for Days 1-90; 7.1% for Days 271-365).

Current label pool: 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.

Table 35: Grade 3 or Higher Treatment-Emergent Adverse Events Occurring in 5% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term - Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA				Current Label Pool	
	Ibrutinib+O		Chlorambucil+O			
	Grade 3-4	Grade 5	Grade 3-4	Grade 5	Grade 3-4	Grade 5
Analysis Set: Safety Population	113		115		981	
Subjects with Any TEAE	77 (68.1%)	10 (8.8%)	79 (68.7%)	3 (2.6%)	618 (63.0%)	69 (7.0%)
System Organ Class Preferred Term						
Infections and infestations	19 (16.8%)	2 (1.8%)	11 (9.6%)	2 (1.7%)	216 (22.0%)	21 (2.1%)
Pneumonia	8 (7.1%)	0	4 (3.5%)	1 (0.9%)	71 (7.2%)	4 (0.4%)
Blood and lymphatic system disorders	52 (46.0%)	1 (0.9%)	65 (56.5%)	0	354 (36.1%)	0
Neutropenia	41 (36.3%)	0	53 (46.1%)	0	254 (25.9%)	0
Thrombocytopenia	21 (18.6%)	0	12 (10.4%)	0	95 (9.7%)	0
Anaemia	4 (3.5%)	0	9 (7.8%)	0	51 (5.2%)	0
Febrile neutropenia	5 (4.4%)	0	7 (6.1%)	0	52 (5.3%)	0
Injury, poisoning and procedural complications	8 (7.1%)	0	11 (9.6%)	0	32 (3.3%)	3 (0.3%)
Infusion related reaction	2 (1.8%)	0	9 (7.8%)	0	4 (0.4%)	0
Cardiac disorders	14 (12.4%)	2 (1.8%)	1 (0.9%)	0	61 (6.2%)	5 (0.5%)
Atrial fibrillation	6 (5.3%)	0	0	0	32 (3.3%)	0

O=obinutuzumab; 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.

Treatment-emergent Adverse Events of Clinical Interest

Hemorrhage

The proportions of subjects with a hemorrhage TEAE of any grade/severity or a major hemorrhagic TEAE in the ibrutinib+Ob arm of Study 1130 (44.2% and 4.4%, respectively) were consistent with those observed in the Current Label Pool (41.4% and 4.5%, respectively).

Tumor Lysis Syndrome

In Study 1130, TLS was reported in 1 subject (0.9%) in the ibrutinib+Ob arm (Grade 2) and in 7 subjects (6.1%) in the Clb+Ob arm (2.6% Grade 3 or 4).

Other Malignancies, Including Non-melanoma Skin Cancer

Table 36: Other Malignancies, by PT in study 1130 and current label pool (safety population)

	PCYC-1130-CA		Current Label
	Ibrutinib+O	Chlorambucil+O	Pool
Analysis Set: Safety Population	113	115	981
Subjects with Treatment Emergent Any Other Malignancy	15 (13.3%)	7 (6.1%)	82 (8.4%)
Type Preferred term			
Non-melanoma skin cancer	7 (6.2%)	3 (2.6%)	57 (5.8%)
Melanoma skin cancer	1 (0.9%)	0	1 (0.1%)
Non-skin cancer	8 (7.1%)	4 (3.5%)	25 (2.5%)

The most common non-skin malignancy in the ib+Ob treatment arm was cancer involving the colon, reported in 3 subjects.

Atrial fibrillation

In Study 1130, atrial fibrillation TEAEs were reported for 14 subjects (12.4%) in the ibrutinib+Ob arm. The atrial fibrillation TEAE in the ibrutinib+Ob arm was Grade 3 or 4 in severity for 6 subjects (5.3%), serious in 5 subjects (4.4%; including 4 subjects with a Grade 3 or 4 event), and resulted in ibrutinib dose reduction in 1 subject (0.9%). For no subject in the ibrutinib+Ob arm did the atrial fibrillation TEAE result in ibrutinib discontinuation or death.

The proportion of subjects with atrial fibrillation events in the ibrutinib+Ob arm was higher than that for the Current Label Pool (any grade: 6.4%; Grade 3 or higher: 3.3%); ibrutinib exposure was also considerably longer in Study 1130 than for the Current Label Pool

No subject in the Clb+Ob arm of Study 1130 had an atrial fibrillation TEAE.

Other Cardiac Arrhythmias (excluding atrial fibrillation)

Table 37: Treatment emergent Other Cardiac Arrhythmias (excluding atrial fibrillation) by PT and max severity in Safety population

Table 14.3.2.4 Treatment Emergent Other Cardiac Arrhythmia Excluding Atrial Fibrillation
by Preferred Term and Maximum Severity
Safety Population

	Ibr+Ob (N=113)			Clb+Ob (N=115)		
MedDRA Preferred Term	Any Grade n(%)	Grade 3 + 4 n(%)	Grade 5 n(%)	Any Grade n(%)	Grade 3 + 4 n(%)	Grade 5 n(%)
Subjects with any TEAE	22(19.5)	3(2.7)	2(1.8)	9(7.8)	1(0.9)	0
Palpitations	7(6.2)	0	0	3(2.6)	0	0
Bradycardia	5(4.4)	0	0	2(1.7)	0	0
Tachycardia	3(2.7)	0	0	0	0	0
Syncope	2(1.8)	1(0.9)	0	0	0	0
Sinus tachycardia	1(0.9)	0	0	1(0.9)	0	0
Ventricular extrasystoles	1(0.9)	0	0	1(0.9)	0	0
Atrial flutter	1(0.9)	1(0.9)	0	0	0	0
Atrial tachycardia	1(0.9)	1(0.9)	0	0	0	0
Cardiac arrest	1(0.9)	0	1(0.9)	0	0	0
Sinus bradycardia	1(0.9)	0	0	0	0	0
Sudden death	1(0.9)	0	1(0.9)	0	0	0
Supraventricular extrasystoles	1(0.9)	0	0	0	0	0
Supraventricular tachycardia	1(0.9)	0	0	0	0	0
Extrasystoles	0	0	0	1(0.9)	0	0
Loss of consciousness	0	0	0	1(0.9)	1(0.9)	0

In the Current Label Pool, 1.0% of subjects had a ventricular tachyarrhythmia TEAE, most of which were Grade 1 or 2 in severity (9/10 subjects) and nonserious (8/10 subjects).

Cytopenia

Table 38: Sumamry of treatment – emergent cytopenia AEs in the Safety population

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Analysis set: Safety Population	113	115	981
Neutropenia			
Any grade	49 (43.4%)	73 (63.5%)	295 (30.1%)
Grade 3 or 4	41 (36.3%)	53 (46.1%)	254 (25.9%)
Serious TEAE	2 (1.8%)	0	12 (1.2%)
TEAE leading to treatment discontinuation	0	1 (0.9%)	5 (0.5%)
TEAE leading to dose reduction	6 (5.3%)	11 (9.6%)	17 (1.7%)
Febrile neutropenia			
Any grade	6 (5.3%)	8 (7.0%)	52 (5.3%)
Grade 3 or 4	5 (4.4%)	7 (6.1%)	52 (5.3%)
Serious TEAE	4 (3.5%)	7 (6.1%)	40 (4.1%)
TEAE leading to treatment discontinuation	0	1 (0.9%)	1 (0.1%)
TEAE leading to dose reduction	1 (0.9%)	1 (0.9%)	3 (0.3%)
Anemia			
Any grade	19 (16.8%)	29 (25.2%)	191 (19.5%)
Grade 3 or 4	4 (3.5%)	9 (7.8%)	51 (5.2%)
Serious TEAE	1 (0.9%)	2 (1.7%)	12 (1.2%)
TEAE leading to treatment discontinuation	0	1 (0.9%)	1 (0.1%)
TEAE leading to dose reduction	0	0	1 (0.1%)
Thrombocytopenia			
Any grade	40 (35.4%)	29 (25.2%)	195 (19.9%)
Grade 3 or 4	21 (18.6%)	12 (10.4%)	95 (9.7%)
Serious TEAE	3 (2.7%)	1 (0.9%)	12 (1.2%)
TEAE leading to treatment discontinuation	2 (1.8%)	1 (0.9%)	6 (0.6%)
TEAE leading to dose reduction	1 (0.9%)	2 (1.7%)	6 (0.6%)

Hypertension

Hypertension TEAEs were reported for 16.8% of subjects in the ibrutinib+Ob arm of Study 1130, with 3.5% of subjects having a Grade 3 or 4 hypertension TEAE. None of these events were serious or resulted in ibrutinib discontinuation. One subject (0.9%) had an ibrutinib dose reduction due to a hypertensive TEAE.

In the Clb+Ob arm of Study 1130, hypertension TEAEs were reported for 4.3% of subjects (3.5% with Grade 3 or 4 events).

While the reported incidence of hypertension TEAEs of any grade was higher for the ibrutinib+Ob arm compared with the Current Label Pool (9.9%) (possibly due to the longer treatment duration in the ibrutinib+Ob arm), the pattern of hypertension TEAEs in the 2 safety populations was similar with respect to the incidence of Grade 3 or 4 TEAEs (3.8%) and very few events that were serious (0.6%) or resulted in ibrutinib dose reduction or discontinuation (0.1% each).

Long-term safety Data – PAM 3038-1

PRAC evaluated this study recently as MEA025 (CHMP conclusion 15/11/2018); please refer to that report.

The MAH's conclusions are as follows: "The results from the Year 4 interim analysis of PAM 3038-1 show no new safety concerns in patients on long-term ibrutinib therapy administered at 420 mg or 560 mg daily to subjects with CLL/SLL or MCL with a median treatment duration of 45.4 and 11.1 months, respectively (33.7 months overall across both indications). The overall known safety profile of ibrutinib-treated patients remained consistent, other than an increasing prevalence of hypertension, with no new safety signals identified.

In addition, the safety of long-term exposure to ibrutinib in a subset of subjects with CLL/SLL (n=330) from Studies 1112 and 1115/1116 was in alignment with that observed for the larger LTS population (n=1,177)".

In the assessment report, it is concluded that "Overall this third interim report is not suggestive of any new safety concerns in patients exposed to ibrutinib for long term and no specific regulatory action is currently required".

Methodology for ADR Analysis

The determination of updated information to Section 4.8 of the SmPC was based on the following steps:

Step I. Data from Study 1130, either alone or with data from Study 1127, were pooled with data from the other 4 randomized controlled trials (1112, 1115, CLL3001, MCL3001). For the pooled analysis involving data from Study 1130 (ibrutinib+Ob arm) and Study 1127 (ibrutinib+rituximab arm of double-blind study), integrated TEAE data from the 1,883 subjects (944 ibrutinib, 939 comparator) comprising this **Randomized Controlled Trial** (**RCT**) population were examined as follows:

- Individual TEAE preferred terms that met the following criteria were identified (note, the same grouped terms as used in the current ADR section of the SmPC were used):
  - TEAE reported in ≥10% of subjects in the pooled RCT ibrutinib group and reported at a ≥5% higher incidence compared to the pooled RCT comparator group.
  - Serious TEAEs reported in ≥2% of subjects in pooled RCT ibrutinib group and reported at a ≥2% higher incidence compared to the pooled RCT comparator group.

Step II. Medical review of each potential ADRs identified in Step I was conducted. In addition, a review all ADRs from the current SmPC and any events from the completed individual studies was conducted to identify additional ADRs that are biologically plausible based on the current biological and clinical knowledge of ibrutinib therapy (eg, mechanism of action, pharmacological profile or well-established ADR for ibrutinib from other clinical trials or postmarketing spontaneous reports, consistent trending across multiple studies).

Step III. A final list of ADRs identified in Steps I and II above was compiled. This list was then applied to the safety population that integrates data from the pivotal studies representing the currently approved and proposed extended indications in CLL/SLL (1130, 1102, 1112, 1115, CLL3001); WM (1118E, 1127 [not included for updated ADR determination based on inclusion of data from 1130 only]); and MCL (1104, MCL3001). This Overall Label Pool represents data from a total of 1,200 subjects receiving ibrutinib as monotherapy or in combination therapy across these 9 studies.

Results

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; please refer to separate SmPC.

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.

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).

Serious adverse event/deaths/other significant events

Table 39: Summary of all deaths in PCYC 1130 and current Label pool; safety population

TSFDTH02A3: Summary of All Deaths - PCYC-1130-CA and Current Label Pool; Safety Population			
	Ibrutinib+O	CHL+O	Current Label Pool
Analysis set: safety population	113	115	981
All deaths	17 (15.0%)	19 (16.5%)	153 (15.6%)
Primary cause of death			
Adverse event	10 (8.8%)	7 (6.1%)	30 (3.1%)
Progressive disease	0	0	87 (8.9%)
Other	4 (3.5%)	9 (7.8%)	21 (2.1%)
Unknown	3 (2.7%)	3 (2.6%)	15 (1.5%)

Current Label Pool includes PCYC-1102, PCYC-1104, PCYC-1112, PCYC-1115, PCYC-1118E, MCL3001, and CLL3001.
Note: Percentages calculated with the number of subjects in safety population as denominator.

TSFDTH01A3: Death Within 30 Days After Last Dose of Study Treatment - PCYC-1130-CA and Current Label Pool; Safety Population			
	Ibrutinib+O	CHL+O	Current Label Pool
Analysis set: safety population	113	115	981
Death within 30 days after last dose	8 (7.1%)	1 (0.9%)	73 (7.4%)
Primary cause of death			
Adverse event	8 (7.1%)	1 (0.9%)	23 (2.3%)
Progressive disease	0	0	33 (3.4%)
Other	0	0	13 (1.3%)
Unknown	0	0	4 (0.4%)

Table 40: Incidence of TEAEs leading to death by SOC and PT – Safety population

	PCYC-1130-CA		Current Label Pool
	Ibrutinib+O	Chlorambucil+O	
Analysis set: Safety Population	113	115	981
Subjects with Any TEAE Leading to Death	10 (8.8%)	3 (2.6%)	69 (7.0%)

Table 41: TEAEs leading to death by PT – Safety population

MedDRA Preferred Term	Ibr+Ob N=113 n (%)	Clb+Ob N=115 n (%)
Subjects with any TEAE	**10 (8.8)**	**3 (2.6)**
Acute myocardial infarction	1 (0.9)	0
Adenocarcinoma gastric	1 (0.9)	0
Aplastic anaemia	1 (0.9)	0
Bacterial sepsis	1 (0.9)	0
Cardiac arrest	1 (0.9)	0
Colorectal cancer metastatic	1 (0.9)	0
Completed suicide	1 (0.9)	0
Death	1 (0.9)	0
Septic shock	1 (0.9)	0
Sudden death	1 (0.9)	0
Neuroendocrine carcinoma of the skin	0	1 (0.9)
Pneumonia	0	1 (0.9)
Sepsis	0	1 (0.9)

Within the first 9 months of treatment, the proportion of subjects with fatal TEAEs was 5.3% (n=6) for the ibrutinib+Ob arm and 2.6% (n=3) in the Clb+Ob arm.

SAEs

Table 42: Incidence of Treatment-emergent Serious Adverse Events Occurring in 2% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term – Study PCYC-1130-CA and Current Label Pool (Safety Population)

	PCYC-1130-CA		Current
	Ibrutinib+O	Chlorambucil+O	Label Pool
Analysis set: Safety Population	113	115	981
Subjects with Any Serious TEAE	65 (57.5%)	40 (34.8%)	466 (47.5%)
System Organ Class/ Preferred Term			
Infections and infestations	18 (15.9%)	11 (9.6%)	216 (22.0%)
Pneumonia	6 (5.3%)	5 (4.3%)	76 (7.7%)
Blood and lymphatic system disorders	9 (8.0%)	10 (8.7%)	75 (7.6%)
Febrile neutropenia	4 (3.5%)	7 (6.1%)	40 (4.1%)
Thrombocytopenia	3 (2.7%)	1 (0.9%)	12 (1.2%)
Cardiac disorders	15 (13.3%)	1 (0.9%)	64 (6.5%)
Atrial fibrillation	5 (4.4%)	0	30 (3.1%)
Acute coronary syndrome	3 (2.7%)	0	0
General disorders and administration site conditions	7 (6.2%)	4 (3.5%)	63 (6.4%)
Pyrexia	4 (3.5%)	4 (3.5%)	25 (2.5%)
Injury, poisoning and procedural complications	9 (8.0%)	11 (9.6%)	43 (4.4%)
Infusion related reaction	2 (1.8%)	8 (7.0%)	4 (0.4%)
Metabolism and nutrition disorders	2 (1.8%)	7 (6.1%)	23 (2.3%)
Tumour lysis syndrome	0	5 (4.3%)	7 (0.7%)

O=obinutuzumab; 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.

	Ibr+Ob N=113 n (%)		Clb+Ob N=115 n (%)	
	Overall	First 9 Months	Overall	First 9 months
Subjects with any SAE	65 (57.5)	43 (38.1)	40 (34.8)	39 (33.9)
Grade ≥3	54 (47.8)	35 (31.0)	32 (27.8)	31 (27.0)
Ibrutinib/chlorambucil-related SAEs[a]	30 (26.5)	21 (18.6)	21 (18.3)	20 (17.4)
Obinutuzumab-related SAEs[a]	17 (15.0)	16 (14.2)	27 (23.5)	26 (22.6)

Laboratory findings

Table 43: chemistry TEAEs worst toxicity grade (safety population)

Laboratory Parameter	Abnormal Direction	Study PCYC-1130-CA				Current Label Pool	
		Ibrutinib+O		Chlorambucil+O			
		All Grades	Grades 3+4	All Grades	Grades 3+4	All Grades	Grades 3+4
Analysis Set: Safety Population		113		115		981	
Sodium	Decrease	4 (3.5%)	1 (0.9%)	7 (6.1%)	4 (3.5%)	204 (20.8%)	48 (4.9%)
	Increase	19 (16.8%)	0	8 (7.0%)	0	186 (19.0%)	5 (0.5%)
Magnesium	Decrease	8 (7.1%)	1 (0.9%)	4 (3.5%)	0	188 (19.2%)	7 (0.7%)
	Increase	2 (1.8%)	0	1 (0.9%)	0	66 (6.7%)	11 (1.1%)
Potassium	Decrease	10 (8.8%)	2 (1.8%)	2 (1.7%)	1 (0.9%)	161 (16.4%)	24 (2.4%)
	Increase	28 (24.8%)	2 (1.8%)	32 (27.8%)	1 (0.9%)	145 (14.8%)	19 (1.9%)
Albumin	Decrease	6 (5.3%)	0	3 (2.6%)	0	226 (23.0%)	8 (0.8%)
Total Bilirubin	Increase	22 (19.5%)	0	13 (11.3%)	0	248 (25.3%)	16 (1.6%)
Creatinine	Increase	8 (7.1%)	1 (0.9%)	3 (2.6%)	0	210 (21.4%)	12 (1.2%)
ALT	Increase	18 (15.9%)	4 (3.5%)	14 (12.2%)	0	174 (17.7%)	9 (0.9%)
AST	Increase	25 (22.1%)	0	10 (8.7%)	0	198 (20.2%)	8 (0.8%)
ALP	Increase	24 (21.2%)	1 (0.9%)	16 (13.9%)	0	179 (18.2%)	5 (0.5%)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; O=obinutuzumab

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: Only subjects whose grade worsened from baseline were counted in numerator. Percentages calculated with the number of subjects in safety population as the denominator.

The occurrence of subjects meeting laboratory criteria for potential drug-induced liver injury (DILI) event post baseline (ALT or AST >3 x ULN, with total bilirubin >2 x ULN and ALP ≤2 x ULN within 28 days after elevation in ALT or AST) (Hy's law criteria) was investigated. No subject in the ibrutinib+Ob or Clb+Ob arms of Study 1130 met these laboratory criteria, while 4 ibrutinib-treated subjects (0.4%) in the Current Label Pool met these criteria.

Discontinuation due to adverse events

Table 44: Discontinuations in Study 1130

	Ibr+Ob N=113 n (%)		Clb+Ob N=115 n (%)	
	Overall	First 9 Months	Overall	First 9 months
Subjects with any AE leading to discontinuation of ibrutinib or chlorambucil	19 (16.8)	11 (9.7)	11 (9.6)	11 (9.6)
Subjects with any AE leading to discontinuation of obinutuzumab	10 (8.8)	10 (8.8)	15 (13.0)	15 (13.0)
Subjects with any AE leading to ibrutinib or chlorambucil dose reduction	17 (15.0)	10 (8.8)	14 (12.2)	14 (12.2)
Subjects with any AE leading to obinutuzumab infusion interruption	42 (37.2)	42 (37.2)	67 (58.3)	67 (58.3)

The only TEAE preferred term that led to ibrutinib discontinuation in >1 subject in the ibr+Ob treatment arm was thrombocytopenia (2 subjects; 1.8%). For 13 of the total of 19 subjects , the TEAE(s) leading to ibrutinib discontinuation were serious, including the 5 subjects who had a fatal TEAE and 8 subjects with non-fatal serious TEAEs (bronchopulmonary aspergillosis, myelodysplastic syndrome, osteoarthritis, pneumonia and cerebrovascular accident, respiratory tract infection, hemoptysis, non-small cell lung cancer, and thrombocytopenia).

In the Clb+Ob arm, 11 subjects (9.6%) had a TEAE that resulted in discontinuation of Clb, with infusion-related reactions being the only TEAE that led to discontinuation in more than 1 subject in this arm (n=2, 1.7%). In the ibrutinib+Ob arm, there were no subjects who discontinued obinutuzumab due to an IRR (based on PT). In the Clb+Ob arm, infusion-related reactions (based on PT) leading to obinutuzumab discontinuation occurred in 7 subjects (6.1%).

The overall incidence of TEAEs leading to ibrutinib discontinuation in the ibrutinib+Ob arm of Study 1130 was consistent with that for the Current Label Pool (11.4%). Those TEAEs that led to ibrutinib discontinuation in 5 or more subjects in the Current Label Pool were pneumonia (n=12, 1.2%), atrial fibrillation (n=7, 0.7%), subdural hematoma (n=7, 0.7%), thrombocytopenia (n=6, 0.6%), sepsis (n=5, 0.5%), and neutropenia (n=5, 0.5%).

Adverse Events Leading to Dose Reduction or Interruption

In Study 1130, TEAEs of any grade leading to an ibrutinib dose reduction were reported for 15.0% of subjects in the ibrutinib+Ob arm. Similarly, TEAEs of any grade led to a reduction in the dose of Clb for 12.2% of subjects. Neutropenia was the only individual TEAE that led to a reduction in the dose of ibrutinib (5.3%) or Clb (9.6%) in 2% or more of subjects.

In the Ibr+Ob arm, infusion-related reactions (based on PT) leading to obinutuzumab interruption occurred in 7 subjects (6.2%); 1 subject (0.9%) experienced a Grade 3 or higher IRR leading to obinutuzumab interruption. In the Clb+Ob arm, infusion-related reactions (based on PT) leading to obinutuzumab interruption occurred in 35 subjects (30.4%); 4 subjects (3.5%) experienced a Grade 3 or higher IRR leading to obinutuzumab interruption.

2.5.1. Discussion on clinical safety

The substantially longer duration of treatment in the Ibr+Obi arm *vs* the Clb+Obi arm of study 1130, and also vs the Current label pool, should be noted when comparing AE rates between the groups. Here, the analysis of AEs and correlated rates in study 1130 during the first 9 months of study is considered of major interest. As could be expected, the differences between the study arms are smaller as compared to the overall analysis.

Fatal AEs were reported for 6 subjects in the experimental arm vs 3 subjects in the control arm. Importantly, within the first 9 months of treatment, the proportion of subjects with fatal TEAEs was 5.3% (n=6) for the experimental arm and 2.6% (n=3) in the control arm. The verbatim for these cases, however, do not suggest any specific pattern of AEs leading to death. Having considered also the AEs leading to death after more than 9 months of treatment, no potentially specific safety signal not previously observed, i.e. non-skin cancer and cardiac, has been identified.

Notwithstanding the different times on therapy, compared to the Current label pool, grade ≥3 events were slightly more prevalent in the experimental arm of study 1130. At the SOC level, blood/lymphatic system disorders, injury/poisoning/procedural complications, and cardiac disorders were numerically more frequent in the experimental arm of study 1130. Grade 3-4 events were overall reported at similar rates between study arms in 1130. At the SOC level, infections/infestations and cardiac disorders were more frequently reported in the experimental arm.

With the exception of higher rates of neutropenia, thrombocytopenia, rash maculo-papular, arthralgia, and infusion-related reaction, which all were more commonly reported in the experimental arm of study 1130, the respective frequencies reasonably correspond to the Current label pool. At the SOC level, GI disorders, infections and infestations, skin and subcutaneous tissue disorders, respiratory/thoracic/mediastinal disorders, musculoskeletal/connective disorders, metabolism/nutrition disorders, and cardiac disorders were clearly more commonly reported in the experimental *vs* the control arm in study 1130. But, again, note the major difference in treatment duration. The prevalence of hypertension and atrial fibrillation seem to increase over time during treatment with ibrutinib.

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. Having considered also the AEs leading to death after more than 9 months of treatment, no

potentially specific safety signal not previously observed, i.e. non-skin cancer and cardiac, has been identified.

Discontinuation of treatment due to AE was more common in the experimental arm of study 1130 as compared to the control arm and the Current label pool; here, as for the outcomes, time on treatment must be considered. Discontinuation due to investigator/sponsor decision, subject refuses further treatment or "other" was more commonly reported in the experimental arm, in 10 subjects vs 1 in the control arm. Median time on study was similar between study arms. The TEAEs leading to most treatment discontinuations of ibrutinib were, in descending order, pneumonia, atrial fibrillation, subdural hematoma, thrombocytopenia, sepsis and neutropenia.

The long-term safety data over 4 years from 1177 patients (CLL/SLL n=807 and MCL n=370) treated with IMBRUVICA were analyzed. The median duration of treatment for CLL/SLL was 45 months with 70% and 40% of patients receiving treatment for more than 2 years and 4 years. The median duration of treatment for MCL was 11 months with 31% and 14% of patients receiving treatment for more than 2 years and 4 years. The overall known safety profile of IMBRUVICA-exposed patients remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), and 8% (year 3-4). The incidence for the 4-year period was 10%.

Considering the first 9 months of study participation, no major differences in terms of AE entity as described in the table above are noted, with the exception of AEs leading to obinutuzumab discontinuation or infusion interruption that were numerically more commonly reported in the control arm and are reflected in section 4.8 of the SmPC.

Given the unclear role/consequences of the QT shortening properties of ibrutinib ventricular arrhythmias are of potential interest to follow. Any grade and grade ≥3 events of cardiac arrhythmias excluding atrial fibrillation were more commonly reported in the experimental arm *vs* the control arm of study 1130, including three cases of tachycardia, two cases of syncope and one case each of ventricular extrasystoles, cardiac arrest and sudden death were noted. The difference in treatment duration, referring to the control arm of study 1130 as well as the Current label pool, complicates the interpretation of this dataset. Further vigilance is indicated.

TEAEs of any other malignancy and non-skin cancer were more common in the experimental arm of study 1130 as compared to the Current label pool, 13.3% vs 8.4% and 7.1% vs 2.5%, respectively. No clear pattern in terms of histology is obvious although 3 subjects in the experimental arm of study 1130 were reported with colon cancer. Most likely the very different exposure/observation times contribute to this finding but further vigilance is indicated.

2.5.2. Conclusions on clinical safety

When adding safety data from the 1130 and 1127 (Waldenstrom's macroglobulinemia, parallel procedure) studies to the Current label pool, no new ADR was identified.

Long-term safety is supported by the outcome of the recently assessed MEA025 (CHMP conclusion 15/11/2018) where it was concluded that overall this third interim report is not suggestive of any new safety concerns in patients exposed to ibrutinib for long term. No regulatory action was required.

Further, the MAH should keep monitoring reports of ventricular arrhythmias and secondary non-skin primary malignancies within the PSURs.

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

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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
54179060NAP4001 Enhanced pharmacovigilance to evaluate the risks of hemorrhage with the administration of IMBRUVICA® (ibrutinib): A post-marketing requirementAdditional Pharmacovigilance Study to Evaluate the Risks of Major Hemorrhage With the Administration of IMBRUVICA® (ibrutinib) Ongoing	To study the risk of serious bleeding from clinical trials and all postmarketing sources	Hemorrhage	Final report	4th Quarter 2018
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	Determine the effect of ibrutinib on the exposure of oral contraceptives	Drug-drug interaction	Final report	2nd Quarter 2020

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Oral Contraceptives, CYP2B6, and CYP3A4 Substrates in Female Subjects with B-cell Malignancy Ongoing				
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

Safety Concern	Routine Risk Minimisation Activities
	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 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:

Safety Concern	Routine Risk Minimisation Activities
	• 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 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

Safety Concern	Routine Risk Minimisation Activities
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 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

Safety Concern	Routine Risk Minimisation Activities
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
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

Safety Concern	Routine Risk Minimisation Activities
	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 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

Safety Concern	Routine Risk Minimisation Activities
	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 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

Safety Concern	Routine Risk Minimisation Activities
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 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

Safety Concern	Routine Risk Minimisation Activities
	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
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. The Package Leaflet has been updated accordingly.

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

CLL is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs; diagnosis requires the presence of ≥5000 B-lymphocytes/µL in the peripheral blood. It is the most common form of adult leukemia in the Western world. Assessment of newly diagnosed patients for deletion of the short arm of chromosome 17 (del17p), deletion of the long arm of chromosome 11 (del11q), mutated TP53, and immunoglobulin heavy-chain variable (IGHV) mutational status has prognostic and predictive value;

3.1.2. Available therapies and unmet medical need

In particular, patients with the del17p abnormality have an increased risk of relapse and death; the median life expectancy is 2 to 3 years from first-line treatment. It should be noted that the Clb+CD20 antibody combination is not recommended in subjects with del 17p/TP53 mutated disease.

3.1.3. Main clinical studies

Pivotal study: PCYC-1130-CA was "A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib in Combination with Obinutuzumab versus Chlorambucil in Combination with Obinutuzumab in Subjects with Treatment-naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma". Randomisation, stratified by ECOG 0-1 *vs* 2, and del 17p *vs* del 11q without del 17p *vs* others, was 1:1, n=229. The study Period was: 06 October 2014 (first informed consent signed) to 26 March 2018 (date of database lock). The study was conducted at a total of 9 sites in the US and 80 sites in rest-of-world (ROW). Patients ≥65 years, or younger with comorbidities or 17p del/TP53 mutation, with previously untreated measurable nodal CLL/SLL requiring treatment were enrolled. A six months treatment period for the control arm was compared with treatment until PD or toxicity for the experimental arm. Subjects on the control arm were eligible to receive ibrutinib monotherapy as next-line treatment.

The event-driven primary endpoint was PFS assessed by IRC using non-EMA censoring rules, no interim analysis was performed. Due to imbalance of high-risk stratification factors between study arms, and new external guidance highlighting the prognostic impact of IGHV mutation status during study conduct, the originally planned stratified analysis of the primary outcome was, prior to database lock, changed to an unstratified analysis. With IGHV mutation status included, high-risk features were balanced between study arms.

3.2. Favourable effects

With a median follow-up of 31.3 months and an event rate of 64% in the control arm and 21% in the experimental arm, an unstratified analysis of IRC assessment of PFS showed a HR of 0.231 (0.145, 0.367), p<0.0001. Use of the stratified Cox regression model showed a consistent outcome. The sensitivity analysis using an unstratified analysis of investigator assessment showed a HR of 0.260. Given the higher proportion of discontinuation of study treatment in the experimental arm, a sensitivity analysis was requested, imputing an event at the time of discontinuation of treatment, instead of censoring, if a PFS event was not determined at a later time. Not unexpectedly, considering the longer time on

treatment in the Ibr+Ob arm, the imputation of treatment discontinuation due to reasons other than progressive disease (PD) as a progressive event increases the hazard of progression. The HR between the Ibr+Ob arm and the Clb+Ob arm is increased from 0.231 (95% CI: 0.145, 0.367) in the CSR submitted to. Nevertheless, the difference between the 2 treatment arms remains statistically significant.

ORR, based on IRC assessment, was 88% in the experimental arm and 73% in the control arm. The corresponding figures for CR were 20% and 8%, respectively. Time to normalisation of absolute lymphocyte count was, however, faster in the control arm, 1.4 weeks vs 8.3 weeks in the experimental arm.

With only 17 (15%) events in the experimental arm and 19 (16%) in the control arm at the time of the primary submission, OS data is immature. With almost a year longer follow-up, with 3 additional events in the experimental arm and 2 in the control arm, the median OS was not reached for either treatment arm; the OS for both arms was similar (HR = 0.969, 95% CI: 0.525, 1.789). OS data is still immature. A further update is expected with the final CSR. The early deaths noted in the experimental arm are discussed below. Overall, no trend for a worse outcome in the experimental arm is noted.

Infusion-related reactions (i.e. obinutuzumab-related) were numerically less frequently noted in the experimental arm.

3.3. Uncertainties and limitations about favourable effects

As a six months treatment period for the control arm is compared with treatment until PD or toxicity for the experimental arm, and progress on *vs* off therapy has different prognostic implications, data on PFS2 would be informative and will be provided along with the final analysis CSR for the 1130 study, in 3Q2020 as recommended by the CHMP.

3.4. Unfavourable effects

In relation to the known safety profile of ibrutinib no new ADRs or safety signals were observed.

The prevalence of hypertension and atrial fibrillation seem to increase over time during treatment with ibrutinib.

3.5. Uncertainties and limitations about unfavourable effects

Having considered also the AEs leading to death after more than 9 months of treatment, no potentially specific safety signal not previously observed, i.e. non-skin cancer and cardiac, has been identified.

Ventricular arrhythmias and secondary non-skin primary malignancies will be monitored in the PSURs.

3.6. Effects Table

Effects Table for study 1130 (data cut-off: 26 March 2018)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	IRC, unstratified	HR			0.231 (0.145, 0.367)	p<0.0001. Based on 21.2 and 63.8% events in the exp and ctrl arm, resp.
	IRC, stratified	HR			0.229 (0.144, 0.366)	P<0.0001
	IRC, high-risk	HR			0.119 (0.046, 0.307)	P<0.0001

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	subpopulation					
	IRC, high-risk population	HR			0.154 (0.087, 0.270)	p<0.0001
ORR	IRC	%	88.5	73.3		Nominal p=0.0035
CR	IRC	%	19.5	7.8		Nominal p=0.0096
OS		HR			0.921 (0.479, 1.772)	Nominal p=0.8057 Based on 15 and 16.4% deaths in the exp and ctrl arm, resp. Immature.
IRR	MedDRA PT, any grade	%	24.8	57.8		Nominal p<0.0001
Unfavourable Effects						
TE ≥grade 3		%	77.0	72.2	Note the 5.7-fold higher median duration of study drug exposure for the exp arm	
SAE		%	57.5	34.8	-"-	
Fatal AE		%	8.8	2.6	-"-	
AE leading to discontinuation of ibr or chl		%	16.8	9.6	-"-	
AE leading to discontinuation of obi		%	8.8	13.0		

Abbreviations:

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The HR for the primary endpoint PFS of 0.231 - which following sensitivity analyses was revised to 0.327 - is statistically significant and considered clinically highly relevant, not least in patients with high-risk disease. Also ORR and CR rates were in favour of the experimental arm, with long-term follow-up of other ibrutinib studies showing deepening responses over time. Thus, the PFS outcome can be considered robustly estimated. With approximately one additional year of follow-up, data remains essentially stable. The outcomes of the subgroup analyses are consistent.

The rate and severity of obintuzumab infusion-related reactions were lower in the experimental arm as it seems Imbruvica has a protective effect over IRS triggered by the monoclonal antibody. OS results are too immature to evaluate but no negative trend for the experimental arm is noted in the KM graph.

No new ADRs or safety signals were observed in relation to the known safety profile of ibrutinib.

3.7.2. Balance of benefits and risks

The improved outcome in terms of PFS consistent among subgroups far outweighs the manageable safety profile of ibrutinib in combination with obinutuzumab.

3.7.3. Additional considerations on the benefit-risk balance

The indication encompasses all patients with previously untreated CLL while the studied population is restricted to patients ≥65 years, or younger with comorbidities or 17p del/TP53 mutation. A similar

extrapolation was extensively discussed in the II-16 variation, where the pivotal 1115 study investigating ibrutinib monotherapy *vs* chlorambucil monotherapy in subjects ≥65 years with previously untreated CLL ultimately lead to the approval of ibrutinib monotherapy in all previously untreated patients with CLL. Consistently, given the safety profile of the ibr+obi combination, there is no reason to restrict the use of this combination to a more narrow population than already approved for ibrutinib monotherapy.

3.8. Conclusions

The overall B/R of Imbruvica in combination with obinutuzumab in CLL is positive.

In addition, the CHMP considered that the applicant should submit the following safety data the next PSUR: Ventricular arrhythmias and secondary non-skin primary malignancies.

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 combination use with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Imbruvica based on data from the phase 3 study PCYC-1130-CA; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) is agreed.

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imbruvica is not similar to obinutuzumab within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

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 combination use with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) for Imbruvica based on data from the

phase 3 study PCYC-1130-CA; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the SmPC and Package Leaflet with minor editorial/administrative changes. An updated RMP (version 12) is agreed.

Summary

Please refer to Scientific Discussion Imbruvica–H-C-3791-II-0047.