23 July 2020
EMA/CHMP/452512/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0059

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Table of contents

List of abbreviations

ADR	adverse drug reaction
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
BCR	B-cell receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
cGVHD	chronic graft versus host disease
CI	confidence interval
CIT	chemoimmunotherapy
Clb	chlorambucil
Clb+Ob	chlorambucil plus obinutuzumab
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CO	clinical overview
CrCl	creatinine clearance
CSR	clinical study report
CTEP	Cancer Therapy Evaluation Program
CV	coefficient of variation
del 11q	deletion of the long arm of chromosome 11
del 17p	deletion of the short arm of chromosome 17
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
ECOG-ACRIN	Eastern Cooperative Oncology Group-American College of Radiology Imaging Network
EOP2	End of Phase 2
ESMO	European Society for Medical Oncology
EU	European Union
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
GCP	good clinical practice
HR	hazard ratio
Ibr+Ob	ibrutinib plus obinutuzumab
Ibr+R	ibrutinib plus rituximab
ICH	International Council on Harmonisation
IGHV	immunoglobulin heavy chain variable region
IND	investigational new drug
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTEP	National Cancer Institute-Cancer Therapy Evaluation Program
NCTN	National Clinical Trials Network
Ob	obinutuzumab
ORR	overall response rate
OS	overall survival

PBRER	Periodic Benefit Risk Evaluation Report
PFS	progression-free survival
SCS	Summary of Clinical Safety
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
sNDA	supplemental New Drug Application
SOC	system organ class
TEAE	treatment-emergent adverse event
TP53	tumor-suppressor protein 53 gene
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 14 January 2020 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, IIIA and IIIB

Extension of indication in chronic lymphocytic leukaemia (CLL) to add combination with rituximab as follows: In combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated CLL.
This extension of the approved CLL indication is based on results from the Phase 3 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG ACRIN) Study E1912 (also referred to as PCYC-1126e-CA).
The SmPC is revised to include information related to the new indication. The PL has been revised accordingly. Minor editorial changes have been implemented in Annex IIIA. An updated RMP has been submitted. Furthermore, the MAH took the opportunity to update the list of local representatives for Hungary in Sweden in the PL.

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

Information relating to orphan designation

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".

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 MAH 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:	14 January 2020
Start of procedure:	1 February 2020
CHMP Rapporteur's preliminary assessment report circulated on:	27 March 2020
PRAC Rapporteur's preliminary assessment report circulated on:	2 April 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	17 April 2020
CHMP Rapporteur's updated assessment report circulated on:	24 April 2020
Request for supplementary information and extension of timetable adopted by the CHMP on:	30 April 2020
MAH's responses submitted to the CHMP on:	19 May 2020
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	25 June 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 June 2020
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on:	1 July 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	9 July 2020
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	16 July 2020
CHMP opinion adopted on:	23 July 2020
The CHMP adopted a report on similarity of Imbruvica with Gazyvaro on:	23 July 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

In combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated CLL.

Epidemiology

CLL is a progressive hematologic disease characterized by an accumulation of monoclonal mature B-cells in the blood, bone marrow, and secondary lymph organs. It is the most common form of adult leukemia in the Western world. An exponential increase in the incidence of CLL with age is observed; the median age at diagnosis is 72 years of age.

Biologic features

Chronic lymphocytic leukemia (CLL) is a progressive hematologic disease characterized by an accumulation of monoclonal mature B-cells (CD5+CD23+) in the blood, bone marrow, and secondary lymph organs. Small lymphocytic lymphoma (SLL) is a condition possessing similar characteristics but without lymphocytosis and is essentially a variant of the same underlying disorder as CLL. Clinically, these similar pathologies constitute one distinct disease collectively referred to as CLL hereafter (Muller-Hermelink 2001).

Clinical presentation, diagnosis and stage/prognosis

An exponential increase in the incidence of CLL with age is observed; the median age at diagnosis is 72 years of age (Molica 2013).

Diagnosis requires the presence of ≥5000 B-lymphocytes/μL in the peripheral blood (Hallek 2013). It is the most common form of adult leukemia in the Western world; worldwide, there are approximately 191,000 cases and 61,000 deaths per year attributed to CLL (Global Burden of Disease Cancer Collaboration 2017).

The clinical course for CLL is associated with diminished bone marrow function, which is a hallmark of leukemia. Assessment of newly diagnosed patients for deletion of the short arm of chromosome 17 (del 17p), del 11q, mutated TP53, and IGHV mutational status has prognostic and predictive value; specifically shorter PFS and OS have been reported in patients with high-risk genomic features when treated with conventional chemoimmunotherapy regimens that include alkylating drugs or purine analogues (Bulian 2012; Byrd 2006; Fink 2013; Zenz 2012). In particular, patients with the del 17p abnormality have an increased risk of relapse and death; the median life expectancy is 2 to 3 years from first-line treatment (Eichhorst 2011; Ghielmini 2013; Stilgenbauer 2010). The recently updated 2018 International Workshop on CLL (iwCLL) guidelines (Hallek 2018) emphasize the importance of testing for these high-risk genomic features, and results should guide therapeutic decisions in clinical practice (Hallek 2018; Kipps 2017).

Management

A representative summary of first-line treatments approved for patients with CLL in the EU is shown in Table 1. Approved agents from 4 different classes are available for the frontline treatment of patients with CLL; these include tyrosine-kinase inhibitors (eg, ibrutinib), alkylating agents (eg, chlorambucil, bendamustine, cyclophosphamide), nucleoside analogs (eg, fludarabine), and anti-CD20 monoclonal antibodies (eg, rituximab, obinutuzumab).

For any given patient, an overall goal for initial therapy is to achieve a robust clinical response while minimizing toxicities of treatment. The choice of therapy in CLL is dependent on the patient's physical ability to tolerate chemo-intensive regimens (patient age, fitness, comorbid conditions, and performance status are taken into consideration) and the presence of disease prognostic factors, such as chromosomal abnormalities, eg, 17p and 11q deletions (Eichhorst 2011; Eichhorst 2015; National Comprehensive Cancer Network [NCCN] 2019; Hallek 2018). Treatment guidelines from the European Society for 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 detection of del 17p or mutated TP53 (Eichhorst 2015; ESMO Guidelines Committee 2017).

Chemoimmunotherapies (CIT; combinations of chemotherapy and anti-CD20 agents) are a mainstay of treatment for frontline CLL (Eichhorst 2015; ESMO Guidelines Committee 2017; NCCN 2019). Fludarabine, cyclophosphamide, and rituximab (FCR) is the most effective CIT treatment, however it is associated with a high rate of hematologic toxicities, and therefore its use is limited to younger, fitter patients without comorbidities (ESMO Guidelines Committee 2017; NCCN 2019; Hallek 2010; Keating 2005; Robak 2018). Phase 3 data from the CLL8 trial established FCR as the standard first-line therapy for young, fit patients with CLL (Hallek 2010). Subjects received a mean 5.2 (range, 0-6) cycles of FCR; of patients receiving study treatment, 26% did not receive the planned 6 cycles of FCR. With a median time on study of 5.9 years, median PFS was 56.8 months. Approximately 25% of patients were unable to tolerate FCR-based CIT, with 56% of patients experiencing Grade 3 to 4 hematological toxicities, 25% experiencing Grade 3 to 4 infections, and 47% requiring dose reductions of any of the 3 drugs by more than 10% (Fischer 2016; Hallek 2010).

By contrast, of the recommended multi-agent CIT regimens, the alkylating-agent based regimens, bendamustine plus rituximab (BR) and 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 Guidelines Committee 2017; NCCN 2019). A need remains for chemotherapy-free treatment options in frontline CLL with demonstrated greater efficacy and acceptable safety profile.

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 historically were few frontline treatment options available with favorable outcomes and the guidelines recommend ibrutinib-based therapy in these high-risk CLL patients (ESMO Guidelines Committee 2017; NCCN, Version 1.2020). 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 United States (US), EU, and globally as well as the approval in the EU of ibrutinib in the first-line treatment of CLL in patients with del 17 p/mutated TP53 who are not suited for CIT (IMBRUVICA SmPC October 2014). Subsequently, Phase 3 data from Study 1115 led to approvals in patients with previously untreated CLL (see SmPC).

The recently updated 2018 iwCLL guidelines (Hallek 2018) and NCCN guidelines (NCCN 2019), 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 (PFS) 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). Providing patients who have these high-risk genomic features with effective therapy options remains an ongoing medical need.

When historically poor prognostic genomic factors were examined in ibrutinib-treated patients in Study 1112, Study CLL3001, and Study 1115/1116, these factors did not confer the same adverse prognosis for PFS (Kipps 2019). Recent results from Study 1130 validated this and demonstrated a PFS benefit in a high-risk population of subjects with del 17p/TP53 mutation, del 11q, or unmutated IGHV treated with Ibr+Ob as compared to Clb+Ob (IMBRUVICA SmPC August 2019; Moreno 2019). As a result of these positive data for patients of any age or comorbidity with newly diagnosed CLL/SLL with del 17p/TP53 mutation, CIT regimens are no longer recommended (ESMO Guidelines Committee 2017; NCCN Version 1.2020).

Table 1: Summary of Approved Treatments for First-line Treatment of CLL in the European Union

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
Ibrutinib +obinutuzumab 2019	Previously untreated CLL	Combination	Phase 3/ chlorambucil	229	PFS, ORR, OS
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
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

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
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

CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukemia; DOR: duration of response; FC: fludarabine + cyclophosphamide; N/A: not available; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TP53=tumor-suppressor protein P53 gene.

[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

Comparative Phase 3 data for ibrutinib-based regimens and commonly used CIT regimens Clb+Ob, BR, and FCR have recently been reported and further demonstrate ibrutinib superiority for first-line treatment across the spectrum of patient age and fitness that previously guided choice of CIT. Data from Study 1130 demonstrated superior PFS with Ibr+Ob compared to Clb+Ob in subjects with treatment-naive CLL or SLL (IMBRUVICA SmPC August 2019; Moreno 2019). Based on these data, together with the results from Studies E1912 (Shanafelt 2019), and Alliance 041202 (Woyach 2018) demonstrating superior outcomes with ibrutinib-based treatment versus FCR and versus BR, respectively, ibrutinib is a preferred treatment regimen for all newly diagnosed patients with CLL/SLL regardless of age, fitness or comorbidities (ESMO Guidelines Committee 2017; NCCN Version 1.2020). For newly diagnosed CLL/SLL without del 17p/TP53 mutation, preferred regimens for treatment of older patients with significant comorbidities are ibrutinib (Category 1) and the BCL2 inhibitor-based regimen venetoclax plus obinutuzumab (Category 2A), whereas previously the BR or Clb+Ob regimens were preferred options. By contrast, for younger patients without significant comorbidities with the same CLL characteristics, ibrutinib is currently the only preferred regimen, whereas previously the FCR regimen was preferred. Because FCR is not a recommended treatment for subjects with del 17p due to the poor response of these patients to FCR (ESMO Guidelines Committee 2017; NCCN Version 1.2020; NCCN Version 1.2014), subjects with del 17p CLL were excluded from Study E1912, in which FCR was the comparator.

Study E1912 was conducted to evaluate whether treatment with ibrutinib in combination with rituximab would prolong PFS compared to the most effective CIT available, FCR, in patients ≤70 years of age with CLL, addressing the need for highly effective, chemotherapy-free therapies with greater efficacy and acceptable safety for this population.

2.1.2. About the product

Ibrutinib is a small molecule BTK inhibitor currently approved as a single agent (European Commission Decision 26 May 2016) or in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL (European Commission Decision 02 August 2019), and as a single agent or in combination with bendamustine and rituximab for the treatment of adult patients with CLL who received at least one prior therapy (European Commission Decision 25 August 2016).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific advice was not requested; Study E1912 was led by the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG ACRIN).

2.2. Non-clinical aspects

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

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. The MAH has provided a justification statement for not submitting an ERA. The proposed modification of the existing ibrutinib CLL indication does not extend the target patient population, and therefore there is no increase in environmental exposure versus the existing approved CLL indications. The justification provided is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Table 1: Description of Efficacy Studies in Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Study	Study Design	Study Population	Endpoints	Region	Number of Subjects	Median Time on Study
E1912	Phase 3, randomized, multicenter, open-label, safety and efficacy study of 420 mg/day Ibr+R compared to FCR.	Treatment-naive CLL/SLL ≥18 and ≤70 years ECOG 0-2 No del 17p	Primary: PFS per ECOG-ACRIN case evaluation. Secondary: OS, PFS in high-risk population (TP53 mutation, del 11q, or unmutated IGHV) per ECOG-ACRIN case evaluation; change in FACT-Leu TOI score at 12 months after beginning of therapy, ORR per investigator assessment.	US	Randomized: 529 (354 Ibr+R, 175 FCR)	36.6 months
1130	Phase 3, randomized, multicenter, international, open-label, safety and efficacy study of 420 mg/day Ibr+Ob compared to Clb+Ob.	Treatment-naive CLL/SLL ≥18 years of age ECOG 0-2 Included del 17p	Primary: IRC-assessed PFS. Secondary: IRC-assessed PFS for high-risk subpopulation (ie, del 17p/TP53 mutation or del 11q), ORR per IRC assessment, rate of MRD-negative response, OS, rate of sustained hemoglobin improvement, rate of sustained platelet improvement, rate of infusion-related reactions, rate of clinically meaningful improvement in EQ-5D-5L utility score. An additional analysis for IRC-assessed PFS was performed in the high-risk population (ie, del 17p/TP53 mutation, del 11q, or unmutated IGHV).	US, Europe, Canada, Australia, Other	Randomized: 229 (113 Ibr+Ob, 116 Clb+Ob)	31.3 months
1115	Phase 3, randomized, multicenter, international, open-label, safety and efficacy study of 420 mg/day ibrutinib compared to chlorambucil.	Treatment-naive CLL/SLL ≥65 years of age ECOG 0-2 No del 17p	Primary: IRC-assessed PFS. Secondary: IRC-assessed ORR, OS, IRC-assessed EFS, sustained hematological improvement (rate of sustained platelet improvement, rate of sustained hemoglobin improvement), rate of MRD-negative responses, improvement in fatigue as measured by FACIT-Fatigue	US, Europe, Canada, Australia, Other	Randomized: 269 (136 ibrutinib, 133 chlorambucil)	18.4 months

1115/1116[a]	Phase 3, randomized, multicenter, international, open-label, safety and efficacy study of 420 mg/day ibrutinib compared to chlorambucil.	Treatment-naive CLL/SLL ≥65 years of age ECOG 0-2 No del 17p	Efficacy evaluations included investigator assessment of both PFS and ORR	US, Europe, Canada, Australia, Other	Randomized: 269 (136 ibrutinib, 133 chlorambucil)	48.1 months

Clb+Ob=chlorambucil+obinutuzumab; CLL=chronic lymphocytic leukemia; del 11q=deletion of long arm of chromosome 11; del 17p=deletion in the short arm of chromosome 17; ECOG-ACRIN=Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; EFS=event-free survival; EQ-5D-5L=EuroQoL, 5-dimension, 5-level, health-related quality of life questionnaire; FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-Leu=Functional Assessment of Cancer Therapy–Leukemia; FCR=fludarabine, cyclophosphamide, and rituximab; Ibr+Ob=ibrutinib + obinutuzumab; Ibr+R=ibrutinib + rituximab; IGHV=immunoglobulin heavy chain variable region; IRC=independent review committee; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; SLL=small lymphocytic lymphoma; TOI=Trial Outcome Index; TP53=tumor-suppressor protein 53 gene; US=United States

[a] Long-term efficacy data for this study were obtained from Study 1115 and its extension study 1116. Study 1115/1116 is the source for long-term efficacy data (ie, PFS and OS landmark estimates) in Section 5.

2.3.2. Pharmacokinetics

No new information on Clinical Pharmacology was provided.

2.3.3. Discussion on clinical pharmacology

Per the protocol, Study E1912 did not collect pharmacokinetic information; therefore, a Clinical Pharmacology package is not provided for this submission. In prior studies, ibrutinib exposures were consistent in subjects with various B-cell malignancies receiving ibrutinib monotherapy or ibrutinib in combination with anti-CD20 agents or chemo-immunotherapy regimens. Reference is made to prior information on ibrutinib in combination with rituximab from Study 1127, which showed that subjects with WM treated with ibrutinib at a dose of 420 mg/day as monotherapy or in combination with rituximab 375 mg/m2 had similar exposures, and the exposures were consistent with those previously observed in subjects with other B-cell malignancies treated with ibrutinib at the same dose of 420 mg/day. In Study 1127, in subjects with WM receiving ibrutinib as monotherapy without concomitant use of CYP3A inhibitors, the mean steady-state maximum observed drug concentration (Cmax) was 94.9 ng/mL and the mean area under the concentration time curve (AUC) from 0 to the last quantifiable concentration (AUClast) was 620 ng.h/mL. The coefficient of variation (CV) was 80.2% for Cmax and 68.5% for AUClast. In the same study, in subjects with WM receiving ibrutinib in combination with rituximab, the mean Cmax was 116 ng/mL and AUClast was 743 ng.h/mL. The CV was 89.8% for Cmax and 72.9% for AUClast.

Similarly, in subjects with CLL/SLL receiving 420 mg/day Ibr+Ob in Study 1130 and in combination with BR in Study CLL3001, the exposures were consistent with those previously observed for ibrutinib monotherapy in other B-cell malignancies.

This approach is acceptable since the PK profile of ibrutinib has previously been studied in the CLL population. The combination with rituximab has been studied in the WM population and no PK interaction between the two substances was detected.

2.4. Clinical efficacy

2.4.1. Main study

Key efficacy and safety data to support the Type II variation to extend the current authorized indication in CLL are derived from the Phase 3 randomized, controlled Study E1912 (Ibr+R versus FCR) (Table 2).

Table 2: Description of Study E1912

Study	Study Design	Study Population	Endpoints	Region	Number of Subjects	Median Time on Study
E1912	Phase 3, randomized, multicenter, open-label, safety and efficacy study of 420 mg/day Ibr+R compared to FCR.	Treatment-naive CLL/SLL ≥18 and ≤70 years ECOG 0-2 No del 17p	Primary: PFS per ECOG-ACRIN case evaluation. Secondary: OS; PFS in high-risk population (TP53 mutation, del 11q, or unmutated IGHV) per ECOG-ACRIN case evaluation; change in FACT-Leu TOI score at 12 months after beginning of therapy; ORR per investigator assessment.	US	Randomized: 529 (354 Ibr+R, 175 FCR)	36.6 months

CLL: chronic lymphocytic leukemia; del 11q: deletion of long arm of chromosome 11; del 17p: deletion of short arm of chromosome 17; ECOG- ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FACT-Leu: Function Assessment of Cancer Therapy□Leukemia; FCR: fludarabine plus cyclophosphamide plus rituximab; Ibr+R: ibrutinib plus rituximab; IGHV: immunoglobulin heavy chain variable region; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; SLL: small lymphocytic lymphoma; TOI: Trial Outcome Index; US: United States

Title: A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL).

General design: Study E1912 was a randomized, open-label, Phase 3 study designed to evaluate the efficacy and safety of ibrutinib plus rituximab (Ibr+R) vs. FCR for previously untreated subjects with CLL age 70 years or younger. Subjects were randomized in a 2:1 ratio to receive Ibr+R (Arm A) or FCR (Arm B), respectively. Randomization was stratified according to age (< 60 years vs. ≥ 60 years), ECOG performance status (0/1 vs. 2), disease stage (Rai stage I/II vs. III/IV), and baseline cytogenetic abnormalities (deletion of the long arm of chromosome 11 [del 11q] vs. other). Subjects in the Ibr+R arm received ibrutinib in combination with 6 cycles of rituximab (after a single cycle of ibrutinib alone) followed by ibrutinib until disease progression. Subjects in the FCR arm received 6 cycles of FCR.

Study Period: 10 March 2014 (first subject enrolled) to 17 July 2018 (data cutoff for primary analysis).

Region: At the time of the data cutoff for primary analysis, there were 201 sites across the United States.

Methods

Study participants

Key eligibility criteria

3.1.1 Diagnosis of CLL according to the NCI/IWCLL criteria or SLL according to the WHO criteria.

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma

  OR

- Diagnosis of CLL according to the NCI/IWCLL criteria as evidenced by <u>all</u> of the following:
  - Peripheral blood lymphocyte count of greater than 5 x10^9/L
  - Immunophenotype consistent with CLL defined as:
    - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc).
    - Clonality as evidenced by κ or λ light chain restriction (typically dim immunoglobulin expression)
- Negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy (e.g. marrow aspirate) <u>or</u> negative immunohistochemical stains for cyclin D1 staining on involved tissue biopsy (e.g. marrow aspirate or lymph node biopsy.

3.1.2 No prior chemotherapy, BTK inhibitor therapy, or monoclonal antibody therapy for treatment of CLL or SLL

3.1.3 Has met **at least one** of the following indications for treatment:

- Evidence of progressive marrow failure as manifested by the development of worsening anemia (Hg < 11 g/dl) and/or thrombocytopenia (Platelets < 100 x 10^9/L)
- Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly.
- One or more of the following disease-related symptoms:
  - Weight loss ≥ 10% within the previous 6 months
  - Grade 2 or 3 fatigue attributed to CLL
  - Fevers >100.5ºF for 2 weeks without evidence of infection
  - Clinically significant night sweats without evidence of infection
- Progressive lymphocytosis (not due to the effects of corticosteroids) with an increase of >50% over a two-month period or an anticipated doubling time of less than six months.

3.1.4 Age ≥ 18 years and ≤ 70

3.1.5 ECOG performance status between 0-2.

3.1.6 Life expectancy of ≥ 12 months

3.1.7 Ability to tolerate FCR based therapy

3.1.8 No deletion of 17p13 on cytogenetic analysis by FISH

3.1.9 The following laboratory values obtained </= 14 days prior to registration:

_____ Glomerular filtration rate (GFR) > 40 mL/minute as calculated by the Cockcroft-Gault Formula:

3.1.10 No active hemolytic anemia requiring immunosuppressive therapy or other pharmacologic treatment. Patients who have a positive Coombs test but no evidence of hemolysis are NOT excluded from participation.

3.1.11 No current use of corticosteroids. EXCEPTION: Low doses of steroids (< 10 mg of prednisone or equivalent dose of other steroid) used for treatment of non-hematologic medical condition (e.g. chronic adrenal insufficiency) is permitted.

3.1.18 Patients must not have any of the following conditions:

- Congestive heart failure or New York Heart Association Functional Classification III or IV congestive heart failure
- History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration.
- Recent infections requiring systemic treatment; need to have completed anti-biotic therapy >14 days before the first dose of study drug.
- Cerebral vascular accident or intracranial bleed within the last 6 months
- Infection with known chronic, active hepatitis C.
- Serologic status reflecting active hepatitis B or C infection. Patients that are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) prior to enrollment (PCR positive patients will be excluded).

3.1.19 Patients are not eligible if they require treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix VIII). For additional information regarding use of moderate CYP3A4/5 inhibitors

3.1.21 Patients may not have received warfarin or another vitamin K antagonist in the preceding 30 days.

Genetic testing

Subjects were tested for del 11q and consenting subjects were tested for the TP53 and IGHV mutational statuses. Prior to registration, del 11q was analyzed by local laboratories and used for stratification. Analyses of TP53 and IGHV mutational statuses were performed by a central laboratory (Mayo Clinic) after registration. Patients with del 17p (assessed by local laboratories prior to registration) were excluded because of the poor outcome of these patients to FCR.

Treatments

Patients in the Ibr+R arm received ibrutinib 420 mg orally daily in combination with 6 cycles of rituximab after a single cycle of ibrutinib alone followed by ibrutinib until disease progression. Subjects in the FCR arm received 6 cycles of FCR.

Ibr+R Arm (App1, Protocol Amendment 8, Sec5.1.1)

- Ibrutinib: 420 mg orally daily of Cycles 1-7, and 420 mg daily after Cycle 7 until disease progression
- Rituximab: 50 mg/m^2 intravenous (IV) Day 1 of Cycle 2, 325 mg/m^2 Day 2 of Cycle 2, and 500 mg/m^2 Day 1 of Cycles 3-7

FCR Arm (App1, Protocol Amendment 8, Sec5.1.3)

- Rituximab: 50 mg/m^2 IV Day 1 of Cycle 1, 325 mg/m^2 Day 2 of Cycle 1, and 500 mg/m^2 Day 1 of Cycles 2-6
- Fludarabine: 25 mg/m^2 IV Days 1, 2 and 3 of Cycles 1-6
- Cyclophosphamide: 250 mg/m^2 IV Days 1, 2, and 3 of Cycles 1-6

Each cycle was 28 days.

Outcomes/endpoints

The primary endpoint is investigator-assessed progression -free survival (PFS) per protocol IWCLL criteria.

Secondary endpoints were: Overall Survival (OS); PFS assessed by investigator in high risk population (del11q/mutated TP53/ unmutated IGHV); QoL assessed as change in FACT-Leu Trial Outcome Index (TOI) Score at 12 Months; Overall response rate (ORR) as assessed by investigator per protocol criteria.

Exploratory endpoints were QoL assessed as change in FACT-Leu TOI Score at 3 months after beginning of therapy; QoL assessed as change in FACT-Leu TOI Score at 6 months after beginning of therapy.

Response criteria were all in accordance with the 2008 iwCLL criteria (Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Hallek 2013; Hallek 2012). Response and progression were assessed by the investigator and confirmed by ECOG-ACRIN case evaluation which included Operations Office (ECOG-ACRIN data management team) and Study Chair review. Any cases requiring adjudication (cases in which the Operations Office/Study Chair disagreed with the investigator, or the Operations Office and Study Chair disagreed with one another) were sent to the designated ECOG-ACRIN Executive Officer for disease progression determination in alignment with the protocol and iwCLL 2008 response criteria.

7. Study Parameters

Rev. 7/14, 8/15

7.1 Therapeutic Parameters

1. Prestudy scans or x-rays used to document measurable or evaluable disease must be done within 2 weeks of registration.
2. Prestudy CBC with differential, LFTs must be done ≤ 2 weeks before registration.
3. All required prestudy chemistries must be done ≤ 2 weeks before registration - unless specifically required on Day 1 as per protocol. If abnormal, they must be repeated within 48 hours prior to registration.

Rev. 3/14, 7/14, 11/16

	Active Monitoring Phase						
Tests/Procedures	**Pre-treatment**	**During Treatment[14]**			**12 Month Response Evaluation**	**Continuation[17]**	**Follow Up[15]**
	≤ 14 days prior to registration	Day 1 of Cycles 1-6 (+/- 4 days) [19]	Prior cycle 7 (arm A) or End of Cycle 6 (arm B) (+/- 4 days)	3 months after end of cycle 6 (+/- 7 days)	52 weeks after Day 1 of cycle 1 (+/- 4 weeks)	Every 90 days (+/- 14 days)	
Tests & Observations							
History and progress note[14]	X	X[18]	X	X	X	X	X
Performance status[14]	X	X[18]	X	X	X	X	
Height	X						
Weight/Body Surface Area[1]	X	X			X		
Physical examination[14]	X	X[18]	X	X	X	X	X
Tumor measurement by physical exam[14]	X[2]	X[2, 18]	X[2]	X[2]	X[2]	X[2]	X[2]
Drug toxicity measurement [14]	X	X[18]	X	X	X	X	
Comorbidity Index	X[3]						
Timed Up and Go (TUG) Test[13]	X						
Laboratory Studies							
CBC with differential[5,14]	X	X[4]	X[4]	X	X	X	X
Serum creatinine and creatinine clearance[16]	X	X[5]					
Uric acid, potassium, phosphate, LDH, Ca+	X	X[5]					
AST, ALT, total bilirubin, alkaline phosphatase[14]	X	X	X	X	X	X	
Peripheral blood immunophenotyping by flow cytometry on peripheral blood or bone marrow[7]	X						
Serum pregnancy test	X[6]						
CLL FISH panel (on peripheral blood or bone marrow aspirate)	X[7]						
Bone marrow aspirate and biopsy[14]	X[8]				X[8]		
Beta-2-microglobulin[14]	X				X		
PT/INR, PTT (aPTT)	X						
Quantitative Immunoglobulins (IgG, IgA, IgM) [14]	X				X		
Hepatitis B (HB) surface antigen, surface Ab and core Ab testing;	X[9]						
Hepatitis C Anti-body testing	X[11]						
Direct Coombs test	X						
CT scan chest, abdomen, pelvis[12]	X				X		
Biological Sample Submissions	See Section 7.2						
QOL Questionnaires[10, 14]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]

Rev. 1/16

Footnotes for Test Schedule

1. Drug doses need not be changed unless the calculated dose changes by >10%
2. Physical exam must measure the spleen and liver noting the maximal distance below the respective costal margins at rest in the mid-clavicular line and must record the bidimensional diameter of the largest palpable node in each lymph node area of involvement including the following 6 sites: cervical/supra-clavicular (right and left) axillary (right and left), inguinal (right and left).
3. Cumulative illness rating scale – see Appendix VII (JCO 16: 1582–1587).
4. For cycle 1, patients with pretreatment platelet counts < $20x10^9$/L, should have a CBC repeated on Day 3. If this platelet count is below $20x10^9$/L, the responsible physician should be contacted and platelets should be transfused, if clinically indicated. As treatment with anti-CD20 monoclonal anti-bodies may result in acute but temporary reduction in platelets, patients with baseline platelet counts < $50x10^9$/L prior to receiving rituximab should have platelet counts repeated after the rituximab infusion is ended to see if platelet transfusion is necessary.
5. In Arm B patients, all tests noted should be collected prior to treatment on Day 2 of Cycle 1 to monitor for tumor lysis.

Rev. 11/16

6. For women of childbearing potential only. Must be done ≤ 14 days prior to registration.
7. Must be done ≤ 3 months prior to registration. It is acceptable for FISH to be performed on either peripheral blood or bone marrow tissue.

Rev. 7/14

8. Bone marrow biopsy is required. If the patient has had a bone marrow biopsy obtained for clinical purposes ≤ 3 months prior to registration this can be used for baseline purposes and a repeat is not required provided slides from this clinical bone marrow can be submitted. At time of response evaluation a bone marrow biopsy is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression. Bone marrow slides for central review must be submitted as outlined in Section 10.
9. All patients must be screened for hepatitis B infection before starting treatment. Those patients who test positive for hepatitis B are ineligible. Tests must be done ≤ 4 weeks prior to registration. See Section 3.1.18.

Rev. 7/14	10. Quality of life will be evaluated at baseline, after the first 3 cycles of therapy; after 6 cycles of therapy; at the time of the 12 month response evaluation, and then every 6 months for 2 years regardless of whether or not the patient progresses. QOL will also be assessed at the time the patient progresses
	11. If Hepatitis C anti-body testing is positive, PCR to evaluate active Hepatitis C. Patients with active Hepatitis C are ineligible (see Section 3.1.17). Tests must be done ≤ 4 weeks prior to registration.
	12. Baseline CT scan requirement can be waived if the patient has had a CT scan ≤ 4 weeks prior to registration. In such cases, the clinical CT scan obtained within the last 4 weeks may serve as the baseline CT scan for measurement purposes. At time of response evaluation CT scan of the chest, abdomen and pelvis is required for all patients with evidence of response (CR, PR) or stable disease but is not required for those with disease progression.
	13. Please see Appendix X for instructions for the Timed Up and Go (TUG) Test.
Rev. 3/14, Rev. 11/16	14. If patient comes off treatment due to any reason other than progression or completion of treatment per protocol (Arm B), please complete all of the noted tests/procedures with 2 weeks in lieu of a 12 Month Response Evaluation.
Rev. 3/14	15. Every 3 months (90 days) until progression. After progression, patient will switch to standard follow-up schedule: every 3 months for first 2 years, every 6 months for years 3-5, and then every 12 months for years 6-10.
Rev. 7/14	16. Creatinine clearance as estimated by the Cockcroft-Gault equation. See Section 3.1.9
	17. All patients on Arm A currently taking Ibrutinib
	18. If pre-registration value is < 21 days from treatment start date, test does not need to be repeated on day 1 cycle 1.
	19. Laboratories required on day 1 of cycles 1-6 of Arm B should be collected prior to start of chemotherapy. For patients on Arm A, these laboratories should be collected prior to the start of rituximab.

Subjects were re-evaluated for progression every 4 weeks (+/-10 days) during the first 6 months of the study by physical exam and complete blood count (CBC), and thereafter every 3 months until progression. After progression, the follow-up schedule was every 3 months for the first 2 years, every 6 months for years 3-5, and then every 12 months for years 6-10.

Formal response evaluation occurred at the 12-month response evaluation (or off study evaluation). Computed tomography (CT) scans at baseline, and at 12 months for all subjects with evidence of response or stable disease were required, but not required for those with disease progression. At the time of the 12-month response evaluation, a bone marrow biopsy was required for all subjects with evidence of response or stable disease but was not required for those with disease progression.

Assessment of progressive disease was based on ALC, physical examination of lymphadenopathy and hepatosplenomegaly, or by both ALC and physical examination (ie, CT scans were not used to determine disease progression) and was confirmed by ECOG-ACRIN case evaluation, which included Operations Office (ECOG-ACRIN data management team) and study chair review.

The rates of progression by physical examination only (as opposed to ALC only or both physical examination and ALC) were monitored by the DSMC every 6 months for potential bias in assessment of progression by physical exam. If the difference in proportion of progression assessed by physical examination only between the arms was larger than the greater of 10 subjects or 20%, the study team would assess possible changes to the criteria for progression for those subjects where progression was based solely on physical examination.

Unscheduled CT Scans: Since this is an open label trial, it is possible that an imbalance in unscheduled CT scans could emerge between arms and influence assessment of disease progression. To address this issue, all unscheduled CT scans performed on both arms as well as the reason for unscheduled CT scans will be recorded. This information will be collected to identify differences in the frequency of such unscheduled CT scans between arms and allow us to detect potential bias in ascertainment of disease progression.

Sample size

This study was designed to evaluate the effect of treatment on PFS as the primary endpoint and was powered for this endpoint. The sample size of 519 subjects was determined based on the following assumptions: PFS is exponentially distributed; 2:1 randomization between the 2 arms; Median PFS is 78 months in treatment arm (Arm A: Ibr+R); Median PFS is 52 months in control arm (Arm B: FCR); Target HR of 0.67 (Arm A vs. Arm B); Two-sided alpha of 0.05.

With the above study assumptions, the study with a total of 203 PFS events would achieve an overall power of 80%. Additionally, assuming the time to 25% of FCR subjects dying was 62.5 months in the

control arm, a total of 125 OS events among 519 subjects would provide for 80% power to detect a target HR of 0.60 (Arm A vs. Arm B) at a 2-sided level of significance of 0.05. This sample size would also allow the study to detect a range of 4.9 to 9.4 in the difference in mean Functional Assessment of Cancer Therapy – Leukemia Trial Outcome Index (FACTLeu TOI) score between the 2 arms with an 80% power at a 2-sided alpha of 0.05, assuming a 50% to 80% compliance rate.

Randomisation and Blinding (masking)

This was an open-label study; no blinding was performed nor deemed feasible given that FCR is administered via IV infusion and ibrutinib is administered orally.

Subjects were randomized in a 2:1 ratio to receive Ibr+R (Arm A) or FCR (Arm B), respectively, using permuted blocks with stratification and dynamic balancing on main institutions. The stratification factors were age (< 60 vs. ≥ 60 years), ECOG performance status (0/1 vs. 2), disease stage (Rai stage I/II vs. III/IV), and baseline cytogenetic abnormalities (del 11q vs. other). Randomization was implemented using Interactive Web Response System (IWRS) operated by ECOG-ACRIN through its Patient Registration System.

Statistical methods

Interim analysis

The interim analysis was performed only after all subjects had the opportunity for at least 2 years (and up to 52 months) of follow-up.

As described in the study protocol and the SAP, prespecified interim analyses for PFS were planned to start at 24 to 27 months after full accrual and continue annually until either the efficacy boundary was crossed or full information (203 PFS events) was reached. The prespecified boundary proposed by CTEP for the first PFS interim analysis was 2.807 on the z-statistics scale, corresponding to a 1-sided p-value of 0.0025 (or 2-sided p-value of 0.005). Nevertheless, the upper boundary for the final analysis was to be determined using the Lan-DeMets error spending function to preserve the overall type-I error rate.

If the primary endpoint PFS achieved statistical significance at an interim analysis, then final analysis for PFS was reached. Interim analyses for OS (first secondary endpoint) were to start when the superiority boundary for PFS was crossed and continue annually until early stopping criteria were met or full information (125 deaths) was reached. For earlier information time, a prespecified truncated version (1-sided p-value of 0.0005 or 2-sided p-value of 0.001) of the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary was to be used.

Per the SAP, if both PFS and OS crossed the prespecified superiority boundaries at an interim analysis, subsequent test of secondary endpoints (PFS in high-risk population, change in FACT-Leu TOI at 12 months, and overall response rate [ORR]) were to be performed at a 2-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure. Secondary endpoints were to be ranked in sequence according to the hierarchical order shown in the Study endpoint table below.

The first interim analysis performed by ECOG-ACRIN, based on a data cutoff of 17 July 2018, crossed the prespecified superiority boundary for the primary endpoint of PFS—the hazard ratio (HR) for PFS favored Ibr+R over FCR—and the Applicant as well as the sites were notified of the results, which were subsequently published. This application is based on an independent analysis by the Applicant with the same 17 July 2018 data cutoff (25 months after full accrual). The data were subject to ongoing study oversight including additional monitoring, with the analysis based on data extracted and transferred

from ECOG-ACRIN to the Applicant on 02 August 2019. The planned analyses, including endpoints and analysis methods as presented in the SAP, were finalized prior to data transfer.

Study endpoints

Table 3: Study endpoints

Endpoints	
Primary	PFS per ECOG-ACRIN case evaluation
Secondary (per prespecified hierarchical testing order as outlined in the SAP [App9, Sec1.2.2])	OS, PFS in high-risk population (TP53 mutation, del 11q, or unmutated IGHV) per ECOG-ACRIN case evaluation, change from baseline in FACT-Leu TOI score at 12 months after beginning of therapy, ORR per investigator assessment
Safety Assessments	Safety and tolerability of ibrutinib in combination with rituximab compared with FCR
Exploratory	Change from baseline in FACT-Leu TOI score at 3 and 6 months after beginning of therapy

del 11q: deletion of the long arm of chromosome 11; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FACT-Leu TOI: Functional Assessment of Cancer Therapy – Leukemia Trial Outcome Index; FCR: fludarabine, cyclophosphamide, and rituximab; IGHV: immunoglobulin heavy chain variable region; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; SAP: statistical analysis plan; TP53: tumor-suppressor protein 53 gene
Source: App9, Sec1.2; Sec3.11.5

Analysis populations

The intent-to-treat (ITT) Population includes all subjects randomized into the study, regardless of actual treatment received. The safety population consists of all subjects in the ITT population who received at least one dose of any study treatment.

Analysis methods

Endpoints and analysis methods based on the Applicant's SAP, are summarized in the table below.

Table 4: Endpoints, Definitions, and Analysis Methods

Endpoint	**Definition**	**Analysis Method**
Primary Endpoint		
PFS	Time from the date of randomization to the date of progressive disease per ECOG-ACRIN case evaluation or date of death from any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy prior to documented progressive disease or death. For subjects with baseline and post-baseline response assessments but without progressive disease and are not known to have died at the time of the analysis, PFS was censored at the date of the last evidence of no progression. For subjects without baseline or post-baseline assessments, PFS was censored on the date of randomization.	Primary analysis The treatment effect of Ibr+R compared to FCR was tested with an unstratified log-rank test. The HR and its 95% CI was estimated using an unstratified Cox regression model. KM approach to estimate the median PFS and its 2-sided 95% CI. Sensitivity analyses • PFS per investigator assessment, where PFS event date was the first progressive disease date assessed by investigator per overall response form or date of death due to any cause, whichever occurred first, regardless of the use of subsequent antineoplastic therapy; censoring performed the same as in the primary analysis. • For subjects with ≥2 consecutively missing disease assessments immediately before the first ECOG-ACRIN case evaluation for progressive disease or death, PFS was censored at the last evidence of no progression prior to the period of consecutively missed assessments. Subgroup analysis HR and its 95% CI based on unstratified Cox regression model for each subgroup.

Secondary Endpoints – Efficacy		
OS	Time from the date of randomization to the date of death from any cause. For subjects who were not known to have died at or prior to the clinical cutoff date, the OS was censored on the date last known alive.	Unstratified log-rank test, unstratified Cox regression model. KM analysis. Two-sided 95% CIs for median OS and HR.
PFS in high-risk population	Defined the same as the primary endpoint.	Unstratified log-rank test, unstratified Cox regression model, and KM analysis.
Quality of life: Change from baseline in FACT-Leu TOI score at 12 months after beginning of therapy	Change from baseline in FACT-Leu TOI score at 12 months after beginning of study treatment. FACT-Leu TOI score was calculated according to FACT-Leukemia scoring guidelines.	Change from baseline in FACT-Leu TOI score up to 12 months was analyzed using the mixed effect repeated measures model. The model includes baseline score as a covariate, treatment, time point, and treatment-by-time point interaction as fixed effects, and subjects as random effect. An unstructured (co)variance structure was used to model the within-subject error. Kenward-Roger's approximation was used to estimate denominator degrees of freedom. The treatment effect (Ibr+R vs. FCR) in change score from baseline to 12 months was tested and the 95% CIs was calculated for the least square means.

Endpoint	Definition	Analysis Method
ORR	Proportion of subjects achieving a best overall response of complete response (CR), complete response with an incomplete marrow recovery (CRi), complete clinical response (CCR), nodular partial response (nPR), or partial response (PR) as assessed by investigator per protocol criteria at or prior to initiation of subsequent non-protocol antineoplastic therapy.	ORR was compared (Ibr+R vs. FCR) using the chi-square test.

Results

Table 5: Study Treatment and Study Disposition (Intent-to-Treat Population)

	Ibr+R N=354 n (%)	FCR N=175 n (%)	Total N=529 n (%)
Treatment status			
Did not receive study treatment	2 (0.6)	17 (9.7)	19 (3.6)
Ongoing	277 (78.2)	0	277 (52.4)
Completed	NA	105 (60.0)	105 (19.8)
Discontinued	75 (21.2)	53 (30.3)	128 (24.2)
Primary reason for discontinuation of study treatment			
Disease progression - relapse during active treatment	13 (3.7)	3 (1.7)	16 (3.0)
Starting therapy of non-assigned arm	0	0	0
Adverse event/side effects/complications	38 (10.7)	36 (20.6)	74 (14.0)
Alternative therapy	0	1 (0.6)	1 (0.2)
Patient off-treatment for other complicating disease	3 (0.8)	2 (1.1)	5 (0.9)
Death on study	2 (0.6)	1 (0.6)	3 (0.6)
Patient withdrawal/refusal after beginning protocol therapy	8 (2.3)	9 (5.1)	17 (3.2)
Other	11 (3.1)	1 (0.6)	12 (2.3)
Study disposition			
Subject status			
On study treatment	277 (78.2)	0	277 (52.4)
Off treatment on study follow up	63 (17.8)	132 (75.4)	195 (36.9)
Off study	14 (4.0)	43 (24.6)	57 (10.8)
Primary reason for study termination			
Death	4 (1.1)	10 (5.7)	14 (2.6)
Withdrawal of consent	10 (2.8)	33 (18.9)	43 (8.1)

FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; NA: not applicable
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.
Source: Att1-Table 14.1.1.4, Att1-Table 14.1.1.5

Recruitment

Study Period: 10 March 2014 (first subject enrolled) to 17 July 2018 (data cutoff for primary analysis).

Region: At the time of the data cutoff for primary analysis, there were 201 sites across the United States.

Conduct of the study

Protocol deviations

Study drug administration important protocol deviations

In the Ibr+R arm, 3 subjects had an overall response of disease progression but ibrutinib dosing was continued for a period of time, and 1 subject received 140 mg of ibrutinib daily for Cycles 1-4 and should have received 420 mg daily (App14). In the FCR arm, 1 subject received 700 mg of rituximab on Day 2 of Cycle 1 and should have received 600 mg of rituximab.

Eligibility criteria important protocol deviations

In the Ibr+R arm, 2 subjects did not have FISH analysis completed ≤ 3 months prior to study registration (1 was completed more than 3 months prior to registration and 1 was not done), and 2 subjects with del 17p were enrolled (1 of whom did not receive study drug) (App14). In the FCR arm, 1 subject did not have FISH analysis completed ≤ 3 months prior to study registration (completed more than 3 months prior to registration).

Table 6: Important Protocol deviations (ITT)

Category	Ibr+R N=354 n (%)	FCR N=175 n (%)	Total N=529 n (%)
Total	**8 (2.3)**	**2 (1.1)**	**10 (1.9)**
Study drug administration	4 (1.1)	1 (0.6)	5 (0.9)
Eligibility criteria	4 (1.1)	1 (0.6)	5 (0.9)

FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab

Table 7: Protocol amendments

Amendment No. and Version Date	Key Changes
1 31 January 2014	• Updated language throughout to reflect all salvage therapy treatment • Clarified schedule of assessments to reflect required tests and procedures
2 30 April 2014	• Corrected stratification factor from "11q23" to read "11q22" • Clarified guidelines for management of infusion reactions to rituximab • Corrected cycle numbers for rituximab administration in Arm A • Revised to reflect the change from AdEERS to CTEP-AERS system • Clarified additional collection and submission requirements for biological samples in correlative studies
3 16 June 2015	• Clarified eligibility language for subjects with Hepatitis B • Clarified guidance for determining complete remission • Clarified treatment plan including language for rituximab administration modifications, antibiotic prophylaxis, distribution of ibrutinib, use of alternative antihistamines to reduce infusion reactions • Updated dose modifications and management of toxicity
4 15 January 2016	• Updated language for safety information for ibrutinib, including CAEPR list • Updated eligibility criteria (eligibility measurements for AST/ALT). Inserted requirement for PT/INR, timing of major/minor surgeries, exclusions for patient conditions, use of CYP3A inhibitors, females of childbearing potential • Clarified dose modifications and management of toxicity • Updated language for supportive care • Updated language for concomitant use of CYP-inhibiting/inducing therapies, QT prolonging medications, anti-platelet agents and anti-coagulants • Updated language for reporting requirements for pregnancy and other adverse events list
5 22 August 2016	• Removed language requiring study medication to be permanently discontinued if interrupted for more than 60 days. Changed to make 42-day interruption the maximum. • Updated language regarding anticoagulation therapy and ibrutinib treatment. • Inserted language regarding ibrutinib and hepatic impairment. • Clarified disease progression requirements. • Updated language regarding ibrutinib use and interactions with CYP3A4 and CYP3A inhibitors. Updated language regarding interactions with supplements such as vitamin E preparations and fish oils. • Updated statistical interim analysis based on faster than expected rate of accrual, from expected interim and final analyses at 60 and 66 months after study activation with upper boundary for first interim analysis of 2.10 to the following: o Interim and final analyses expected to occur at 53 and 63 months after study activation. The upper boundary for the first interim analysis is 2.807, corresponding to 1-sided p-value of 0.0025. The upper boundary for the final analysis will be determined using the Lan-DeMets error spending function to preserve the overall type-I error rate. • Distinguished guidelines for Bone Marrow Smears and Bone Marrow Biopsy Sections/Slides. • Clarified RAI staging is based on physical exam only.
6 01 December 2016	• Updated safety information for ibrutinib, including an updated CAEPR version, and addition of language for Risk Mitigation Plan
7 31 July 2017	• Updated the ibrutinib CAEPR version
8 25 May 2018	• Updated expedited AE reporting via CTEP-AERS to CTCAE v 5.0. Routine AE reporting and dose modification guidelines continued to use CTCAE v 4.0

AdEERS: Adverse Event Expedited Reporting System; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAEPR: Comprehensive Adverse Events and Potential Risks; CTCAE: Common Terminology Criteria for Adverse Events; CTEP-AERS: Cancer Therapy Evaluation Program-Adverse Event Reporting System; CYP: cytochrome P450; PT/INR: prothrombin time/international normalized ratio

Changes in the planned Analyses:

- In the SAP, the primary analysis of PFS was based on investigator assessment, however in the CSR it was based on ECOG-ACRIN case evaluation, for consistency with the interim analysis – and was supported by investigator assessment as a sensitivity analysis.
- Supportive analysis of the DOR was not done.

- Serious TEAEs were not summarised; the CRF was not designed to distinguish serious vs non-serious events.
- TEAEs leading to treatment discontinuation or dose reduction and major haemorrhage TEAEs were summarised for the investigational Arm only.

Baseline data

Table 8: Demographic characteristics (ITT)

	Ibr+R N=354	FCR N=175	Total N=529
Age (years)			
Mean (standard deviation)	56.7 (7.49)	56.7 (7.22)	56.7 (7.40)
Median	58.0	57.0	58.0
Min, Max	31, 70	28, 70	28, 70
Age groups - n (%)			
<60 years	209 (59.0)	105 (60.0)	314 (59.4)
≥60 years	145 (41.0)	70 (40.0)	215 (40.6)
<65 years	311 (87.9)	155 (88.6)	466 (88.1)
≥65 years	43 (12.1)	20 (11.4)	63 (11.9)
Gender - n (%)			
Male	236 (66.7)	120 (68.6)	356 (67.3)
Female	118 (33.3)	55 (31.4)	173 (32.7)
Race - n (%)			
American Indian or Alaska Native	0	1 (0.6)	1 (0.2)
Asian	6 (1.7)	3 (1.7)	9 (1.7)
Black or African American	22 (6.2)	6 (3.4)	28 (5.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	318 (89.8)	160 (91.4)	478 (90.4)
Multiple	0	1 (0.6)	1 (0.2)
Not reported/unknown	8 (2.3)	4 (2.3)	12 (2.3)
Ethnicity - n (%)			
Hispanic or Latino	7 (2.0)	3 (1.7)	10 (1.9)
Not Hispanic or Latino	334 (94.4)	167 (95.4)	501 (94.7)
Not reported/unknown	13 (3.7)	5 (2.9)	18 (3.4)

FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab

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

Table 9: Baseline characteristics (ITT)

	Ibr+R N=354	FCR N=175	Total N=529
Time from initial diagnosis to randomization (months)			
n	353	175	528
Mean (standard deviation)	32.1 (42.81)	32.5 (34.92)	32.2 (40.33)
Median	18.1	22.5	18.9
Min, Max	0.03, 341.8	0.03, 167.5	0.03, 341.8
Indication[a]			
CLL	311 (87.9%)	155 (88.6%)	466 (88.1%)
SLL	43 (12.1%)	20 (11.4%)	63 (11.9%)
Rai stage			
Stage 0/I/II	198 (55.9%)	103 (58.9%)	301 (56.9%)
Stage III/IV	156 (44.1%)	72 (41.1%)	228 (43.1%)
Bulky disease[b]			
≥10 cm	26 (7.3%)	13 (7.4%)	39 (7.4%)
≥5 cm	134 (37.9%)	60 (34.3%)	194 (36.7%)
Cytopenia			
Hemoglobin ≤110 g/L	114 (32.2%)	53 (30.3%)	167 (31.6%)
Platelets ≤100 x 10^9/L	76 (21.5%)	42 (24.0%)	118 (22.3%)
Absolute neutrophil count ≤1.5 x 10^9/L	38 (10.7%)	15 (8.6%)	53 (10.0%)
Any of the above	173 (48.9%)	83 (47.4%)	256 (48.4%)
Baseline ECOG PS per CRF			
0	226 (63.8%)	109 (62.3%)	335 (63.3%)
1	119 (33.6%)	63 (36.0%)	182 (34.4%)
2	9 (2.5%)	3 (1.7%)	12 (2.3%)
Creatinine clearance (mL/min)			
n	352	158	510
Mean (standard deviation)	99.9 (32.22)	106.7 (42.92)	102.0 (35.97)
Median	94.5	98.5	95.8
Min, Max	41.0, 242.1	34.0, 368.2	34.0, 368.2
<30	0	0	0
30 - <60	29 (8.2%)	13 (7.4%)	42 (7.9%)
≥60	323 (91.2%)	145 (82.9%)	468 (88.5%)
Missing	2 (0.6%)	17 (9.7%)	19 (3.6%)
Beta-2 microglobulin (mg/L)			
n	351	175	526
Mean (standard deviation)	4.0 (2.05)	4.0 (1.93)	4.0 (2.01)
Median	3.6	3.4	3.6
Min, Max	1.3, 14.4	1, 13.1	1, 14.4
≤3.5	171 (48.3%)	91 (52.0%)	262 (49.5%)
>3.5	180 (50.8%)	84 (48.0%)	264 (49.9%)
Missing	3 (0.8%)	0	3 (0.6%)

ALC: absolute lymphocyte count; CLL: chronic lymphocytic leukemia; CRF: case report form; CT: computed tomography; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; SLL: small lymphocytic lymphoma

N=number of subjects in the specified population and denominator of percentages.

Baseline is defined as the last measurement taken on or prior to first dose date of study drug or the date of randomization for non-treated subjects.

[a] SLL was identified by ALC <5 x 10^9/L at screening visit.

[b] Bulky disease is based on the largest longest diameter of target lymph node at screening per CT scan.

Table 9 Baseline Genomic Characteristics (Intent-to-Treat Population)

	Ibr+R N=354 n (%)	FCR N=175 n (%)	Total N=529 n (%)
High risk (TP53 mutation, del 11q, or unmutated IGHV)[a]			
Yes	230 (65.0)	83 (47.4)	313 (59.2)
No	124 (35.0)	92 (52.6)	216 (40.8)
TP53			
Mutated	27 (7.6)	4 (2.3)	31 (5.9)
Not mutated	272 (76.8)	130 (74.3)	402 (76.0)
Unknown	55 (15.5)	41 (23.4)	96 (18.1)
Del 11q			
Yes	78 (22.0)	39 (22.3)	117 (22.1)
No	274 (77.4)	136 (77.7)	410 (77.5)
Unknown	2 (0.6)	0	2 (0.4)
IGHV			
Unmutated	210 (59.3)	71 (40.6)	281 (53.1)
Mutated	69 (19.5)	43 (24.6)	112 (21.2)
Unknown	75 (21.2)	61 (34.9)	136 (25.7)

del 11q: deletion of the long arm of chromosome 11; del 17p: deletion of the short arm of chromosome 17; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; IGHV: immunoglobulin heavy chain variable region; TP53: tumor-suppressor protein 53 gene

N=number of subjects in the specified population and denominator of percentages.

Baseline is defined as the last measurement taken on or prior to first dose date of study drug or the date of randomization for non-treated subjects.

[a] 2 subjects with del 17p were enrolled in the Ibr+R arm; both subjects are TP53 mutated and IGHV unmutated. "Yes" includes subjects with ≥1 of the 3 risk factors: TP53 mutation, del 11q, and unmutated IGHV; "No" includes all other subjects.

Numbers analysed

Table 10: Analysis populations (ITT)

	Ibr+R (N=354) n (%)	FCR (N=175) n (%)	Total (N=529) n (%)
ITT Population	354 (100.0)	175 (100.0)	529 (100.0)
Safety Population	352 (99.4)	158 (90.3)	510 (96.4)
Subjects Excluded from Safety Population	2 (0.6)	17 (9.7)	19 (3.6)
Reason for Exclusion (i.e. Withdrawal without study treatment)			
Patient Ineligible	2 (0.6)	0 (0.0)	2 (0.4)
Medical Decision	0 (0.0)	1 (0.6)	1 (0.2)
Starting Therapy of Non-Assigned Arm	0 (0.0)	1 (0.6)	1 (0.2)
Withdrawal by Subject	0 (0.0)	12 (6.9)	12 (2.3)
Other	0 (0.0)	3 (1.7)	3 (0.6)

Outcomes and estimation

The results presented are based on the interim analysis, which crossed the prespecified superiority boundary and therefore is considered the primary analysis for Study E1912 with a data cutoff of 17 July 2018.

The median time on study for the ITT population was 36.6 months overall (range: 0.03 to 52.3 months); 37.7 months (range: 0.03 to 52.3 months) for the Ibr+R arm and 33.7 months (range: 0.1 to 51.4 months) for the FCR arm.

- **Primary endpoint: PFS based on ECOG-ACRIN case evaluation**

At the time of the primary analysis, overall median follow-up was 36.6 months.

Table 11: Progression free survival – primary analysis (ITT)

Progression-free Survival	Ibr+R N=354	FCR N=175	Comparison/Difference Ibr+R vs. FCR
Events - n (%)	41 (11.6)	44 (25.1)	
Disease progression- n	39	38	
Death - n	2	6	
Censored - n (%)	313 (88.4)	131 (74.9)	
Median (months) (95% CI)[a]	NE (49.4, NE)	NE (47.1, NE)	
Min, Max	0.03+, 51.22+	0.03+, 51.32+	
P value[b]			<0.0001
Hazard ratio (95% CI)[c]			0.340 (0.222, 0.522)
Landmark Estimates - % (95% CI)[a]			
6 Months	99.7 (98.0, 100.0)	96.3 (92.0, 98.3)	3.4 (0.4, 6.3)
12 Months	97.4 (95.1, 98.6)	93.2 (88.0, 96.2)	4.3 (0.0, 8.5)
18 Months	96.3 (93.7, 97.8)	86.0 (79.5, 90.6)	10.3 (4.5, 16.0)
24 Months	93.1 (89.8, 95.3)	83.3 (76.5, 88.3)	9.7 (3.3, 16.2)
30 Months	91.0 (87.4, 93.6)	76.9 (69.0, 82.9)	14.2 (6.6, 21.7)
36 Months	88.7 (84.5, 91.8)	70.3 (61.3, 77.6)	18.4 (9.5, 27.3)
42 Months	87.2 (82.5, 90.8)	65.3 (55.2, 73.7)	21.9 (11.7, 32.1)

CI: confidence interval; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; 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.

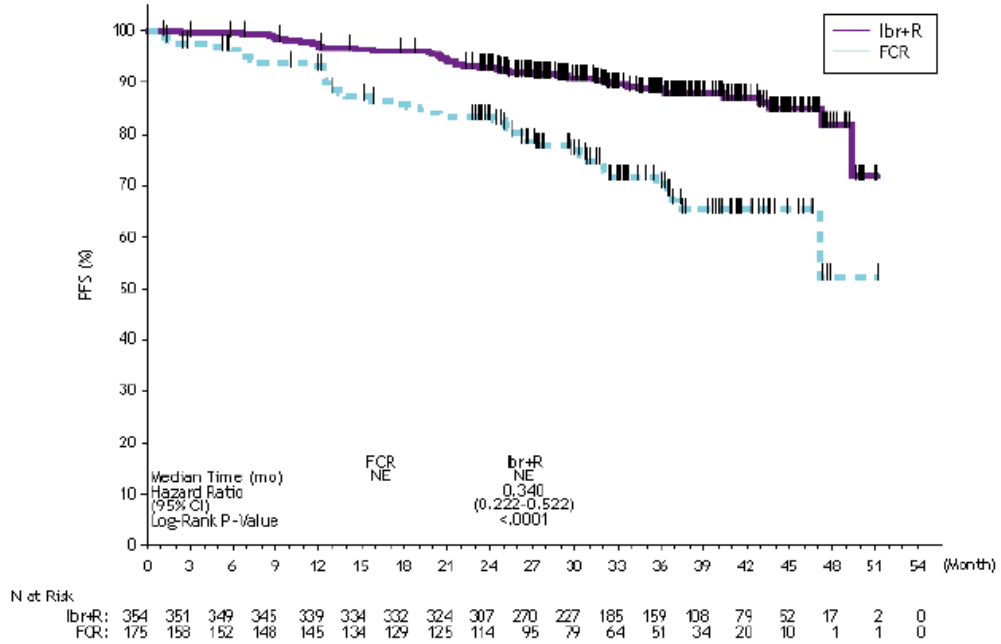
The PFS for primary analysis is based on ECOG-ACRIN case evaluation.

[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.

Figure 1 **Kaplan-Meier Curves of Progression-free Survival – Primary Analysis (Intent-to-Treat Population)**



The PFS is based on ECOG-ACRIN case evaluation.
P-Value is from unstratified log-rank test. Hazard ratio is estimated using unstratified Cox regression model.
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CI: confidence interval; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; NE: not estimable; PFS: progression-free survival

Table 12: Sensitivity analyses for PFS (ITT)

	Ibr+R vs. FCR	
Analysis	**Hazard Ratio (95% CI)[a]**	**P-value[b]**
PFS analysis per investigator assessment	0.330 (0.214, 0.508)	<0.0001
PFS analysis for impact of 2 or more consecutive missed assessments[c]	0.355 (0.230, 0.548)	<0.0001

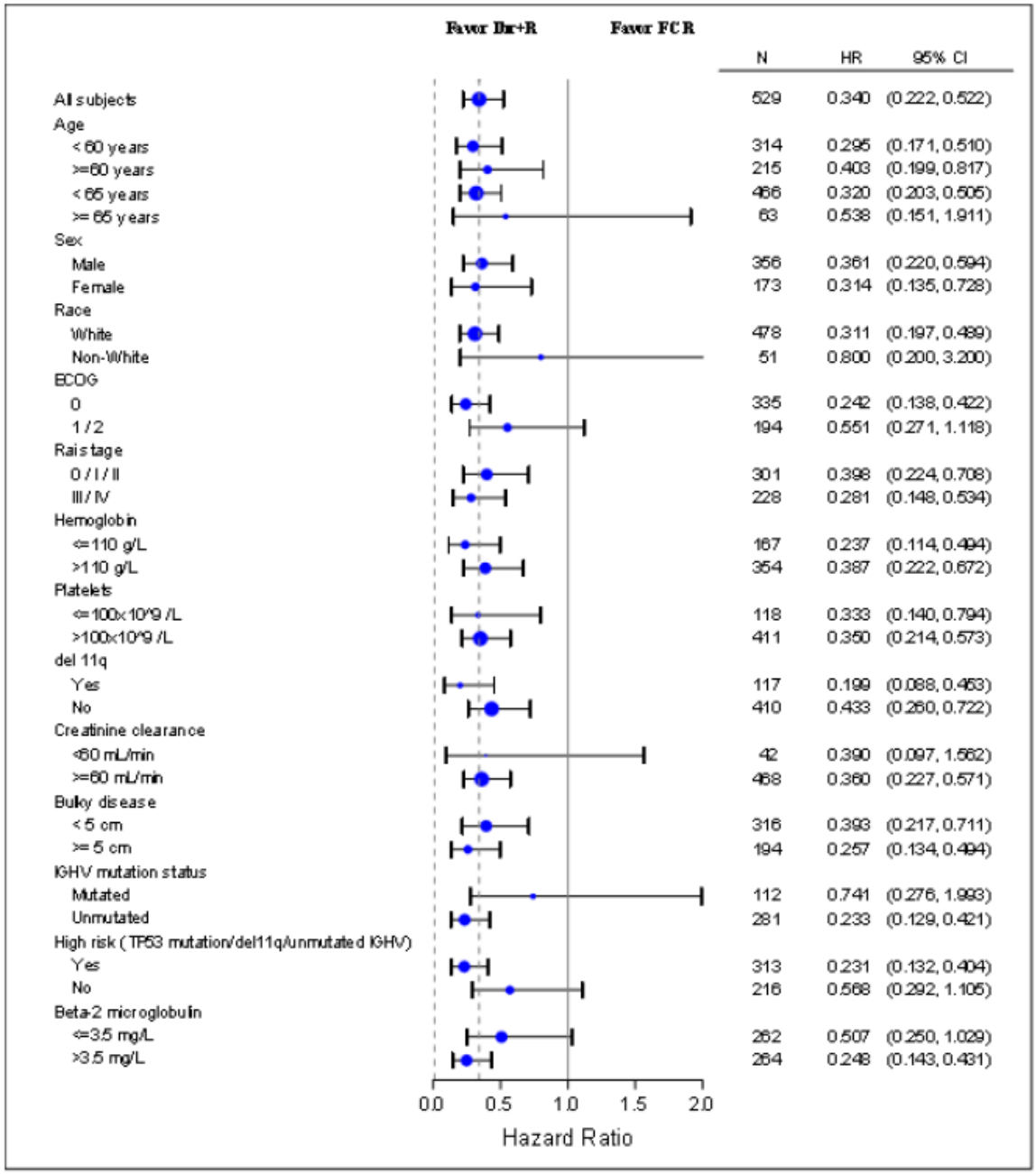
CI: confidence interval; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; PFS: progression-free survival

[a] Hazard ratio is estimated using unstratified Cox regression model.

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

[c] PFS is censored at the last adequate response assessment prior to progression per ECOG-ACRIN case evaluation or death for subjects who missed ≥2 consecutively planned disease assessments (197 days) immediately prior to progression or death

Figure 3 Forest Plot of Hazard Ratios for Progression-free Survival – Subgroup Analyses (Intent-to-Treat Population)



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CI: confidence interval; del 11q: deletion of the long arm of chromosome 11; del 17p: deletion of the short arm of chromosome 17; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; ECOG: Eastern Cooperative Oncology Group; FCR: fludarabine, cyclophosphamide, and rituximab; HR: hazard ratio; Ibr+R: ibrutinib + rituximab; IGHV: immunoglobulin heavy-chain variable region; PFS: progression-free survival; TP53: tumor-suppressor protein 53 gene

The PFS is based on ECOG-ACRIN case evaluation. Scale for hazard ratio is linear.

2 subjects with del 17p were enrolled in the Ibr+R arm; both subjects are TP53 mutated and IGHV unmutated.

Table 14 Modality of Progressive Disease – Subjects with Progressive Disease per ECOG-ACRIN Case Evaluation

	Ibr+R N=39 n (%)	FCR N=38 n (%)
Absolute lymphocyte count only	23 (59.0)	19 (50.0)
Physical exam only	12 (30.8)	13 (34.2)
Absolute lymphocyte count and physical exam	4 (10.3)	5 (13.2)
Other - Biopsy of conglomerate mass in right upper lobe lung	0	1 (2.6)

ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network, FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.
Basis of progressive disease per ECOG-ACRIN case evaluation are summarized on this table.

The difference in rates of progression by physical examination only (as opposed to ALC only or both physical examination and ALC) between the 2 arms was reviewed before each DSMC meeting throughout study conduct and never exceeded the prespecified threshold.

Table 15 Computed Tomography Scan Use (Intent-to-Treat Population)

	Ibr+R (N=354) n (%)	FCR (N=175) n (%)
Number of subjects with CT scan	354 (100.0)	174 (99.4)
Baseline	354 (100.0)	174 (99.4)
Post-baseline	342 (96.6)	147 (84.0)
12-month response evaluation[a]	326 (92.1)	112 (64.0)
Number of post-baseline CT scans per subject		
In ITT population - N	354	175
Median (Min, Max)	1 (0, 7)	1 (0, 6)
0	12 (3.4)	28 (16.0)
1	230 (65.0)	86 (49.1)
2	67 (18.9)	32 (18.3)
≥3	45 (12.7)	29 (16.6)
In progressive disease subjects[b] - N	39	38
Median (Min, Max)	1 (0, 4)	1 (0, 6)
0	2 (5.1)	7 (18.4)
1	18 (46.2)	18 (47.4)
2	13 (33.3)	7 (18.4)
≥3	6 (15.4)	6 (15.8)

CT: computed tomography; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; ITT: intent-to-treat
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.
[a] Number of subjects with a CT scan within the time window: study day 358 (Week 52 day 1) +/- 90 days.
[b] Based on ECOG-ACRIN case evaluation.

Per protocol, CT scans at baseline, and at 12 months for all subjects with evidence of response or stable disease, were required.

Secondary endpoints

Because the primary endpoint (PFS) achieved statistical significance, testing for OS (first secondary endpoint) was performed subsequently per the prespecified boundary (2-sided p-value of 0.001). Because both PFS and OS crossed the prespecified superiority boundaries at the interim analysis, subsequent tests of secondary endpoints (PFS in high-risk population, change in FACT-Leu TOI score at

Month 12, and ORR per investigator) were performed at a 2-sided significance level of 0.05 in the sequential hierarchical manner given above, based on a closed testing procedure.

- **Overall survival**

Table 13: Overall Survival (ITT)

Overall Survival	Ibr+R N=354	FCR N=175	Comparison/Difference Ibr+R vs. FCR
Deaths - n (%)	4 (1.1)	10 (5.7)	
Censored - n (%)	350 (98.9)	165 (94.3)	
Median (months) (95% CI)[a]	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.03+, 52.27+	0.07+, 51.35+	
P-value[b]			0.0007
Hazard ratio (95% CI)[c]			0.170 (0.053, 0.541)
Landmark Survival - % (95% CI)[a]			
6 Months	99.7 (98.0, 100.0)	99.4 (95.8, 99.9)	0.3 (-1.0, 1.6)
12 Months	99.7 (98.0,100.0)	98.8 (95.1, 99.7)	1.0 (-0.8, 2.7)
18 Months	99.4 (97.7, 99.9)	98.1 (94.3, 99.4)	1.3 (-0.9, 3.6)
24 Months	99.1 (97.4, 99.7)	96.1 (91.6, 98.2)	3.0 (-0.2, 6.2)
30 Months	98.8 (96.9, 99.6)	95.4 (90.7, 97.8)	3.4 (-0.1, 6.9)
36 Months	98.8 (96.9, 99.6)	92.2 (85.7, 95.8)	6.6 (1.7, 11.6)
42 Months	98.8 (96.9, 99.6)	92.2 (85.7, 95.8)	6.6 (1.7, 11.6)
48 Months	98.8 (96.9, 99.6)	92.2 (85.7, 95.8)	6.6 (1.7, 11.6)

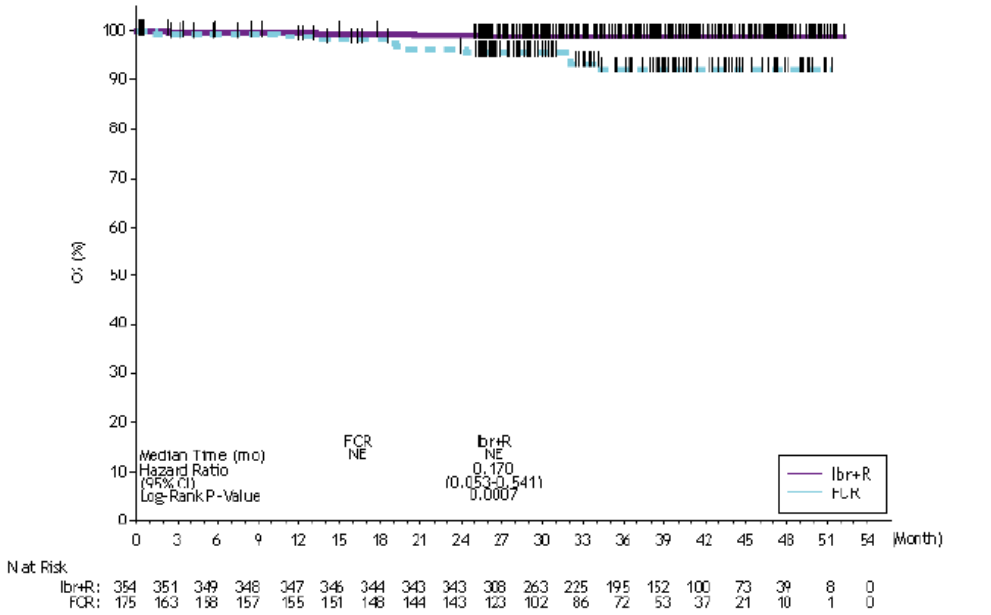
CI: confidence interval; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; NE: not estimable
N: number of subjects in the specified population. Percentages are calculated by 100*n/N. + Indicates censored observation.

[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.

Figure 5 Kaplan-Meier Curves for Overall Survival (Intent-to-Treat Population)



P-Value is from unstratified log-rank test. Hazard ratio is estimated using unstratified Cox regression model.
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CI: confidence interval; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; NE: not estimable; OS: overall survival

- **PFS in the high-risk population**

Overall, 59.2% of subjects were assessed as having high-risk disease (TP53 mutation, del 11q, or unmutated IGHV); 65.0% of subjects in the Ibr+R arm and 47.4% of subjects in the FCR arm.

Table 14: PFS in the high-risk population TP53 mutation, del 11q, or unmutated IGHV) – ITT

Progression-free Survival	Ibr+R N=230	FCR N=83	Comparison/Difference Ibr+R vs. FCR
Events - n (%)	24 (10.4)	26 (31.3)	
Disease progression - n	24	21	
Death - n	0	5	
Censored - n (%)	206 (89.6)	57 (68.7)	
Median (months) (95% CI)[a]	NE (49.4, NE)	NE (31.9, NE)	
Min, Max	0.03+, 51.09+	0.03+, 51.32+	
P-value[b]			<0.0001
Hazard ratio (95% CI)[c]			0.231 (0.132, 0.404)
Landmark Estimates - % (95% CI)[a]			
6 Months	100.0 (NE, NE)	96.2 (88.8, 98.8)	3.8 (-0.4, 8.0)
12 Months	97.8 (94.8, 99.1)	93.6 (85.4, 97.3)	4.2 (-1.6, 9.9)
18 Months	96.5 (93.1, 98.2)	84.3 (74.0, 90.8)	12.2 (3.7, 20.7)
24 Months	94.3 (90.3, 96.6)	80.2 (69.3, 87.6)	14.1 (4.6, 23.5)
30 Months	91.2 (86.5, 94.3)	69.7 (57.0, 79.3)	21.5 (9.7, 33.2)
36 Months	90.4 (85.4, 93.7)	60.3 (46.2, 71.8)	30.1 (16.6, 43.6)
42 Months	89.5 (84.2, 93.1)	56.5 (41.4, 69.2)	33.0 (18.3, 47.7)

CI: confidence interval; del 11q: deletion of the long arm of chromosome 11; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; IGHV: immunoglobulin heavy-chain variable region; NE: not estimable; PFS: progression-free survival; TP53: tumor-suppressor protein 53 gene

N=number of subjects in the specified population. n=number of subjects with PFS events. %=100*n/N.

+ Indicates censored observation.

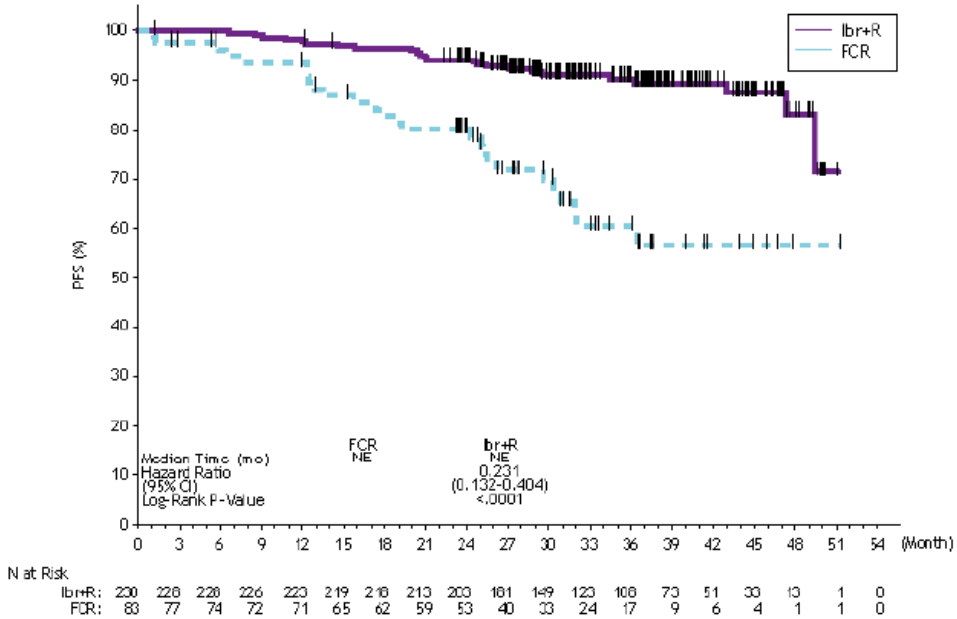
The PFS for primary analysis is based on ECOG-ACRIN case evaluation.

[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.

Figure 6 **Kaplan-Meier Curves for Progression-free Survival in High Risk (TP53 mutation/del 11q/unmutated IGHV) Subjects (High Risk Subjects in Intent-to-Treat Population)**



The PFS is based on ECOG-ACRIN case evaluation.
P-Value is from unstratified log-rank test. Hazard ratio is estimated using unstratified Cox regression model.
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CI: confidence interval; del 11q: deletion of the long arm of chromosome 11; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; IGHV: immunoglobulin heavy-chain variable region; NE: not estimable; PFS: progression-free survival; TP53: tumor-suppressor protein 53 gene

Updated analyses with data cutoff 2 August 2019 (presented in the response to the first LoQ)

Data cutoff 2 August 2019

PFS ITT (event rate 30% control arm): unstratified and stratified HR 0.374

OS ITT (event rate 7% control arm): unstratified HR 0.365, stratified HR 0.340

PFS TP53-negative (n=272 exp arm, 130 ctrl arm; event rate 31.5% control arm): unstratified HR 0.348

PFS High-risk (n=230 exp arm, 83 ctrl arm; event rate 40% control arm): unstratified HR 0.260, stratified HR 0.287.

Data cutoff 17 July 2018 (for comparison)

PFS ITT (event rate 25% control arm): unstratified HR 0.340

OS ITT (event rate 6% control arm): unstratified HR 0.170

PFS High-risk (event rate 31% control arm): unstratified HR 0.231

The analyses have been provided and do not remarkably differ from the primary analyses. OS is still, for natural reasons, immature.

- **Change in FACT-Leu TOI Score at 12 Months**

Baseline mean FACT-Leu TOI scores were similar between the treatment arms. While an improvement from baseline was observed in both treatment arms in FACT-Leu TOI scores at Month 12, no difference between the treatment arms was observed: least squares mean (LS mean) difference in the change from baseline was -0.9, 95% CI -3.8-2.0, p = 0.5452.

- **Overall response rate**

Table 15: ORR per Investigator (ITT)

	Ibr+R N=354 n (%)	FCR N=175 n (%)	Ibr+R vs. FCR
Overall Response Rate (CR, CRi, CCR, nPR, PR)	343 (96.9)	150 (85.7)	
Rate ratio (95% CI)[a]			1.130 (1.061, 1.204)
P-value[a]			<0.0001
Best overall response			
Complete response (CR, CRi)	193 (54.5)	102 (58.3)	
CR	186 (52.5)	96 (54.9)	
CRi	7 (2.0)	6 (3.4)	
Partial response (CCR, nPR, PR)	150 (42.4)	48 (27.4)	
Stable disease	8 (2.3)	8 (4.6)	
Progressive disease	0	3 (1.7)	
Unknown/Missing	3 (0.8)	14 (8.0)	

CI: confidence interval; CR: complete response; CCR: complete clinical response; CRi: complete response with incomplete marrow recovery; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; nPR: nodular partial response; PR: partial response

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

This summary is based on investigator assessments.

[a] Rate ratios and p-values for overall response rate are based on chi-square test.

Summary of main study (E1912)

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).

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 16: Summary of Efficacy for trial E1912

Title: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG ACRIN) Study E1912	
Study identifier	E1912

Design	A Randomized open-label, Phase III Study of ibrutinib plus rituximab (Ibr+R) vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in previously untreated patients with Chronic Lymphocytic Leukemia (CLL) - age 70 years or younger, excluding subjects with del 17p disease. Subjects were randomized in a 2:1 ratio to receive IbrR ibrutinib in combination with 6 cycles of rituximab (after a single cycle of ibrutinib alone) followed by ibrutinib until disease progression or FCR respectively.			
Hypothesis	Superiority			
Treatments groups	Arm A		Ibrutinib + rituximab Ibr+R N= 354	
	Arm B		FCR N= 175	
Endpoints and definitions	Primary endpoint	PFS	Assessed by the Investigator and confirmed by ECOG - ACRIN	
	Secondary endpoint	OS		
	Secondary endpoint	PFS in the high-risk population	PFS in patients with *TP53 mutation, del 11q, unmutated IGHV*	
	Secondary endpoint	QoL	Change in FACT-Leu TOI Score at 12 Months	
	Secondary endpoint	Overall response rate	Response criteria in accordance with the 2008 iwCLL criteria	
Database lock	Study Period: 10 March 2014 (first subject enrolled) to 17 July 2018 (data cutoff for primary analysis).			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat ITT 354 (Arm A) vs 175 (Arm B) Median follow up 36.6 months			
Descriptive statistics and estimate variability / Effect estimate per comparison	Treatment group	Arm A	Arm B	
	Number of subject	354	175	
	PFS (months) INV Median	NE	NE	
	Min, Max p-value HR (95% CI)	0.03, 51.22+	0.03, 51.32+	<0.0001 0.330 (0.214, 0.508)

	PFS ECOG-ACRIN median	NE	NE	
	Min, Max p-value HR (95% CI)	0.03+, 51.22+	0.003+, 51.32+	 <0.0001 0.340 (0.222, 0.522)
	OS Deaths n (%) Median (months) Min, Max p-value HR (95% CI)	4 (1.1%) NE 0.03+, 52.27+	10 (5.7%) NE 0.07+, 51.35+	 <0.0007 0.170 (0.053, 0.541)
	PFS in high risk population Events n (%) p-value HR (95% CI)	 24 (10.4%)	 26 (31.3%)	 <0.0001 0.231 (0.132 0.404)
	ORR Rate ratio n (%) CR	 343 (96.9 %) 193 (54.5%)	 150 (85.7 %) 102 (58.3%)	<0.0001
Notes	Change in FACT-Leu TOI Score at 12 Months; Baseline mean FACT-Leu TOI scores were similar between the treatment arms. While an improvement from baseline was observed in both treatment arms in FACT-Leu TOI scores at Month 12, no difference between the treatment arms was observed: least squares mean (LS mean) difference in the change from baseline was -0.9, 95% CI -3.8-2.0, p = 0.5452.			
Analysis description	primary Analysis			

Analysis performed across trials

Table 17: Comparison of PFS across studies with ibrutinib in treatment-naïve CLL.

Table 9: Progression-Free Survival Results Across Studies

	Study E1912				Study 1130				Study 1115			
	INV		ECOG-ACRIN Case Evaluation		INV		IRC		INV		IRC	
	Ibr+R N=354	FCR N=175	Ibr+R N=354	FCR N=175	Ibr+Ob N=113	Clb+Ob N=116	Ibr+Ob N=113	Clb+Ob N=116	Ibr N=136	Clb N=133	Ibr N=136	Clb N=133
Median Follow up	36.6 months				31.3 months				18.4 months			
PFS (months)												
Median	NE	NE	NE	NE	NE	21.9	NE	19.0	NE	15.0	NE	18.9
Min, Max	0.03+, 51.22+	0.03+, 51.32+	0.03+, 51.22+	0.03+, 51.32+	0.16, 35.32+	0.03+, 35.22+	0.16, 35.32+	0.03+, 35.22+	0.03+, 24.71+	0.03+, 22.57+	0.03+, 24.71+	0.03+, 23.98+
P-value	<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001	
Hazard Ratio (95% CI)	0.330 (0.214, 0.508)		0.340 (0.222, 0.522)		0.260 (0.163, 0.415)		0.231 (0.145, 0.367)		0.086 (0.043, 0.172)		0.161 (0.091, 0.283)	

CI=confidence interval; Clb=chlorambucil; Clb+Ob=chlorambucil + obinutuzumab; ECOG-ACRIN=Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FCR=fludarabine, cyclophosphamide, and rituximab; Ibr=ibrutinib; Ibr+Ob=ibrutinib + obinutuzumab; Ibr+R=ibrutinib + rituximab; INV=investigator; IRC=independent review committee; NE=not estimable; PFS=progression-free survival

+ Indicates censored observation.

Note: Hazard ratio and its 95% CI are estimated using a stratified Cox regression model for Study 1115 and an unstratified Cox regression model for Studies E1912 and 1130.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Key efficacy and safety data to support the Type II variation to extend the current authorized indication in CLL are derived from Study E1912: "A Randomized Phase III Study of Ibrutinib (PCI-32765)-based Therapy vs Standard Fludarabine, Cyclophosphamide, and Rituximab (FCR) Chemoimmunotherapy in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL)".

Study E1912 was a randomized, open-label, Phase 3 study designed to evaluate the efficacy and safety of ibrutinib plus rituximab (Ibr+R) vs. FCR for previously untreated subjects with CLL age 70 years or younger, excluding subjects with del 17p disease. Subjects were randomized in a 2:1 ratio to receive Ibr+R (Arm A) or FCR (Arm B), respectively. Randomization was stratified according to age (< 60 years vs. ≥ 60 years), ECOG performance status (0/1 vs. 2), disease stage (Rai stage I/II vs. III/IV), and baseline cytogenetic abnormalities (deletion of the long arm of chromosome 11 [del 11q] vs. other). Subjects in the Ibr+R arm received ibrutinib in combination with 6 cycles of rituximab (after a single cycle of ibrutinib alone) followed by ibrutinib until disease progression. Subjects in the FCR arm received 6 cycles of FCR.

Response criteria were all in accordance with the 2008 iwCLL criteria (Hallek 2008) with incorporation of the clarification for treatment-related lymphocytosis (Hallek 2013; Hallek 2012). Response and progression were assessed by the investigator and confirmed, unblinded to treatment, by ECOG-ACRIN case evaluation which included Operations Office (ECOG-ACRIN data management team) and Study Chair review. Any cases requiring adjudication (cases in which the Operations Office/Study Chair disagreed with the investigator, or the Operations Office and Study Chair disagreed with one another) were sent to the designated ECOG-ACRIN Executive Officer for disease progression determination in alignment with the protocol and iwCLL 2008 response criteria.

The data were subject to ongoing study oversight including additional monitoring, with the primary analysis based on data extracted and transferred from ECOG-ACRIN to the MAH on 02 August 2019. Updated analyses, including stratified analyses where appropriate, with a data cutoff of 2 August 2019 were provided as responses to the CHMP RSI.

This is an open-label study. The proportion of subjects not receiving study treatment differs significantly between the two treatment groups (0.6% and 9.7% in the experimental group and the control group respectively). This raises questions of the comparability of the groups actually treated. Furthermore, the proportion of subjects who discontinued study due to withdrawal of consent differs between treatment groups (2.8% and 18.9% in the experimental group and the control group respectively). These issues were further addressed by the MAH. Although the exact meaning of these imbalances remains unclear and selection bias is deemed likely to be at hand, the tipping point analysis performed for PFS suggest that the ITT analysis is robust to the discontinuation pattern.

Response and progression were assessed by the investigator and confirmed by ECOG-ACRIN case evaluation which included Operations Office (ECOG-ACRIN data management team) and Study Chair review. Any cases requiring adjudication (cases in which the Operations Office/Study Chair disagreed with the investigator, or the Operations Office and Study Chair disagreed with one another) were sent to the designated ECOG-ACRIN Executive Officer for disease progression determination in alignment with the protocol and iwCLL 2008 response criteria. The MAH has clarified that non-investigator assessment/confirmation of OR and PD was not blinded to treatment, meaning that, despite undertaken mitigation procedures, a potential bias affecting the efficacy evaluation cannot be ruled out in this open study.

Cross-over from the control arm was not formally part of the protocol. As information on post-progression therapy is largely lacking and treatment with commercial ibrutinib monotherapy obviously was an option at time of PD in the control arm, OS is hard to interpret.

Efficacy data and additional analyses

Demographic and general baseline characteristics were reasonably balanced. Fractions with *known* high-risk disease (TP53 mutation, del 11q or unmutated IGHV) were 65% in the experimental arm and 47% in the control arm. However, the study was genetically only stratified for del 11q but when it comes to TP53 mutation and IGHV mutation only consenting subjects were tested and the fractions with unknown status (16% and 21% in the experimental arm, respectively; 23% and 35% in the control arm, respectively) are deemed too large to allow a conclusion on balance between study arms.

The evaluation of efficacy data is not considered substantially hampered by the performed protocol amendments or changes in planned analyses, or the protocol deviations.

The time-dependent efficacy outcomes consistently favour the experimental arm, Ibr+R, over the control arm, FCR. This holds true also for the updated efficacy evaluation with data cutoff 2 August 2019, with ITT event rates of 30% for PFS (25% at the primary analysis, 17 July 2018, with a median follow-up of 37 months) and 7% for OS in the control arm. However, as information on post-progression therapy is largely lacking and treatment with commercial ibrutinib monotherapy obviously was an option at time of PD in the control arm, OS is hard to interpret. The significant differences between study arms in proportions of subjects not receiving study treatment or discontinuing the study due to withdrawal of consent is of concern, especially in an open-labelled study, although less so after the tipping point analysis for PFS provided in the response to the first LoQ. Further, as treatment regimens with different treatment duration are compared, data on PFS2 or a relevant proxy would be very informative, but will unfortunately not be available.

At the time of study initiation analysis of TP53 mutational status was not recommended in the US (NCCN) CLL treatment guidelines, and assays were not available across all study sites. FCR is nowadays not a valid treatment option for TP53-mutated disease.

Regarding the efficacy evaluation in the high-risk population it should be noted that TP53 mutation and IGHV mutation status were only tested in consenting subjects, with higher fractions with unknown status in the control arm (23% and 35% in the control arm, respectively; 16% and 21% in the experimental arm, respectively). Original consent for genetic testing was obtained before subject randomization but this does not exclude possible selection bias as withdrawal of consent could also result in missing test results. The issue was further addressed and although potential bias cannot be fully excluded, the outcome of the primary analysis is considered robust.

When isolation of contribution of each drug in the Ibr+R combination is considered, the pivotal study does not provide information. However, from a regulatory point of view, and as has been previously accepted in other procedures, ibrutinib could be viewed as a substitution of F+C in the guideline-recommended combination with rituximab. The MAH is encouraged to further investigate the efficacy of ibrutinib + rituximab *vs* ibrutinib monotherapy.

The sought indication is broader, i.e. encompassing all treatment-naïve CLL subjects, than the population studied in the pivotal study, i.e. subjects ≤ 70 years of age with previously untreated CLL/SLL without del 17p in need of treatment and deemed eligible for FCR. From a strict efficacy point of view, it is considered reasonable to assume similar activity of the combination in patients non-fit for FCR. Regarding activity in del 17p disease too few patients with TP53 mutation, sharing similar dismal prognostic value as for del 17p in the setting of CIT, were enrolled in the pivotal study to allow any conclusion. However, in several earlier studies ibrutinib, as monotherapy or in combination therapy, was shown to be highly effective also in del 17p disease.

2.4.3. Conclusions on the clinical efficacy

The time-dependent efficacy outcomes consistently favour the experimental arm, Ibr+R, over the control arm, FCR. The efficacy of Imbruvica in the sought indication has been demonstrated.

2.5. Clinical safety

Introduction

In addition to safety tabulations and analyses of the two arms of the pivotal study E1912 the MAH has provided an overall reference to the Current Label Pool (=the safety profile presented in the current SmPC), representing integrated data for 1,200 subjects receiving ibrutinib as monotherapy or in combination therapy across the 9 studies representing the currently approved indications in CLL (Studies 1102 [420 mg/day treatment arm only], 1112, 1115, 1130, and CLL3001), WM (Studies 1118E and 1127 [Arms A and C]), and MCL (Studies 1104 and MCL3001).

Patient exposure

Table 18: Patient exposure E1912 and current Label Pool; Safety population

	E1912/PCYC-1126e-CA		
	Ibr+R	FCR	Current Label Pool
Analysis Set: Safety Population	352	158	1200
Treatment duration (months)			
N	352	158	1200
Mean (SD)	32.840 (12.3674)	4.143 (1.6194)	15.174 (8.7381)
Median	34.333	4.698	14.702
Range	(0.23; 52.17)	(0.07; 7.72)	(0.03; 37.22)
0 - < 3 months	14 (4.0%)	35 (22.2%)	112 (9.3%)
3 - < 6 months	8 (2.3%)	116 (73.4%)	77 (6.4%)
6 - < 9 months	2 (0.6%)	7 (4.4%)	146 (12.2%)
9 - < 12 months	6 (1.7%)	0	131 (10.9%)
12 - < 15 months	9 (2.6%)	0	160 (13.3%)
15 - < 18 months	5 (1.4%)	0	132 (11.0%)
18 - < 24 months	13 (3.7%)	0	258 (21.5%)
>= 24 months	295 (83.8%)	0	184 (15.3%)
Average dose level per administration			
CLL/SLL (mg/day for Ibrutinib)			
N	352	NA	781
Mean (SD)	390.729 (50.8440)		392.225 (47.4547)
Median	410.445		413.393
Range	(90.00; 456.25)		(140.65; 430.26)
Relative dose intensity (%)			
N	352	NA	1200
Mean (SD)	93.031 (12.1057)		93.790 (11.0041)
Median	97.725		98.571
Range	(21.43; 108.63)		(30.30; 102.44)

CLL/SLL=chronic lymphocytic leukemia/small lymphocytic lymphoma; FCR=fludarabine, cyclophosphamide, and rituximab; Ibr+R=ibrutinib plus rituximab; MCL=mantle cell lymphoma; SD=standard deviation; WM=Waldenstrom's Macroglobulinemia. Current Label Pool includes PCYC-1102, PCYC-1104, PCYC-1112, PCYC-1115, PCYC-1118E, MCL3001, CLL3001, PCYC-1127 (Arm A and C), and PCYC-1130.

Adverse events

Table 19: Overview of TEAEs (Safety population)

	Ibr+R N=352		FCR N=158	
	Overall n (%)	First 6 Months[e] n (%)	Overall n (%)	First 6 Months[e] n (%)
Subjects with any TEAEs	352 (100.0)	351 (99.7)	157 (99.4)	157 (99.4)
Grade ≥3	320 (90.9)	289 (82.1)	142 (89.9)	142 (89.9)
Subjects with any related TEAEs[a]	347 (98.6)	333 (94.6)	156 (98.7)	156 (98.7)
Grade ≥3	238 (67.6)	185 (52.6)	129 (81.6)	129 (81.6)
Subjects with any ibrutinib related TEAEs[b]	338 (96.0)	317 (90.1)	NA	NA
Grade ≥3	203 (57.7)	156 (44.3)	NA	NA
Subjects with any TEAEs leading to ibrutinib discontinuation[c]	38 (10.8)	12 (3.4)	NA	NA
Subjects with any TEAEs leading to ibrutinib dose reduction	45 (12.8)	14 (4.0)	NA	NA
Fatal TEAE	3 (0.9)	1 (0.3)	2 (1.3)	2 (1.3)
Treatment emergent major hemorrhage[d]	12 (3.4)	6 (1.7)	NA	NA
Grade ≥3 treatment emergent bleeding events	9 (2.6)	6 (1.7)	2 (1.3)	2 (1.3)

AE: adverse event; CNS: central nervous system; CRF: case report form; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; NA: not applicable; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event

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

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

[b] Attributed to ibrutinib per investigator's judgment.

[c] Subjects whose primary reason for treatment discontinuation was AE and AE action taken for ibrutinib contains permanently withdrawn.

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

[e] TEAEs occurred within first 7 cycles for Ibr+R subjects who were treated >7 cycles and all TEAEs for FCR subjects or Ibr+R subjects who discontinued treatment within first 7 cycles.

Note: Information from second primary CRF pages are not included in this table. Summaries of other malignancies are presented on Att3-Table 14.3.2.1 and Att3-Table 14.3.2.2.

Table 20 : TEAEs in ≥ 10% of patients in either arm (safety population)

System Organ Class MedDRA Preferred Term	Ibr+R N=352 n (%)			FCR N=158 n (%)		
	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5
Subjects with any TEAE	**352 (100.0)**	**317 (90.1)**	**3 (0.9)**	**157 (99.4)**	**140 (88.6)**	**2 (1.3)**
Blood and lymphatic system disorders	268 (76.1)	82 (23.3)	0	129 (81.6)	51 (32.3)	0
Anaemia	251 (71.3)	24 (6.8)	0	127 (80.4)	28 (17.7)	0
Leukocytosis	58 (16.5)	58 (16.5)	0	7 (4.4)	7 (4.4)	0
Febrile neutropenia	8 (2.3)	7 (2.0)	0	25 (15.8)	25 (15.8)	0
Gastrointestinal disorders	297 (84.4)	29 (8.2)	0	123 (77.8)	5 (3.2)	0
Diarrhoea	187 (53.1)	15 (4.3)	0	42 (26.6)	2 (1.3)	0
Nausea	141 (40.1)	4 (1.1)	0	101 (63.9)	1 (0.6)	0
Stomatitis	70 (19.9)	3 (0.9)	0	13 (8.2)	1 (0.6)	0
Vomiting	62 (17.6)	6 (1.7)	0	44 (27.8)	0	0
Constipation	61 (17.3)	0	0	50 (31.6)	0	0
Abdominal pain	57 (16.2)	5 (1.4)	0	15 (9.5)	2 (1.3)	0
Dyspepsia	50 (14.2)	0	0	5 (3.2)	0	0
Gastrooesophageal reflux disease	47 (13.4)	0	0	9 (5.7)	0	0
General disorders and administration site conditions	308 (87.5)	20 (5.7)	2 (0.6)	138 (87.3)	8 (5.1)	0
Fatigue	281 (79.8)	7 (2.0)	0	123 (77.8)	4 (2.5)	0
Oedema peripheral	100 (28.4)	4 (1.1)	0	27 (17.1)	0	0
Pyrexia	96 (27.3)	2 (0.6)	0	43 (27.2)	2 (1.3)	0
Pain	80 (22.7)	7 (2.0)	0	13 (8.2)	0	0
Chills	38 (10.8)	1 (0.3)	0	27 (17.1)	1 (0.6)	0
Infections and infestations	219 (62.2)	38 (10.8)	0	55 (34.8)	13 (8.2)	1 (0.6)
Upper respiratory tract infection	102 (29.0)	3 (0.9)	0	30 (19.0)	3 (1.9)	0
Skin infection	41 (11.6)	4 (1.1)	0	3 (1.9)	1 (0.6)	0
Lung infection	37 (10.5)	9 (2.6)	0	9 (5.7)	4 (2.5)	0
Injury, poisoning and procedural complications	162 (46.0)	4 (1.1)	0	55 (34.8)	2 (1.3)	0
Contusion	115 (32.7)	0	0	6 (3.8)	0	0
Infusion related reaction	33 (9.4)	1 (0.3)	0	40 (25.3)	1 (0.6)	0
Investigations	334 (94.9)	261 (74.1)	0	150 (94.9)	135 (85.4)	0
Lymphocyte count increased	264 (75.0)	204 (58.0)	0	63 (39.9)	49 (31.0)	0
Platelet count decreased	215 (61.1)	17 (4.8)	0	122 (77.2)	28 (17.7)	0
Neutrophil count decreased	188 (53.4)	114 (32.4)	0	105 (66.5)	71 (44.9)	0
Blood creatinine increased	127 (36.1)	3 (0.9)	0	32 (20.3)	1 (0.6)	0
Blood bilirubin increased	109 (31.0)	12 (3.4)	0	28 (17.7)	0	0
Aspartate aminotransferase increased	103 (29.3)	12 (3.4)	0	46 (29.1)	1 (0.6)	0
White blood cell count decreased	98 (27.8)	21 (6.0)	0	121 (76.6)	64 (40.5)	0
Lymphocyte count decreased	96 (27.3)	34 (9.7)	0	125 (79.1)	106 (67.1)	0
Alanine aminotransferase increased	64 (18.2)	8 (2.3)	0	30 (19.0)	1 (0.6)	0
Weight increased	55 (15.6)	3 (0.9)	0	8 (5.1)	0	0
Blood alkaline phosphatase increased	54 (15.3)	2 (0.6)	0	30 (19.0)	0	0

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System Organ Class MedDRA Preferred Term	Ibr+R N=352 n (%)			FCR N=158 n (%)		
	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5
Metabolism and nutrition disorders	243 (69.0)	42 (11.9)	0	94 (59.5)	18 (11.4)	0
Hyperglycaemia	103 (29.3)	16 (4.5)	0	37 (23.4)	9 (5.7)	0
Hypocalcaemia	84 (23.9)	0	0	37 (23.4)	1 (0.6)	0
Hyperuricaemia	65 (18.5)	3 (0.9)	0	7 (4.4)	0	0
Decreased appetite	53 (15.1)	0	0	31 (19.6)	1 (0.6)	0
Hyponatraemia	53 (15.1)	11 (3.1)	0	19 (12.0)	3 (1.9)	0
Hyperkalaemia	48 (13.6)	5 (1.4)	0	9 (5.7)	2 (1.3)	0
Hypokalaemia	44 (12.5)	2 (0.6)	0	17 (10.8)	1 (0.6)	0
Hypoalbuminaemia	40 (11.4)	0	0	13 (8.2)	2 (1.3)	0
Musculoskeletal and connective tissue disorders	264 (75.0)	30 (8.5)	0	66 (41.8)	5 (3.2)	0
Myalgia	153 (43.5)	7 (2.0)	0	38 (24.1)	1 (0.6)	0
Arthralgia	144 (40.9)	18 (5.1)	0	15 (9.5)	2 (1.3)	0
Back pain	82 (23.3)	7 (2.0)	0	17 (10.8)	1 (0.6)	0
Pain in extremity	82 (23.3)	7 (2.0)	0	10 (6.3)	0	0
Muscle spasms	42 (11.9)	0	0	2 (1.3)	0	0
Nervous system disorders	223 (63.4)	24 (6.8)	0	76 (48.1)	7 (4.4)	0
Headache	142 (40.3)	4 (1.1)	0	43 (27.2)	1 (0.6)	0
Dizziness	75 (21.3)	3 (0.9)	0	21 (13.3)	1 (0.6)	0
Peripheral sensory neuropathy	61 (17.3)	2 (0.6)	0	17 (10.8)	1 (0.6)	0
Psychiatric disorders	111 (31.5)	7 (2.0)	0	45 (28.5)	3 (1.9)	0
Insomnia	55 (15.6)	4 (1.1)	0	30 (19.0)	1 (0.6)	0
Anxiety	51 (14.5)	1 (0.3)	0	16 (10.1)	0	0
Depression	48 (13.6)	2 (0.6)	0	9 (5.7)	0	0
Renal and urinary disorders	95 (27.0)	6 (1.7)	0	31 (19.6)	2 (1.3)	0
Haematuria	49 (13.9)	2 (0.6)	0	5 (3.2)	0	0
Respiratory, thoracic and mediastinal disorders	203 (57.7)	15 (4.3)	1 (0.3)	73 (46.2)	8 (5.1)	0
Cough	111 (31.5)	1 (0.3)	0	39 (24.7)	0	0
Dyspnoea	76 (21.6)	7 (2.0)	0	33 (20.9)	2 (1.3)	0
Oropharyngeal pain	45 (12.8)	1 (0.3)	0	8 (5.1)	0	0
Nasal congestion	41 (11.6)	0	0	11 (7.0)	0	0
Skin and subcutaneous tissue disorders	234 (66.5)	16 (4.5)	0	70 (44.3)	8 (5.1)	0
Rash maculo-papular	145 (41.2)	11 (3.1)	0	41 (25.9)	8 (5.1)	0
Pruritus	45 (12.8)	1 (0.3)	0	13 (8.2)	0	0
Dry skin	38 (10.8)	1 (0.3)	0	9 (5.7)	0	0
Vascular disorders	180 (51.1)	67 (19.0)	0	62 (39.2)	14 (8.9)	0
Hypertension	148 (42.0)	66 (18.8)	0	35 (22.2)	10 (6.3)	0
Hot flush	39 (11.1)	0	0	15 (9.5)	0	0

CRF: case report form; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; TEAE: treatment-emergent adverse event
N=Number of subjects in specified treatment arm of safety population. n=number of subjects with the specified event. %=100*n
Subjects are counted once only at each level of summarization using maximum severity.
Events are sorted by system organ class alphabetically, decreasing frequency of preferred term by Any Grade column in the Ibr+R group, decreasing frequency of preferred term by Any Grade column in the FCR group, and then alphabetic order of preferred terms.
Note: Information from second primary CRF pages are not included in this table. Summaries of Other Malignancies are presented on Att3-Table 14.3.2.1 and Att3-Table 14.3.2.2.
Adverse events are coded by MedDRA Version 22.0.

Of those TEAEs reported in at least 20% of subjects in either treatment arm in Study E1912, lymphocyte count increased, blood creatinine increased, blood bilirubin increased, edema peripheral, pain, diarrhea, myalgia, arthralgia, back pain, pain in extremity, rash maculo-

papular, headache, upper respiratory tract infection, hypertension, and contusion occurred at a higher incidence (≥10% higher) in the Ibr+R arm compared with the FCR arm.

Of those TEAEs reported in at least 20% of subjects in either treatment arm in Study E1912, platelet count decreased, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, nausea, vomiting, constipation, and infusion-related reaction occurred at a higher incidence (≥10% higher) in the FCR arm compared with the Ibr+R arm.

Among the most commonly (≥20% of subjects in either arm) reported TEAEs for the Ibr+R and FCR treatment arms for the first 6 months, a difference between arms of ≥10% and higher in the Ibr+R arm was observed for lymphocyte count increased (73.6% Ibr+R versus 39.9% FCR), diarrhea (41.5% Ibr+R versus 26.6% FCR), arthralgia (25.9% Ibr+R versus 9.5% FCR), and contusion (21.6% Ibr+R versus 3.8% FCR).

Table 22 Grade 3 or Higher Treatment-emergent Adverse Events in ≥ 2% of Subjects in Either Arm (Safety Population)

	Ibr+R N=352 n (%)				FCR N=158 n (%)			
MedDRA Preferred Term	Grade 3-5	Grade 3	Grade 4	Grade 5	Grade 3-5	Grade 3	Grade 4	Grade 5
Subjects with any TEAE	**320 (90.9)**	**233 (66.2)**	**84 (23.9)**	**3 (0.9)**	**142 (89.9)**	**66 (41.8)**	**74 (46.8)**	**2 (1.3)**
Lymphocyte count increased	204 (58.0)	204 (58.0)	0	0	49 (31.0)	49 (31.0)	0	0
Neutrophil count decreased	114 (32.4)	56 (15.9)	58 (16.5)	0	71 (44.9)	32 (20.3)	39 (24.7)	0
Hypertension	66 (18.8)	65 (18.5)	1 (0.3)	0	10 (6.3)	10 (6.3)	0	0
Leukocytosis	58 (16.5)	57 (16.2)	1 (0.3)	0	7 (4.4)	7 (4.4)	0	0
Lymphocyte count decreased	34 (9.7)	31 (8.8)	3 (0.9)	0	106 (67.1)	56 (35.4)	50 (31.6)	0
Anaemia	24 (6.8)	24 (6.8)	0	0	28 (17.7)	22 (13.9)	6 (3.8)	0
White blood cell count decreased	21 (6.0)	19 (5.4)	2 (0.6)	0	64 (40.5)	39 (24.7)	25 (15.8)	0
Arthralgia	18 (5.1)	18 (5.1)	0	0	2 (1.3)	2 (1.3)	0	0
Platelet count decreased	17 (4.8)	8 (2.3)	9 (2.6)	0	28 (17.7)	18 (11.4)	10 (6.3)	0
Hyperglycaemia	16 (4.5)	14 (4.0)	2 (0.6)	0	9 (5.7)	9 (5.7)	0	0
Diarrhoea	15 (4.3)	15 (4.3)	0	0	2 (1.3)	2 (1.3)	0	0
Aspartate aminotransferase increased	12 (3.4)	11 (3.1)	1 (0.3)	0	1 (0.6)	1 (0.6)	0	0
Blood bilirubin increased	12 (3.4)	11 (3.1)	1 (0.3)	0	0	0	0	0
Rash maculo-papular	11 (3.1)	11 (3.1)	0	0	8 (5.1)	8 (5.1)	0	0
Hyponatraemia	11 (3.1)	11 (3.1)	0	0	3 (1.9)	3 (1.9)	0	0
Atrial fibrillation	11 (3.1)	9 (2.6)	2 (0.6)	0	2 (1.3)	1 (0.6)	1 (0.6)	0
Lung infection	9 (2.6)	8 (2.3)	1 (0.3)	0	4 (2.5)	4 (2.5)	0	0
Alanine aminotransferase increased	8 (2.3)	6 (1.7)	2 (0.6)	0	1 (0.6)	1 (0.6)	0	0
Febrile neutropenia	7 (2.0)	7 (2.0)	0	0	25 (15.8)	21 (13.3)	4 (2.5)	0
Fatigue	7 (2.0)	7 (2.0)	0	0	4 (2.5)	4 (2.5)	0	0
Dyspnoea	7 (2.0)	6 (1.7)	1 (0.3)	0	2 (1.3)	2 (1.3)	0	0
Back pain	7 (2.0)	7 (2.0)	0	0	1 (0.6)	1 (0.6)	0	0
Myalgia	7 (2.0)	7 (2.0)	0	0	1 (0.6)	1 (0.6)	0	0
Syncope	7 (2.0)	7 (2.0)	0	0	1 (0.6)	1 (0.6)	0	0
Pain	7 (2.0)	7 (2.0)	0	0	0	0	0	0
Pain in extremity	7 (2.0)	7 (2.0)	0	0	0	0	0	0
Sepsis	5 (1.4)	0	5 (1.4)	0	5 (3.2)	0	4 (2.5)	1 (0.6)
Haemolysis	2 (0.6)	2 (0.6)	0	0	4 (2.5)	3 (1.9)	1 (0.6)	0

CRF: case report form; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; TEAE: treatment-emergent adverse event

N=Number of subjects in specified treatment arm of safety population. n=number of subjects with the specified event. %=100*n/N. Subjects are counted once only at each level of summarization using maximum severity.

Events are sorted by decreasing frequency of preferred term by Grade 3-5 column in the Ibr+R group, decreasing frequency of preferred term Grade 3-5 column in the FCR group, and then alphabetic order of preferred terms.

Note: Information from second primary CRF pages are not included in this table. Summaries of Other Malignancies are presented on Att3-Table 14.3.2.1 and Att3-Table 14.3.2.2.

Adverse events are coded by MedDRA Version 22.0.

Lymphocyte count increased (58.0%), neutrophil count decreased (32.4%), hypertension (18.8%), leukocytosis (16.5%), lymphocyte count decreased (9.7%), anemia (6.8%), white blood cell count decreased (6.0%), and arthralgia (5.1%) were the most common (≥5% of subjects) Grade 3 or 4 TEAEs in the Ibr+R arm, and the incidence rates for lymphocyte count increased, leukocytosis, arthralgia, and hypertension were at least 2% higher than those in the FCR arm. Common (≥5% of subjects) Grade 3 or 4 TEAEs in the FCR arm that occurred at a ≥2% higher rate compared with the Ibr+R arm were lymphocyte count decreased (67.1%), neutrophil count decreased (44.9%), white blood cell count decreased (40.5%), platelet count decreased (17.7%), anemia (17.7%), febrile

neutropenia (15.8%), and rash maculo-papular (5.1%).

During the first 6 months of study treatment, 82.1% of subjects in the Ibr+R arm and 89.9% of subjects in the FCR arm had a TEAE of Grade 3 or higher. The most common (≥5% of subjects) Grade 3 or higher TEAEs for the first 6 months in the Ibr+R arm were: lymphocyte count increased (58.0%), neutrophil count decreased (22.7%), leukocytosis (15.1%), hypertension (7.4%), anaemia (6.0%), and lymphocyte count decreased (5.7%).

Serious adverse event/deaths/other significant events

Serious adverse events

Serious TEAEs were not summarized. The CRF was not designed to distinguish serious vs. non-serious events, hence SAEs were not able to be identified from the clinical database.

Deaths

Table 23 Treatment-emergent Adverse Events Leading to Death (Safety Population)

MedDRA Preferred Term	Ibr+R N=352 n (%)	FCR N=158 n (%)
Subjects with any TEAE	**3 (0.9)**	**2 (1.3)**
Death[a]	1 (0.3)	0
Multiple organ dysfunction syndrome	1 (0.3)	0
Respiratory failure	1 (0.3)	0
Leukaemia[b]	0	1 (0.6)
Sepsis	0	1 (0.6)

FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; TEAE: treatment-emergent adverse event
N=Number of subjects in specified treatment arm of safety population. n=number of subjects with the specified event.
%=100*n/N. Subjects are counted once only at each level of summarization using maximum severity.
Events are sorted by decreasing frequency of preferred term in the Ibr+R group, decreasing frequency of preferred term in the FCR group, then alphabetic order of preferred terms.
Adverse events are coded by MedDRA Version 22.0.
[a] Cause of death: Unknown (Att3-Listing 14.3.1.10).
[b] Cause of death: Acute myeloid leukemia (Att3-Listing 14.3.1.10).

During the first 6 months of study treatment, the incidence of fatal TEAEs was 0.3% (n=1) for Ibr+R vs. 1.3% (n=2) for FCR.

During the entire study period, there were 4 deaths on the Ibr+R arm (1.1% of subjects) including pleural effusion/lung cancer, CLL (due to underlying disease/PT term: multiple organ dysfunction syndrome), unknown (PT: death), and respiratory failure occurring in 1 subject each. During the entire study period, there were 10 deaths (6.3% of subjects) on the FCR arm including CLL (3 subjects), acute myeloid leukemia (2 subjects), unknown (2 subjects), sepsis (1 subject), metastatic colon cancer (1 subject), and drug overdose (1 subject, unrelated to study treatment).

Table 21 Deaths in Safety population

Listing 14.3.1.10 All Deaths
Safety Population

Treatment Arm: Ibr+R

Subject ID (Age/sex /Race[1])	Treatment Duration (Days)	Death Date (Day) [2]	Days from Last Dose[3]	Cause of Death	AE Resulted in Death			
					Preferred Term	Reporting Period [2]	Related to Study Treatment	Related to IBR
[redacted] (58/M/BL)	62	[redacted] (780)	718	PLEURAL EFFUSION, ACUTE ON CHRONIC RESP. FAILURE, HX OF LUNG ADENOCARCINOMA STAGE IV				
[redacted] (54/M/WH)	367	[redacted] (399)	32	DUE TO THIS DISEASE	Multiple organ dysfunction syndrome	15 Months Post Registration (1) (TEAE)	POSSIBLE	No
[redacted] (63/M/WH)	50	[redacted] (50)	0	UNKNOWN	Death	Arm A Treatment Cycle (2) (TEAE)	UNLIKELY	No
[redacted] (62/M/WH)	612	[redacted] (625)	13	ACUTE RESPIRATORY FAILURE	Respiratory failure	Arm A Continuing Treatment Cycles 19 - 21 (TPIP)	POSSIBLE	No

Listing 14.3.1.10 All Deaths
Safety Population

Treatment Arm: FCR

Subject ID (Age/sex /Race[1])	Treatment Duration (Days)	Death Date (Day) [2]	Days from Last Dose[3]	Cause of Death	AE Resulted in Death			
					Preferred Term	Reporting Period [2]	Related to Study Treatment	Related to IBR
[redacted] (60/M/WH)	178	[redacted] (402)	224	DRUG OVERDOSE	Death	15 Months Post Registration (1) (NOT TEAE)	UNRELATED	
[redacted] (52/M/WH)	142	[redacted] (1031)	889	UNKNOWN				
[redacted] (55/M/WH)	142	[redacted] (577)	435	UNKNOWN				
[redacted] (56/M/WH)	115	[redacted] (574)	459	METASTATIC COLON CANCER				
[redacted] (59/F/WH)	3	[redacted] (314)	311	DUE TO THIS DISEASE				
[redacted] (59/F/WH)	3	[redacted] (44)	41	SEPTIC SHOCK	Sepsis	Arm B Treatment Cycle (2) (TEAE)	POSSIBLE	
[redacted] (57/M/WH)	3	[redacted] (733)	730	AML				
[redacted] (62/M/WH)	157	[redacted] (958)	801	DUE TO THIS DISEASE				
[redacted] (57/M/WH)	141	[redacted] (604)	463	DUE TO THIS DISEASE				

Adverse events of clinical interest and other safety observations

- **Haemorrhage events**

Table 22: Bleeding events by PT and severity

	Ibr+R (n=352)			FCR (n=158)		
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	186(52.8)	9(2.6)	0	18(11.4)	2(1.3)	0

Table 14.3.1.14 Treatment Emergent Bleeding Events by Preferred Term and Maximum Severity
for the First 6 Months of Study Treatment
Safety Population

	Ibr+R (n=352)			FCR (n=158)		
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	123(34.9)	6(1.7)	0	18(11.4)	2(1.3)	0

Major haemorrhage includes serious or Grade ≥ 3 haemorrhage and central nervous system (CNS) haemorrhage at any grade among bleeding events identified by Haemorrhage SMQ excluding laboratory terms. Major haemorrhage TEAEs were only summarized for the Ibr+R arm.

Table 23 Major Haemorrhage TEAEs (Safety population)

	Ibr+R N=352 n (%)		
MedDRA Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**
Subjects with any TEAE	**12 (3.4)**	**9 (2.6)**	**0**
Haematoma	3 (0.9)	2 (0.6)	0
Haematuria	2 (0.6)	2 (0.6)	0
Haemorrhage intracranial	2 (0.6)	1 (0.3)	0
Gastric haemorrhage	1 (0.3)	1 (0.3)	0
Post procedural haemorrhage	1 (0.3)	0	0
Procedural haemorrhage	1 (0.3)	1 (0.3)	0
Rectal haemorrhage	1 (0.3)	0	0
Renal haemorrhage	1 (0.3)	1 (0.3)	0
Upper gastrointestinal haemorrhage	1 (0.3)	1 (0.3)	0
Epistaxis	0	0	0

CNS: central nervous system; Ibr+R: ibrutinib + rituximab; SMQ: standardized MedDRA query; TEAE: treatment-emergent adverse event

N=Number of subjects in specified treatment arm of safety population. n=number of subjects with the specified event. %=100*n/N. Subjects are counted once only at each level of summarization using maximum severity.

Events are sorted by decreasing frequency of preferred term by Any Grade column in the Ibr+R group, and then alphabetic order of preferred terms.

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

Adverse events are coded by MedDRA Version 22.0.

- **Tumour lysis syndrome**

Tumour lysis syndrome TEAEs occurred in 0.6% of subjects in Ibr+R arm and 1.3% of subjects in the FCR arm; all events were Grade 3. These incidences are unchanged compared to those during the first 6 months of study treatment.

- **Cytopenia adverse events**

Table 24: Cytopenia adverse events in the Safety population

	Ibr+R (N=352)			FCR (N=158)		
System Organ Class 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	352(100.0)	317(90.1)	3(0.9)	157(99.4)	140(88.6)	2(1.3)
Blood and lymphatic system disorders	268(76.1)	82(23.3)	0	129(81.6)	51(32.3)	0
Anaemia	251(71.3)	24(6.8)	0	127(80.4)	28(17.7)	0
Leukocytosis	58(16.5)	58(16.5)	0	7(4.4)	7(4.4)	0
Lymph node pain	10(2.8)	0	0	1(0.6)	0	0
Febrile neutropenia	8(2.3)	7(2.0)	0	25(15.8)	25(15.8)	0

Table 14.3.1.12 Treatment Emergent Adverse Events (TEAEs) by System Organ Class, Preferred Term, and Maximum Severity for the First 6 Months of Study Treatment
Safety Population

	Ibr+R (N=352)			FCR (N=158)		
System Organ Class 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	351(99.7)	288(81.8)	1(0.3)	157(99.4)	140(88.6)	2(1.3)
Blood and lymphatic system disorders	254(72.2)	75(21.3)	0	129(81.6)	51(32.3)	0
Anaemia	234(66.5)	21(6.0)	0	127(80.4)	28(17.7)	0
Leukocytosis	53(15.1)	53(15.1)	0	7(4.4)	7(4.4)	0
Lymph node pain	8(2.3)	0	0	1(0.6)	0	0
Febrile neutropenia	5(1.4)	5(1.4)	0	25(15.8)	25(15.8)	0

- Infections including viral reactivation

Table 25: infections (safety population)

	Ibr+R (N=352)			FCR (N=158)		
System Organ Class MedDRA Preferred Term	Any Grade n(%)	Grade 3 + 4 n(%)	Grade 5 n(%)	Any Grade n(%)	Grade 3 + 4 n(%)	Grade 5 n(%)
Infections and infestations	219(62.2)	38(10.8)	0	55(34.8)	13(8.2)	1(0.6)

In the I+R arm, treatment-emergent AEs potentially representative of viral reactivation included herpes zoster (1.1%), herpes simplex, herpes zoster disseminated, and parvovirus B19 infection (0.3% each, 1 subject each). In the FCR arm, treatment-emergent AEs of herpes zoster (1.9%) were reported.

During the first 6 months of study treatment, infections in this SOC of any grade (28.4% I+R vs. 34.8% FCR) and Grade 3 or 4 (3.7% I+R vs. 8.2% FCR) were reported.

- Cardiac arrhytmias

Table 26: Cardiac disorders (safety population)

System Organ Class MedDRA Preferred Term	Ibr+R (N=352) Any Grade n(%)	Ibr+R (N=352) Grade 3 + 4 n(%)	Ibr+R (N=352) Grade 5 n(%)	FCR (N=158) Any Grade n(%)	FCR (N=158) Grade 3 + 4 n(%)	FCR (N=158) Grade 5 n(%)
Cardiac disorders	84(23.9)	24(6.8)	0	16(10.1)	3(1.9)	0
Palpitations	30(8.5)	0	0	3(1.9)	0	0
Atrial fibrillation	28(8.0)	11(3.1)	0	4(2.5)	2(1.3)	0
Sinus bradycardia	16(4.5)	1(0.3)	0	3(1.9)	0	0
Sinus tachycardia	11(3.1)	0	0	6(3.8)	0	0
Angina pectoris	9(2.6)	3(0.9)	0	1(0.6)	0	0
Atrial flutter	3(0.9)	3(0.9)	0	0	0	0
Supraventricular tachycardia	3(0.9)	2(0.6)	0	0	0	0
Acute coronary syndrome	2(0.6)	0	0	1(0.6)	1(0.6)	0
Tachycardia	2(0.6)	1(0.3)	0	1(0.6)	0	0
Cardiac failure	2(0.6)	2(0.6)	0	0	0	0
Pericardial effusion	2(0.6)	2(0.6)	0	0	0	0
Ventricular arrhythmia	2(0.6)	0	0	0	0	0
Ventricular extrasystoles	2(0.6)	0	0	0	0	0
Atrial tachycardia	1(0.3)	0	0	0	0	0
Bundle branch block left	1(0.3)	0	0	0	0	0
Cardiac arrest	1(0.3)	1(0.3)	0	0	0	0
Cardiomegaly	1(0.3)	0	0	0	0	0
Coronary artery occlusion	1(0.3)	1(0.3)	0	0	0	0
Extrasystoles	1(0.3)	0	0	0	0	0
Pericarditis	1(0.3)	0	0	0	0	0
Ventricular tachycardia	1(0.3)	1(0.3)	0	0	0	0

During the first 6 months of study treatment, incidences of any grade atrial fibrillation (3.1% I+R vs. 2.5% FCR) and Grade 3 or 4 atrial fibrillation (1.4% I+R vs. 1.3% FCR) were reported.

In the I+R arm, atrial fibrillation TEAEs leading to ibrutinib discontinuation occurred in 0.9% of subjects and atrial fibrillation TEAEs leading to ibrutinib dose reduction occurred in 0.9% of subjects.

Cardiac arrhythmia TEAEs excluding atrial fibrillation: all grade 18.8%, grade 3-4 4.3% in the I+R arm; all grade 8.9%, grade 3-4 0.6% in the FCR arm.

- **Other malignancies**

Table 27: other malignancies during the entire study period (Safety population)

Subcategory Preferred Term	Ibr+R N=352 Any Grade n (%)	FCR N=158 Any Grade n (%)
Non-melanoma skin cancer	20 (5.7)	5 (3.2)
Basal cell carcinoma	15 (4.3)	4 (2.5)
Squamous cell carcinoma	4 (1.1)	1 (0.6)
Squamous cell carcinoma of skin	2 (0.6)	1 (0.6)
Penile squamous cell carcinoma	1 (0.3)	0
Skin cancer	1 (0.3)	0
Melanoma skin cancer	7 (2.0)	1 (0.6)
Malignant melanoma	6 (1.7)	1 (0.6)
Malignant melanoma in situ	1 (0.3)	0
Non-skin cancer (malignant)	11 (3.1)	9 (5.7)
Prostate cancer	3 (0.9)	1 (0.6)
Breast cancer	2 (0.6)	0
Adenocarcinoma pancreas	1 (0.3)	0
Essential thrombocythaemia	1 (0.3)	0
Gastric cancer	1 (0.3)	0
Invasive papillary breast carcinoma	1 (0.3)	0
Mucinous breast carcinoma	1 (0.3)	0
Papillary thyroid cancer	1 (0.3)	0
Squamous cell carcinoma of lung	1 (0.3)	0
Myelodysplastic syndrome	0	2 (1.3)
Adenocarcinoma of colon	0	1 (0.6)
Bladder cancer	0	1 (0.6)
Breast cancer stage I	0	1 (0.6)
Colon cancer metastatic	0	1 (0.6)
Leukaemia[a]	0	1 (0.6)
Rhabdomyosarcoma	0	1 (0.6)
Sarcomatoid carcinoma of the lung	0	1 (0.6)

AE: adverse event; CRF: case report form; FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab
N=Number of subjects in specified treatment arm of safety population. n = number of subjects with the specified event.
%=100*n/N
Subjects with multiple events for a given preferred term are counted once only using maximum severity for each preferred term.
Events are sorted by decreasing frequency of preferred term in any grade column of the Ibr+R group, decreasing frequency of preferred term in any grade column of the FCR group, and then alphabetic order of preferred terms.
AEs that started or worsened from the first dose date of study treatment up to study exit date are all included.
Note: Table includes Other Malignancies reported on the Adverse Event CRFs and/or the Second Primary CRF.
Adverse events are coded by MedDRA Version 22.0.
[a] Acute myeloid leukemia (Att3-Listing 14.3.1.10).

During the treatment-emergent study period, non-melanoma skin cancer (5.7% Ibr+R vs. 1.9% FCR), melanoma skin cancer (2.0% Ibr+R vs. 0% FCR), and non-skin cancer (3.1% Ibr+R vs. 1.9% FCR) malignancies were observed.

- **Hypertension**

Blood pressure data were not collected on CRFs. Hypertension events were identified by Hypertension SMQ (narrow) search.

During the first 6 months of study treatment, the incidences of any grade hypertension were 26.1% Ibr+R vs. 22.2% FCR, and Grade 3 or 4 hypertension 7.4% Ibr+R vs. 6.3% FCR. The additional approximately 16% any grade hypertension in the Ibr+R arm over the remaining course of the study occurred over an additional 30 months, in alignment with the overall prevalence of hypertension with longer term follow-up in years 2 and 3 with ibrutinib treatment in prior studies.

Laboratory findings

- **Haematology**

Table 28: worst post-baseline toxicity grade – haematology (safety population)

Laboratory Parameter	Direction of Toxicity	Ibr+R N=352 n (%)		FCR N=158 n (%)	
		Any Grade	Grade 3+4	Any Grade	Grade 3+4
Hemoglobin	Low	92 (26.1)	0	81 (51.3)	3 (1.9)
Platelet	Low	152 (43.2)	26 (7.4)	109 (69.0)	39 (24.7)
Absolute neutrophil count	Low	185 (52.6)	107 (30.4)	111 (70.3)	69 (43.7)

FCR: fludarabine, cyclophosphamide, and rituximab; Ibr+R: ibrutinib + rituximab; iwCLL: International Workshop on Chronic Lymphocytic Leukemia
N=number of subjects in the specified treatment arm in the safety population. n=number of subjects who worsened from baseline. %=100*n/N. Graded using the iwCLL 2008 guidelines.
Data up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent antineoplastic therapy, whichever comes first, are included.

During the first 6 months of study treatment, Grade 3 or 4 decreases in hemoglobin (0% Ibr+R vs. 1.9% FCR), platelets (4.8% Ibr+R vs. 24.7% FCR), and ANC (19.0% Ibr+R vs. 43.7% FCR) were observed.

- **Clinical chemistry**

During the first 6 months of study treatment, Grade 3 or 4 increases in AST (1.1% Ibr+R vs. 0.6% FCR) and bilirubin (0.6% Ibr+R vs. 0% FCR) were observed.

During the first 6 months of study treatment, Grade 3 or 4 increases in creatinine (0% Ibr+R vs. 1.3% FCR) and Grade 3 or 4 decreases in CrCl (0.3% Ibr+R vs. 1.3% FCR) were observed.

Discontinuation due to adverse events

TEAEs leading to treatment discontinuation and information on dose reductions were collected separately for Ibr, fludarabine, and cyclophosphamide. Dose-reduction was not allowed for rituximab.

Treatment discontinuation of the complete study medication due to AEs was reported for 11% of subjects in the experimental arm and 15% in the control arm.

TEAEs reported as the primary reason for ibrutinib discontinuation as well as study treatment (ibrutinib and/or rituximab) occurred in 10.8% of subjects; the most common events (≥ 1.0% of subjects) were arthralgia (2.0%), and anemia (1.1%).

TEAEs leading to dose reduction were reported in 13% of subjects for ibrutinib and 33% for fludarabine or cyclophosphamide.

TEAEs leading to ibrutinib dose reduction occurred in 12.8% of subjects; the most common events (≥ 1.0% of subjects) were arthralgia (3.1%), fatigue (1.7%), myalgia (1.7%), diarrhea (1.4%), and neutrophil count decreased (1.1%).

2.5.1. Discussion on clinical safety

The study E1912 safety set for the experimental arm includes 352 subjects with a median treatment duration of 34 months (range: 0.23-52.17), and 295 subjects with a treatment duration ≥24 months.

Given the heterogeneity of the Current Label Pool (=the safety profile presented in the current SmPC) and the overall major differences in terms of therapeutic setting and study population versus study

E1912, a direct comparison is not considered informative and therefore largely omitted in this AR. Importantly, according to protocol, SAEs and duration of AEs were not captured.

Safety data from Study E1912 were integrated with those for the Current Label Pool, ie, the registrational studies supporting the currently approved indications in the ibrutinib SmPC, for determination of the adverse drug reaction (ADR) profile for ibrutinib as a single agent or in combination therapy. The integrated population of Study E1912 and the Current Label Pool is referred to as the Overall Label Pool and represents data from 1,552 ibrutinib-treated subjects.

It should be noted that a treatment of fixed duration (control arm) is compared to a treatment until PD or intolerance (experimental arm). Safety data retrieved from the full study period as well as covering the first six months of therapy, where available and relevant, are presented.

The safety profile of ibrutinib must nowadays be considered reasonably known. Safety data obtained in subjects ≥65 years of age in the PCYC-1130-CA study with ibrutinib in combination with obinutuzumab, an anti-CD20 antibody with a more pronounced toxicity than rituximab, were assessed as acceptable. Therefore, the lack of data on SAEs and duration of AEs is a weakness but not deemed critical for the assessment of B/R for the Ibr+R combination.

Relative to the currently approved ADR table for ibrutinib in the SmPC, the only new ADR identified was blood creatinine increased (see SmPC section 4.8). No major differences in terms of overall grade ≥3 events were reported but it is noted that overall grade ≥3 bleeding events were twice as common in the experimental arm. The safety profile of the experimental arm roughly adheres to what has previously been described for ibrutinib. Some modifications in the incidences of adverse reactions were made in the table under section 4.8. of the SmPC.

Treatment-emergent haemorrhage AEs were more commonly noted in the experimental arm, overall 53% with grade 3+4 2.6% *vs* 11% and 1.2% in the control arm, respectively. These AEs were more common in the experimental arm also during the first six months. Major haemorrhage TEAEs were reported only for the experimental arm: overall 3.4%, grade 3+4 2.6%. Haemorrhage is part of ibrutinib's safety profile.

Cardiac arrhytmias are part of ibrutinib's known safety profile and reflected also in this study. Ventricular arrhytmias were noted only in the experimental arm.

Looking at the entire study period, melanoma as well as non-melanoma skin cancer were more commonly reported in the experimental arm. Haematological toxicity was more pronounced in the control arm.

TEAEs leading to treatment discontinuation and information on dose reductions were collected separately for Ibr, fludarabine, and cyclophosphamide. Dose-reduction was not allowed for rituximab. TEAEs leading to dose reduction were reported in 13% of subjects for ibrutinib and 33% for fludarabine or cyclophosphamide. Treatment discontinuation of the complete study medication due to AEs was reported for 11% of subjects in the experimental arm and 15% in the control arm.

In the context of the ongoing II/61 the MAH should include in the RMP a new date when analysis of aggregate clinical study data concerning haemorrhage risk in patients receiving antiplatelet and/or anticoagulant drugs is expected.

2.5.2. Conclusions on clinical safety

Safety data from Study E1912 do not raise any new concerns. Relative to the currently approved ADR table for ibrutinib in the SmPC, based on the addition of data from Study E1912, 1 new ADR (blood

creatinine increased) was added and modifications in the incidences of adverse drug reactions were implemented.

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 MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 16.1 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

The MAH should include in the RMP new date when analysis of aggregate clinical study data concerning haemorrhage risk in patients receiving antiplatelet and/or anticoagulant drugs is expected.

The CHMP endorsed this advice.

Safety concerns

Table: Summary of Safety Concerns

Important identified risks	Hemorrhage
	Hepatotoxicity (including hepatic failure)
	Non-melanoma skin cancer
	Interstitial lung disease (ILD)
	Atrial fibrillation
	Hypertension
Important potential risks	Drug-drug interaction
	Progressive multifocal leukoencephalopathy (PML)
	Infections (including viral reactivation)
	Cardiac arrhythmia (including ventricular tachyarrhythmias)
	Severe GI disorders
	Other malignancies (excluding non-melanoma skin cancer)
	Eye disorders
	Severe cutaneous adverse reactions
Missing information	Use in patients with severe cardiac disease
	Use in patients with severe hepatic impairment

Pharmacovigilance plan

Table 29: Ongoing and Planned Additional Pharmacovigilance Activities

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				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
PCI-32765MCL3002 A randomized, double-blind, placebo-controlled Phase 3 study of the Bruton's Tyrosine Kinase (BTK) inhibitor, PCI-32765 (ibrutinib), in combination with bendamustine and rituximab (BR) in subjects with newly diagnosed mantle cell lymphoma Ongoing	Evaluate efficacy and safety of ibrutinib in combination with BR versus BR alone	Overall safety profile	Final report	3rd Quarter 2020
54179060CLL1017 A Drug-Drug Interaction Study to Evaluate the Effect of Ibrutinib on the Pharmacokinetics of Oral Contraceptives, CYP2B6, and CYP3A4 Substrates in Female Subjects with B-cell Malignancy Ongoing	Determine the effect of ibrutinib on the exposure of oral contraceptives	Drug-drug interaction	Final report	2nd Quarter 2020

Risk minimisation measures

Table 30: Summary Table of Risk Minimization Activities by Safety Concern

Safety Concern	**Risk Minimization Measures**
Hemorrhage	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Hepatotoxicity (including hepatic failure)	**Routine risk minimization measures:** • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Non-melanoma skin cancer	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None

Safety Concern	Risk Minimization Measures
Interstitial lung disease (ILD)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4 • Recommendations regarding management of patients developing symptoms that are consistent with ILD (including treatment interruption) are provided in SmPC Section 4.4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Atrial fibrillation	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 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, are provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Hypertension	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Drug-drug interaction	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.5

Safety Concern	Risk Minimization Measures
	• SmPC Section 5.2 • PL Section 2 • Recommendations regarding management of patients concomitantly using moderate or strong CYP3A4 inhibitors (dosage reduction or treatment interruption) are 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Infections (including viral reactivation)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • Distribution of a DHPC to inform prescribers of the risk of Hepatitis B reactivation, provide background on the safety concern and recommendations
Cardiac arrhythmia (including ventricular tachyarrhythmias)	**Routine risk minimization measures:**

Safety Concern	Risk Minimization Measures
	• SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 5.1 • PL Section 2 • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Severe GI disorders	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Other malignancies (excluding non-melanoma skin cancer)	**Routine risk minimization measures:** • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Eye disorders	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Severe cutaneous adverse reactions	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None

Safety Concern	Risk Minimization Measures
Use in patients with severe cardiac disease	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 4 • Recommendations regarding management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are 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, are provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None
Use in patients with severe hepatic impairment	**Routine risk minimization measures:** • SmPC Section 4.2 • PL Section 2 • 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 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Hungary and Sweden.

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

Imbruvica is intended in combination with rituximab in previously untreated CLL.

3.1.2. Available therapies and unmet medical need

Approved agents from 4 different classes are available for the frontline treatment of patients with CLL; these include tyrosine-kinase inhibitors (eg, ibrutinib), alkylating agents (eg, chlorambucil, bendamustine, cyclophosphamide), nucleoside analogs (eg, fludarabine), and anti CD20 monoclonal antibodies (eg, rituximab, obinutuzumab). Chemoimmunotherapies (CIT; combinations of chemotherapy and anti-CD20 agents) are a mainstay of treatment for frontline CLL. Fludarabine, cyclophosphamide, and rituximab (FCR) is the most effective CIT treatment, however it is associated with a high rate of hematologic toxicities, and therefore its use is limited to younger, fitter patients without comorbidities. Phase 3 data from the CLL8 trial established FCR as the standard first-line therapy for young, fit patients with CLL. Subjects received a mean 5.2 (range, 0-6) cycles of FCR; of patients receiving study treatment, 26% did not receive the planned 6 cycles of FCR. With a median time on study of 5.9 years, median PFS was 56.8 months. Approximately 25% of patients were unable to tolerate FCR based CIT, with 56% of patients experiencing Grade 3 to 4 hematological toxicities, 25% experiencing Grade 3 to 4 infections, and 47% requiring dose reductions of any of the 3 drugs by more than 10%. Notably, CIT, including FCR, is considerably less effective in CLL with high-risk features, including del 17 or TP53 mutation.

Further, 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 unfavourable outcomes in terms of shorter PFS and OS with conventional CIT regimens used in CLL including alkylating drugs or purine analogues (Thompson 2016; Fink 2013; Byrd 2006). Providing patients who have these high-risk genomic features with effective therapy options remains an ongoing medical need.

Ibrutinib is currently approved as monotherapy or in combination with obinutuzumab in previously untreated CLL.

3.1.3. Main clinical studies

Study E1912 was a randomized, open-label, Phase 3 study designed to evaluate the efficacy and safety of ibrutinib plus rituximab (Ibr+R) vs. FCR for previously untreated subjects with CLL age 70 years or younger without del 17p. Subjects were randomized in a 2:1 ratio to receive Ibr+R (Arm A, n=354) or FCR (Arm B, n=175), respectively. Randomization was stratified according to age (< 60 years vs. ≥ 60 years), ECOG performance status (0/1 vs. 2), disease stage (Rai stage I/II vs. III/IV), and baseline cytogenetic abnormalities (deletion of the long arm of chromosome 11 [del 11q] vs. other). Subjects in the Ibr+R arm received ibrutinib in combination with 6 cycles of rituximab (after a single cycle of ibrutinib alone) followed by ibrutinib until disease progression. Subjects in the FCR arm received 6 cycles of FCR.

3.2. Favourable effects

At a median follow-up of 37 months, and a maturity of 25% in the control arm and 12% in the experimental arm, the interim analysis for PFS based on ECOG-ACRIN evaluation, the primary outcome, showed a HR of 0.340 (0.222, 0.522), p<0.0001 with an unstratified log-rank test. The outcome is supported by the performed sensitivity analyses and no worrisome trend is noted in the subgroup analyses. With 13 months longer follow-up, an updated analysis with 30% maturity in the control arm and 16% in the experimental arm, showed a HR of 0.374, p<0.0001.

At data cutoff the OS maturity was, as expected in this population, low: 1% in the experimental arm and 6% in the control arm with a HR of 0.170 (0.053, 0.541), p<0.007 with an unstratified log-rank test. The updated analysis (as above for PFS) showed a HR of 0.365, p=0.019, at a maturity of 7% in the control arm and 3% in the experimental arm.

PFS for the high-risk population showed a HR of 0.231 (0.132, 0.404), p<0.0001, with an unstratified log-rank test, at a maturity level of 31% in the control arm and 10% in the experimental arm. The updated analysis (as above) showed a HR of 0.260, p<0.0001, at a maturity of 40% in the control arm and 16% in the experimental arm.

The ORR per investigator was 97% in the experimental arm and 86% in the control arm, rate ratio 1.130 (1.061, 1.204), p<0.0001, due to a higher fraction of PRs in the experimental arm. Fractions reaching CR/CRi were 53% in the experimental arm and 58% in the control arm. This is in line with the known efficacy profile of ibrutinib.

3.3. Uncertainties and limitations about favourable effects

There are no remaining uncertainties about the favourable effects.

3.4. Unfavourable effects

The median treatment duration was 34 months in the experimental arm and 5 months in the control arm. Safety data retrieved from the full study period as well as covering the first six months of therapy were provided.

In terms of overall grade ≥3 events, no major differences between study arms were reported but it is noted that overall grade ≥3 bleeding events were twice as common in the experimental arm. Discontinuation of ibrutinib due to AEs was reported for 11% of subjects with arthralgia and anaemia as the most prevalent reasons.

Treatment-emergent haemorrhage AEs were more commonly noted in the experimental arm, overall 53% with grade 3+4 2.6% *vs* 11% and 1.2% in the control arm, respectively. These AEs were more common in the experimental arm also during the first six months. Major haemorrhage TEAEs were reported only for the experimental arm: overall 3.4%, grade 3+4 2.6%. Haemorrhage is part of ibrutinib's safety profile.

Grade 3+4 anaemia and febrile neutropenia were more commonly reported in the control arm.

Cardiac arrhytmias are part of ibrutinib's known safety profile and reflected also in this study. Ventricular arrhytmias were noted only in the experimental arm.

Treatment discontinuation of the complete study medication due to AEs was reported for 11% of subjects in the experimental arm and 15% in the control arm.

In terms of adverse events, the safety profile of the experimental arm roughly adheres to what has previously been described for ibrutinib. Relative to the currently approved ADR table for ibrutinib in the SmPC, based on the addition of data from Study E1912, 1 new ADR, blood creatinine increased, was identified and added to the ADRs table under section 4.8 of the SmPC.

Looking at the entire study period, melanoma as well as non-melanoma skin cancer were more commonly reported in the experimental arm.

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties about the unfavourable effects.

3.6. Effects Table

Table 31: Effects Table for Imbruvica in combination with rituximab in CLL

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	ECOG-ACRIN, unstratified	HR			0.340 (0.222, 0.522)	p<0.0001, based on 25% event rate in ctrl arm
	ECOG-ACRIN, high-risk group, unstratified	HR			0.231 (0.132, 0.404)	p<0.0001, based on 31% event rate ctrl arm, not all subjects characterized
OS		HR			0.170 (0.053, 0.541)	p<0.0007, based on 6% event rate ctrl arm
ORR	Rate ratio	%	96.9	85.7	1.130 (1.061, 1.204)	p<0.0001
Unfavourable Effects						
AEs grade ≥3		%	90.9	89.9		
SAEs		%	NA	NA		
AEs fatal		%	0.9%	1.3%		
AEs leading to discont		%	10.8%	15%		

Abbreviations: NA=not available

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The time-dependent efficacy outcomes consistently favour the experimental arm, Ibr+R, over the control arm, FCR. This holds true also for the updated efficacy evaluation with data cutoff 2 August 2019, with ITT event rates of 30% for PFS (25% at the primary analysis, 17 July 2018, with a median follow-up of 37 months) and 7% for OS in the control arm. However, as information on post-progression therapy is largely lacking and treatment with commercial ibrutinib monotherapy obviously

was an option at time of PD in the control arm, OS is hard to interpret. The significant differences between study arms in proportions of subjects not receiving study treatment or discontinuing the study due to withdrawal of consent is of concern, especially in an open-labelled study, although less so after the tipping point analysis for PFS provided in the response to the first LoQ. Further, as treatment regimens with different treatment duration are compared, data on PFS2 or a relevant proxy would be very informative, but will unfortunately not be available.

When isolation of contribution of each drug in the Ibr+R combination is considered, the pivotal study does not provide information. However, from a regulatory point of view, and as has been previously accepted in other procedures, ibrutinib could be viewed as a substitution of F+C in the guideline-recommended combination with rituximab. The MAH is encouraged to further investigate the efficacy of ibrutinib + rituximab *vs* ibrutinib monotherapy.

The sought indication is broader, i.e. encompassing all treatment-naïve CLL subjects, than the population studied in the pivotal study, i.e. subjects ≤ 70 years of age with previously untreated CLL/SLL without del 17p in need of treatment and deemed eligible for FCR. From an efficacy point of view, it is considered reasonable to assume similar activity of the combination in patients non-fit for FCR. Regarding activity in del 17p disease too few patients with TP53 mutation, sharing similar dismal prognostic value as for del 17p in the setting of CIT, were enrolled in the pivotal study to allow any conclusion. However, in several earlier studies ibrutinib, as monotherapy or in combination therapy, was shown to be highly effective also in del 17p disease. From a safety and tolerability point of view, the safety profile of ibrutinib is nowadays considered reasonably known. Safety data obtained in subjects ≥65 years of age in the PCYC-1130-CA study with ibrutinib in combination with obinutuzumab, an anti-CD20 antibody with a more pronounced toxicity than rituximab, were assessed as acceptable. Therefore, the lack of data on SAEs and duration of AEs is a weakness but not deemed critical for the assessment of B/R for the Ibr+R combination. The only new ADR identified with the Ibr+R combination, as compared to the Current Label Pool, was "blood creatinine increased".

3.7.2. Balance of benefits and risks

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Imbruvica in combination with rituximab in the treatment of CLL is positive.

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	Type II	I, IIIA and IIIB

	approved one		

Extension of indication in chronic lymphocytic leukaemia (CLL) to add combination with rituximab as follows: In combination with rituximab or obinutuzumab for the treatment of adult patients with previously untreated CLL.
This extension of the approved CLL indication is based on results from the Phase 3 Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG ACRIN) Study E1912 (also referred to as PCYC-1126e-CA).
The SmPC is revised to include information related to the new indication. The PL has been revised accordingly. Minor editorial changes have been implemented in Annex IIIA. An updated RMP has been submitted. Furthermore, the MAH took the opportunity to update the list of local representatives for Hungary in Sweden in the PL.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

Similarity with authorised orphan medicinal products

The CHMP by consensus decision is of the opinion that Imbruvica is not similar to Gazyvaro 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

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Imbruvica-H-C-3791-II-0059.