EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/667445/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0070

Note

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

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List of abbreviations

ADR	adverse drug reactions
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASO-PCR	allele-specific oligonucleotides-polymerase chain reaction
AST	aspartate aminotransferase
BCL-2	B-cell lymphoma-2
BCR	B cell receptor
BM	bone marrow
BTK	Bruton's tyrosine kinase
CHMP	Committee for Medicinal Products for Human Use
CIRS	Cumulative Illness Rating Scale
Clb+Ob	chlorambucil plus obinutuzumab
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus Disease 2019
CR	complete response
CrCl	creatinine clearance
CRi	complete response with an incomplete marrow recovery
CSRs	clinical study reports
Ctrough	concentration at end of dosing interval
[24h] del17p	deletion of the short arm of chromosome
17 DLBCL	diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	exposure-response
ERIC	European Research Initiative on CLL
ESMO	European Society for Medical Oncology
EU	European Union
FCR	fludarabine, cyclophosphamide, and rituximab
FD	fixed duration
FOIA	Freedom of Information Act
HR	hazard ratio
Ibr+Ob	ibrutinib plus obinutuzumab
Ibr+R	ibrutinib plus rituximab
Ibr+Ven	ibrutinib plus venetoclax
ICH	International Conference on Harmonisation
IGHV	immunoglobulin heavy-chain variable region
IRC	Independent Review Committee
iwCLL	International Workshop in CLL
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MPN	myeloproliferative neoplasm
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NGS	Next-Generation Sequencing
NF-κB	nuclear factor-kappa B

ORR	overall response rate
OS	overall survival
PB	peripheral blood
PBRER	Periodic Benefit Risk Evaluation Report
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PSA	propensity score analysis
PT	preferred term
RMP	Risk Management Plan
SAE(s)	serious adverse event(s)
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMQ	standardized MedDRA query
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAEs	Treatment-emergent serious adverse events
TLS	tumor lysis syndrome
T-PLL	T-cell prolymphocytic leukemia
TP53	tumor-suppressor protein 53
uMRD	Undetectable minimal residual disease
Ven+Ob	venetoclax plus obinutuzumab
WM	Waldenstrom’s macroglobinemia

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 N.V. submitted to the European Medicines Agency on 30 November 2021 an application for a variation.

The following variation was requested:

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

Extension of the existing CLL indication to include combination treatment with venetoclax for previously untreated patients based on efficacy and safety data from phase 3 study GLOW and phase 2 study CAPTIVATE; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. The RMP was amended as version 18.4 in line with the extension of indication.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0337/2021; on PIP Number: EMEA-001397-PIP03-14-M06.

For the purposes of this Type II variation application, and as previously agreed with the EMA, cross reference is made to both procedures no. EMEA/H/C/003791/II/0047 (EC Decision 02 August 2019) and EMEA/H/C/003791/II/0059 (EC decision 28 August 2020).

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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH sought Scientific Advice at the CHMP on clinical aspects.

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: Aaron Sosa Mejia

Timetable	Actual dates
Submission date	30 November 2021
Start of procedure	25 December 2021
CHMP Rapporteur's preliminary assessment report circulated on	18 February 2022
CHMP Rapporteur's preliminary assessment report circulated on	25 February 2022
Updated PRAC Rapporteur's assessment report circulated on	3 March 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 March 2022
Updated CHMP Rapporteur's assessment report circulated on	17 March 2022
Request for supplementary information adopted by the CHMP on	24 March 2022
MAH's responses submitted to the CHMP on	21 April 2022
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	25 May 2022
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	27 May 2022
Updated PRAC Rapporteur's assessment report on the MAH's responses circulated on	2 June 2022
PRAC RMP advice and assessment overview adopted by PRAC on	10 June 2022
Updated CHMP Rapporteur's assessment report on the MAH's responses circulated on	16 June 2022
CHMP opinion adopted on	23 June 2022
The CHMP adopted a report on similarity of Imbruvica with Gazyvaro on date	23 June 2022
The CHMP adopted a report on the significant clinical benefit for Imbruvica in comparison with existing therapies	23 June 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic lymphocytic leukemia (CLL). Small lymphocytic lymphoma (SLL) is a variant of CLL characterized by the absence of lymphocytosis. Clinically, these two entities are considered and managed as the same disease.

Claimed the therapeutic indication

"IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab ***or venetoclax*** is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL)".

Epidemiology

CLL is the most prevalent adult leukemia in Western countries with an incidence of 4.2/100,000/year and a median age of 72 years at diagnosis.

Biologic features

CLL/SLL is a neoplastic disorder characterized by the clonal expansion of mature B cells in PB, BM, and lymphoid tissues driven primarily by chronic B cell receptor (BCR)–dependent signaling and impaired programmed cell death. Tonic BCR signaling in CLL results in the activation of a host of downstream effectors that modulate several pathways affecting the survival, proliferation, and migration of CLL cells. Among the key kinases that are constitutively activated are BTK and phosphatidyl-inositol 3 kinase (PI3K), effectors that trigger secondary signaling pathways such as JNK, ERK, mTOR, and NF-κB. Activation of the later pathway promotes the overexpression of the BCL-2 family of anti-apoptotic proteins (eg, BCL-2, Bcl-xL, Mcl-1) allowing CLL cells to survive and escape programmed apoptosis.

Clinical presentation, diagnosis

The disease is characterized by a spectrum of clinical manifestations, ranging from indolent disease requiring no treatment for decades, to markedly aggressive disease that requires urgent intervention.

Management

Therapy for patients with previously untreated CLL includes agents with distinct mechanisms of action such as BTK inhibitors (ibrutinib, acalabrutinib), alkylating agents (chlorambucil, bendamustine, cyclophosphamide), a nucleoside analogue (fludarabine), anti-CD20 monoclonal antibodies (rituximab, obinutuzumab), and a BCL-2 inhibitor (venetoclax). Treatment regimens approved for previously untreated CLL are administered for a fixed duration (eg, combination regimen fludarabine, cyclophosphamide, and rituximab (FCR)or continuously until disease progression or unacceptable toxicity (eg, ibrutinib and acalabrutinib). Ibrutinib is approved in this indication as a single-agent or in combination with an anti-CD20 antibody (i.e., rituximab, obinutuzumab).

Combination chemoimmunotherapy, particularly FCR, has the potential to induce deep responses (40% to 45% of patients achieve CR). However, even with FCR treatment, many patients (including those who achieve CR) eventually relapse and in patients with high-risk features, such as unmutated IGHV and del17p/TP53 mutation, chemoimmunotherapy results in inferior outcomes. In addition, exposure to chemoimmunotherapy may be associated with significant toxicities including myelosuppression, immune suppression, and treatment-related malignancies such as myelodysplasia, and acute myeloid leukemia.

As continuous therapy in patients with previously untreated CLL, ibrutinib is associated with marked improvement in PFS and OS (24-month landmark: 89% and 95%, respectively across a broad spectrum of patients including those with high-risk disease. However, single-agent ibrutinib results in a limited rate of complete remissions (10% at a median follow-up of 28 months) and is rarely associated

with undetectable MRD, thus requiring the use of continuous therapy. When used in combination with anti-CD20 antibodies, the rate of complete remissions increases (54.5% per investigator for Ibr+R, 19.5% per IRC for ibrutinib plus obinutuzumab.

The choice of upfront therapy in treatment-demanding disease is generally guided by patient factors, such as age and comorbidities, as well as disease-related factors, notably high-risk features.

Figure 1 Treatment options - ***From the ESMO GL on CLL, 2020***

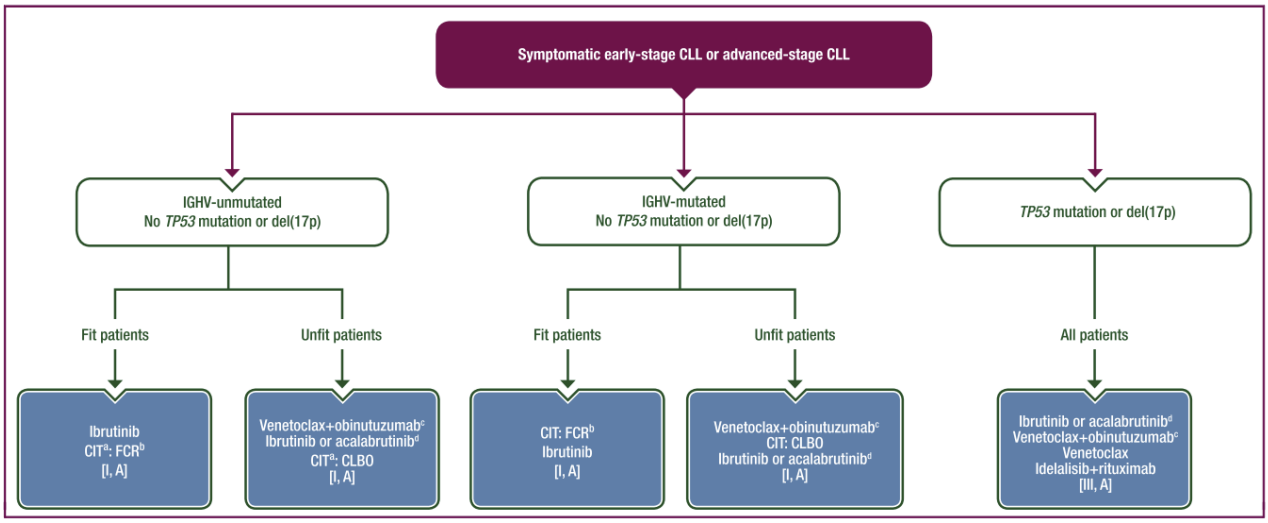


Figure 1. Front-line therapy.
The order of the recommended treatments for each subgroup is based on expert opinion considering time-limited as more valuable therapy, if there is equal evidence for two different treatment options.
BR, bendamustine plus rituximab; CIT, chemoimmunotherapy; CLBO, chlorambucil plus obinutuzumab; CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab; IGHV, immunoglobulin heavy chain variable.
[a] CIT as alternative treatment, only if reasons against treatment with targeted therapies or non-availability.
[b] BR might be considered alternatively in patients above the age of 65 years.
[c] If available.
[d] If approved and available.

Time-limited therapy with the combination of venetoclax and obinutuzumab (Ven+Ob) was recently approved in patients with previously untreated CLL based on the results of Study CLL14, which showed a significant improvement in PFS versus Clb+Ob (PFS at 24-month landmark: 88% vs 64% with Ven+Ob and Clb+Ob, respectively). The combination was associated with a CR rate of 50% and MRD negativity rates of 57% and 76% in the BM and PB. However, updated results from the study based on longer follow-up (median follow up of 52.4 months) show that PFS in patients with high-risk features (eg, positive for del17p or TP53 mutation) are not sustained and MRD negativity in PB rapidly declines.

More effective targeted regimens that result in deeper responses and longer remissions without the need for continuous administration are needed to allow for a clinically meaningful treatment-free period for patients with newly diagnosed CLL.

Table 1: Summary of Approved Treatments for First-line Treatment of CLL in Europe

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
Acalabrutinib+/- obinutuzumab 2020	Previously untreated CLL	Combination	Phase 3/acalabrutinib monotherapy and obinutuzumab+ chlorambucil	535	PFS, OS, ORR, DOR
Venetoclax+ obinutuzumab 2020	Previously untreated CLL	Combination	Phase 3/ obinutuzumab+ chlorambucil	432	PFS, ORR, MRD negativity rate
Ibrutinib+ rituximab 2020	Previously untreated CLL	Combination	Phase 3/FCR	529	PFS, OS, ORR
Ibrutinib +obinutuzumab 2019	Previously untreated CLL	Combination	Phase 3/chlorambucil +obinutuzumab	229	PFS, ORR, OS
Ibrutinib 2016	Previously untreated CLL	Monotherapy	Phase 3/chlorambucil	269	PFS, ORR, OS
Idelalisib + rituximab 2014	Previously untreated CLL with 17p deletion or *TP53* mutation in patients who are not eligible for any other therapies	Combination	Phase3/ rituximab	220	PFS, OS
Obinutuzumab + chlorambucil 2014	Treatment of patients with previously untreated CLL 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 R/R CLL)	Combination	Phase 3/ FC	817	PFS
Bendamustine[a] 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 1957	CLL (unspecified)	Monotherapy	Unknown	Unknown	Unknown
Fludarabine	CLL in patients with sufficient BM reserves; only initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of PD.	Monotherapy	Phase 3/ chlorambucil	394	ORR, CR rate, DOR, TTP

BM=bone marrow; CLL=chronic lymphocytic leukemia; CR=complete response; DOR=duration of response; FC=fludarabine + cyclophosphamide; FCR=fludarabine + cyclophosphamide + rituximab; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; R/R=relapsed/refractory; *TP53*=tumor-suppressor protein P53 gene; TTP=time to progression

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

2.1.2. About the product

Ibrutinib is a small molecule BTK inhibitor with a molecular weight of 440.50 g/mole (anhydrous basis). It is a small molecule drug that inhibits B-cell proliferation and survival by irreversibly binding the protein Bruton's tyrosine kinase (BTK). Blocking BTK inhibits the B-cell receptor pathway, which is often aberrantly active in B cell cancers. The Chemical Abstracts Service Registry Number is 936563-96-1. Ibrutinib has a single chiral center, which is the R enantiomer.

Currently approved indications:

> IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

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

IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.

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

The MAH was given SA EMA/CHMP/SAWP/718302/2017 on clinical aspects, such as: the scientific rationale supporting the development of the combination of ibrutinib and venetoclax, the proposed clinical package; the proposed Phase 3 study design, the proposed choice of the comparator arm, the patient population as defined by the eligibility criteria, the choice of independently reviewed PFS as the primary endpoint, the choice of secondary endpoints.

2.1.4. General comments on compliance with GLP, GCP

N/A

2.2. Non-clinical aspects

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

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

Key efficacy and safety data to support this Type II variation to extend the current authorized indication in CLL are derived from the Phase 3 randomized, controlled Study CLL3011 (Ibr+Ven versus Clb+Ob) and Phase 2 Study 1142 (*Table 1*).

Table 1. Description of Studies CLL3011 and 1142

Study	Study Design	Study Population	Endpoints	Region	Number of Subjects	Median Time on Study
CLL3011	Phase 3, randomized, open-label, multicenter, international efficacy and safety study of Ibr+Ven versus Clb+Ob	Previously untreated CLL/SLL (without del17p or known *TP53* mutation); ≥65 years of age or 18 to 64 years of age with comorbidities	Primary: PFS as assessed by IRC Secondary: MRD negativity rate by NGS in BM, CR rate, ORR, OS, rate of sustained platelet improvement, rate of sustained hemoglobin improvement, and time to improvement in FACIT-Fatigue score, and safety	US, EU, ROW (Canada; Great Britain; Israel; Russia; Turkey)	Randomized: 211 (106 Ibr+Ven, 105 Clb+Ob)	27.7 months (primary analysis); 34.1 months (extended follow-up)
1142	Phase 2, multicenter, international efficacy and safety study of Ibr+Ven	Previously untreated CLL/SLL (with or without del17p/*TP53* mutation); **FD cohort**: ≤70 years of age with an ECOG PS of 0-2 **MRD cohort**: <70 years of age with an ECOG PS of 0-1	**FD cohort**: Primary: CR rate (per INV assessment) Secondary: DOR, MRD-negativity rate, ORR, TLS risk reduction, PFS, OS, and safety **MRD cohort**: Primary: 1-yr DFS rate in confirmed uMRD subjects Secondary: MRD-negativity rate, ORR, CR rate, DOR, TLS risk reduction, PFS, and OS, and safety, PK of Ibr+Ven	US, EU (Spain, Italy), ROW (Australia, New Zealand)	**FD cohort**: 159 subjects incl. 136 subjects without del17p **MRD cohort**: 164	FD cohort: 27.9 months (primary analysis); 38.7 months (extended follow-up); MRD cohort 38.2 months (primary analysis of FD cohort); 47.8 months (extended follow-up)

BM=bone marrow; Clb+Ob=chlorambucil plus obinutuzumab; CLL=chronic lymphocytic leukemia; CR=complete response; del17p=deletion of short arm of chromosome 17; DFS=disease-free survival; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; EU=European Union; FACIT=Functional Assessment of Chronic Illness Therapy; FD=fixed duration; Ibr+Ven=ibrutinib plus venetoclax; INV=investigator; IRC=Independent Review Committee; MRD=minimal residual disease; NGS=Next-Generation Sequencing; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetics; ROW=rest of world; SLL=small lymphocytic lymphoma; TLS=tumor lysis syndrome; *TP53*=tumor-suppressor protein 53; uMRD=undetectable minimal residual disease; US=United States

Source: Mod5.3.5.1/CLL3011; Mod5.3.5.2/1142

2.3.2. Pharmacokinetics

Bioanalytical methods

Analytical methods for ibrutinib and its metabolite JNJ-54243761 (PCI-45227) were validated and have been assessed earlier and deemed acceptable. Ibrutinib and JNJ-54243761 (PCI-45227) samples were analysed within 665 days of storage, which is within the 973 days established with an earlier method. QCs and calibration standards performed within preset acceptance criteria in both studies GLOW (54179060CLL3011) and PCYC-1142-CA, including ISR in the latter. Testing for interference of venetoclax with the analysis of ibrutinib and PCI-45227 within 15% of the low QC nominal values, showing no interference.

An LC-MS/MS method for the concentration determination of venetoclax in K2EDTA anticoagulated plasma was developed at Abbvie, report A1195425 (ABT199). Samples from studies GLOW and PCYC-1142-CA were analysed within the established long term stability for venetoclax. No ISR was performed for venetoclax. QCs and calibration standards performed within preset acceptance criteria.

Population PK analysis of ibrutinib administered with and without venetoclax

The pharmacokinetics of ibrutinib were analysed using population pharmacokinetic analysis approach (using NONMEM software (Icon)). The first-order condition estimation approximation was used as the estimation method. Furthermore, because log-transformed data were used, the INTERACTION option was not applied in NONMEM. The NONMEM analysis was performed in a validated environment, based on Good Automated Manufacturing Practice and in accordance with Title 21 of the Code of Federal Regulations Part 11 and Good Clinical Practice regulations. Small modifications to the analysis dataset, exploratory analysis, diagnostic graphics, post-processing of NONMEM analysis results, and the statistical analysis were carried out using R Project for Statistical Computing, Version 3.4.1 or higher (Comprehensive R Network, http://cran.r-project.org [R Development Core Team 2012]).

Studies and data that were used to develop the population pharmacokinetic model are summarized in *Table 1* and described briefly in *Table 2*. The subjects' ages at baseline ranged from 28 to 93 years of age, with a median of 64 years, and their body weights at baseline ranged from 47 to 140 kg, with a median of 78 kg. The majority of subjects were White (approximately 87%) and male (approximately 59%).

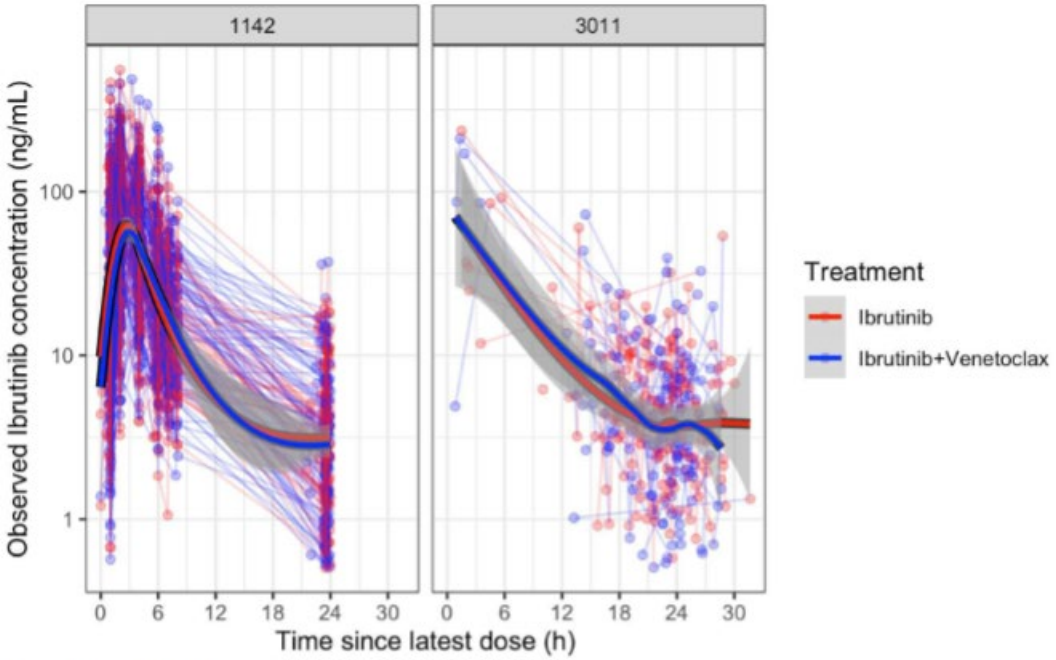
Table 2. Overview of Studies Included in the Population Pharmacokinetics analysis

	PCYC-1142-CA (CAPTIVATE, 1142)	54179060CLL3011 (GLOW, CLL3011)
Type of study	Multicenter, 2-cohort, Phase 2 study of the combination of Ibr+Ven in subjects with treatment-naïve CLL/SLL	Randomized, open-label, multicenter, Phase 3 study of the combination of Ibr+Ven versus Clb+Ob for the first-line treatment of subjects with CLL/SLL
Indication	Treatment-naïve CLL/SLL, including those with del 17p or *TP53* mutation	Treatment-naïve CLL/SLL without del 17p or known *TP53* mutation
Objective(s)	Assess ability of Ibr+Ven to achieve complete clinical response, MRD negative response, and durability of response in the setting of ibrutinib discontinuation	Determine efficacy and safety of Ibr+Ven compared with Clb+Ob
Type of subjects	MRD cohort only (n=164)	Subjects assigned to Ibr+Ven (n=106)
No. of subjects with PK data available	149	104
Dose	Ibrutinib: 420 mg once daily	Ibrutinib: 420 mg once daily
	Venetoclax dose ramp-up: 20-400 mg once daily over 5 weeks	Venetoclax dose ramp-up: 20-400 mg once daily over 5 weeks
Route of administration	Oral	Oral
Formulation	Ibrutinib: 140 mg capsules	Ibrutinib: 140 mg capsules
	Venetoclax: 10 mg, 50 mg, or 100 mg tablets	Venetoclax: 10 mg, 50 mg, or 100 mg tablets
Sampling times	PK: samples collected at predose, 1, 2, 4, 6, 8 h on Cycle 2 Day 1 (ibrutinib at steady-state) and Cycle 6 Day 1 (Ibr+Ven at steady-state)	PK: samples collected at predose on Cycle 2/3 Day 1 (ibrutinib at steady-state) and Cycle 5/6 Day 1 (Ibr+Ven at steady-state)
Bio-analytical method	LC-MS/MS	LC-MS/MS
Limit of quantification (ng/mL)	Ibrutinib: 0.500	Ibrutinib: 0.500
	PCI-45227: 0.500	PCI-45227: 0.500
	Venetoclax: 2.14	Venetoclax: 2.11

Clb+Ob=obinutuzumab plus chlorambucil; CLL=chronic lymphocytic leukemia; Ibr+Ven=ibrutinib plus venetoclax; LC-MS/MS=liquid chromatography with tandem mass spectrometry; MRD=minimal residual disease; PK=pharmacokinetic; SLL=small lymphocytic lymphoma

The potential differences between Study 1142 and Study CLL3011 were explored graphically by overlaying concentration data from the 2 studies. The observed plasma concentration is presented in Figure 2.

Figure 2. Log-linear Plot of Ibrutinib Concentrations vs Time Since Latest Dose by Study



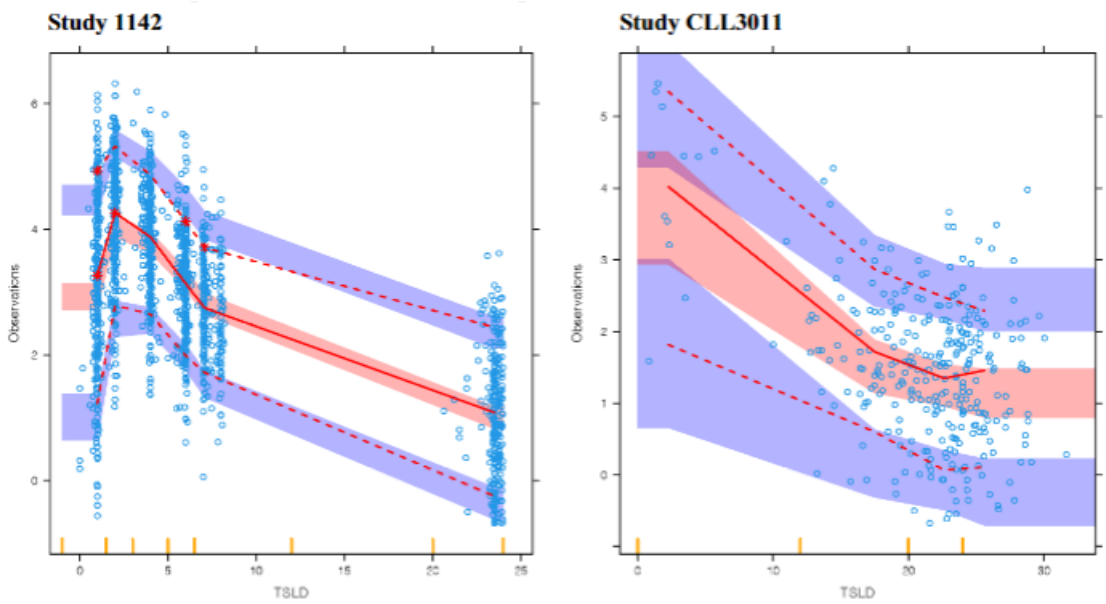
CI=confidence interval.
Individual subject profiles (dots and thin lines); smooth (thick lines) and 95% CI of the smooth (grey area).

Ibrutinib disposition was described by an previously developed (Population Pharmacokinetic Analysis of Ibrutinib 2015) open, 2-compartment disposition model with linear elimination. The absorption of ibrutinib was best described by a sequential zero-first order process, characterized by lag time, D1, and ka. The previously developed population PK model was first used, without re-estimation (maximum a posteriori approach), to describe the attained plasma concentrations from studies 1142 and 3011. The VPCs indicated that, while the model described Ctrough data well, the ibrutinib peak was under-predicted for Study 1142 (Figure 4). Also, for Study 1142 the ETAs were not centered on zero, with highly significant deviations ($p<0.0001$) for V2, Q, V3, and lag time; the largest deviation was a median ETA of 0.3 for V2, corresponding to a 35% higher V2.

Several sets of re-estimations of model parameters were attempted, resulting in a final model (run 310) where all structural parameters (CL, V2, Q, V3, ka, D1 for subjects on fasting and modified fasting regimen, lag time, and the residual unexplained variability) were re-estimated, but the covariate effects (CYP3A inhibitors and age on F1) and random effects were fixed to previous estimates. The fit of this model was significantly improved, as indicated by a fall in objective function of 111.6 points.

The comparison between the re-estimated and the original parameters indicates a longer lag time (by 58%) and duration of the zero-order absorption process (by 28%). The apparent volume of distribution at steady-state (estimated as the sum of V2/F and V3/F; 6,904 L) was 24% smaller than the previous estimate, and apparent intercompartmental clearance was reduced by approximately 45% compared with the original. However, no large difference was observed between the original and re-estimated values for CL/F (−8%). Visual predictive check with updated model is shown in *Figure 2*, and model parameters for the final model are shown in *Table 3*. After re-estimation of parameters, tests for differences in CL and F1 of ibrutinib when administered alone or with venetoclax were not significant, suggesting no meaningful interaction of venetoclax on the pharmacokinetics of ibrutinib.

Figure 3. Visual Predictive Check of Concentrations in the Current Dataset vs Time Since Latest Dose, Compared with Predictions of the Updated Model



TSLD=time since latest dose (hours).
Observations: ibrutinib plasma concentrations (ng/mL).
Circles: concentration observations. Lines: median (solid), 5th, 95th percentiles (dashed) of the binned observations. Red band: confidence intervals of the median of the model prediction. Blue bands: confidence interval of the 5th and 95th percentiles of the model predictions (1,000 replicates).

Table 3. Updated Parameter Estimates of the Previous Population PK Model (run 310)

Parameter	Population Mean Estimate	%SEM	BSV (%CV)	%SEM
CL/F (L/h)	1,002	2.0	-	-
V2/F (L)	306	56	154.6	-
Q/F (L/h)	392	15	64.9	-
V3/F (L)	6,597	11	56.0	-
k_a (h^{-1})	0.443	2.7	-	-
ALAG1 (h)	0.357	6.0	72.5	-
D1 fast/mod fast (h)	1.65	2.0	-	-
D1 fed (h) (fixed)	3.29	-	-	-
F1 mod fast/fed (fixed)	1	-	67.5	-
F1 fast (fixed)	0.666	-	-	-
Effect of CYP3A inhibitors (ratio, fixed)	1.59	-	-	-
Effect of age (power, fixed)	0.699	-	-	-
RUV	65.1	3.3		

ALAG1=temporal delay (lag time) before absorption process is started; BSV=between-subject variability; %CV=percent coefficient of variation; CL/F=apparent clearance; CYP=cytochrome P450; D1=duration of the zero-order absorption process; F1=relative bioavailability; k_a=first-order absorption rate constant; PK=pharmacokinetic; Q/F=apparent intercompartmental clearance; RUV=residual unexplained variability; SEM=relative standard error of the mean parameter; V2/F=apparent central volume of distribution; V3/F=apparent peripheral volume of distribution.

Noncompartmental analysis of the effect of Venetoclax on the Pharmacokinetics of Ibrutinib

Mean steady-state ibrutinib exposure, as based on the AUC0-24, was similar when administered as a single agent at 420 mg once daily to MRD cohort subjects with CLL/SLL during the lead-in period of

Study 1142 (641 ng.h/mL) or in combination with 400 mg venetoclax (637 ng.h/mL). Mean steady-state ibrutinib exposures for subjects receiving 420 mg/day i n combination with venetoclax in Study 1142 were also similar to those observed previously in CLL/SLL subjects at a 420 mg daily dose. The reported AUC0-24 at steady-state in Study 1142 was 641 ng.h/mL (as single agent) versus 708 ng.h/mL in Study PCYC-1102-CA. For Study CLL3011, based on the modeling results, no effect of venetoclax on ibrutinib pharmacokinetics was observed.

Noncompartmental analysis of the effect of Ibrutinib on the Pharmacokinetics of Venetoclax

The effect of ibrutinib on the pharmacokinetics of venetoclax was investigated by comparing steady-state pharmacokinetic data from Study 1142, in which venetoclax was administered in combination with ibrutinib, with historical monotherapy data for venetoclax from Study M12-175 (*Table 4*). Study M12-175 evaluated the pharmacokinetics of venetoclax at a once-daily dose of 20 to 1,200 mg in subjects with relapsed or refractory CLL/SLL and non-Hodgkin lymphoma. Pharmacokinetic data for this study are provided for subjects with relapsed or refractory CLL/SLL who received venetoclax alone without concomitant use of moderate or strong CYP3A inhibitors under low-fat conditions.

An increase of approximately 1.8-fold (based on AUC0-24) in venetoclax exposure was observed in subjects receiving venetoclax in combination with ibrutinib in Study 1142 compared with subjects receiving venetoclax alone in Study M12-175. The venetoclax observed mean Ctrough in study 3011 was higher in Cycle 6 Day 1 (1,765 ng/mL), reflecting the mean steady-state Ctrough at 400 mg, compared with Cycle 5 Day 1 (1,139 ng/mL), reflecting the mean steady-state Ctrough at 200 mg, due to the venetoclax ramp-up period. Venetoclax trough concentrations at steady-state were higher in this study in combination with ibrutinib compared with monotherapy based on historical data (mean range of 630 to 810 ng/mL).

The biological reason for this increase in systemic exposure is unclear. In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. Venetoclax is a P-gp and BCRP substrate, as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. Therefore, the observed increase in venetoclax exposure, when administered with ibrutinib, may be due to a transporter-mediated interaction, which may increase the bioavailability and/or reduce the clearance of the compound.

Table 4. Steady-state PK Parameters of Venetoclax Following Once-daily Oral Administration of 400 mg Venetoclax Alone or 400 mg Venetoclax in Combination With 420 mg Ibrutinib in Subjects With CLL/SLL (Without Moderate/Strong CYP3A Inhibitors; Studies M12-175 and PCYC-1142-CA)

Parameter	Study M12-175 Venetoclax 400 mg Alone	Study M12-175 Venetoclax 400 mg Alone[a]	Study PCYC-1142-CA Venetoclax 400 mg qd +Ibrutinib 420 mg qd
N	8	60	131
t_{max}, median (range), h	7.0 (4.0–11.2)	6.0 (2.0–24.7)	6.00 (0.0–8.08)
C_{max}, mean (SD), ng/mL	2,180 (1,080)	2,070 (1,070)	3,532 (1,987)
AUC_{0-24}, mean (SD), ng.h/mL	35,500 (20,300)	31,800 (15,500)	58,965 (39,040)

AUC=area under the plasma concentration-time curve; AUC_{0-24}=area under the plasma concentration-time curve from time 0 to 24 hours; CLL=chronic lymphocytic leukemia; C_{max}=observed maximum concentration; CYP=cytochrome P450; N=maximum number of subjects with data; PK=pharmacokinetic; qd=once daily; SD=standard deviation; SLL=small lymphocytic lymphoma; t_{max}=time of the maximum concentration.

[a] Steady-state data at Week 7 Day 1 in the expansion cohort.

Source: Roberts 2016 (Supplemental Appendix, TableS7), Mod5.3.5.2/1142PKreport/Tab2.3

2.3.3. Pharmacodynamics

Mechanism of action

Ibrutinib and venetoclax have complementary mechanisms of action targeting distinct B-cell pathways involved in the propagation of CLL cells. Ibrutinib arrests CLL cell proliferation. Venetoclax is pro-apoptotic and induces early cell death. Ibrutinib also affects the adhesion and migration of CLL cells, resulting in rapid efflux of CLL cells from tissue compartments, especially lymph nodes and spleen, into the peripheral blood. Venetoclax treatment results in effective clearance of the blood and bone marrow, but residual disease can be observed in lymph nodes. Together the 2 drugs are expected to provide complementary and effective clearance of disease.

2.3.4. PK/PD modelling

The clinical study design was not optimal for PK/PD modelling (a single-dose level, dose adjustments, relatively high correlation between metrics, no information on monotherapy treatment). In addition, the current assessment evaluated numerous endpoints without any correction for multiplicity. Therefore, the analysis should be considered purely exploratory and only general information on the PKPD modelling is presented as interpretation of these findings should be done cautiously.

Exposure-efficacy analysis

PFS was explored by Kaplan-Meier plots. Splitting PFS by study, survival curves appeared different, therefore, the graphical exploration of PFS was performed for each study separately. No relationship between PFS with exposure could be observed in any of the plots.

The rates of response for CRR, ORR, and MRD negativity by flow cytometry and NGS were plotted by quartiles of the summary exposure measures. CRR and ORR appear to be essentially independent of ibrutinib or venetoclax concentrations. However, for MRD negativity by flow cytometry and MRD negativity by NGS, there is a trend towards an increase with increasing systemic exposure for both ibrutinib and venetoclax, further assessed using regression analysis.

All ibrutinib and venetoclax systemic exposure summaries had significant effects on MRD negativity by flow cytometry and MRD negativity by NGS (the latter available only for Study CLL3011), with ibrutinib Ctrough providing the most significant effect for both MRD negativity by flow cytometry ($p=0.00144$) and MRD negativity by NGS ($p=0.00126$). The relationships between venetoclax observed Ctrough and MRD negativity by flow cytometry and MRD negativity by NGS were also significant ($p=0.00561$ and $p=0.00603$, respectively). When including the most significant ibrutinib descriptor of systemic exposure (Ctrough) together with the venetoclax effect (Ctrough_obs_venetoclax) in the model, and their interaction, both were highly significant ($p<0.01$) for MRD negativity by flow cytometry and NGS, but with a significant negative interaction. Covariates were added in a stepwise fashion to the MRD negativity by flow cytometry model, in which Ctrough and venetoclax observed Ctrough are the independent variables, resulted in a significant effect of the IGHV prognostic factor. The probability of MRD negativity by flow cytometry is lower in subjects with mutated IGHV than in subjects with unmutated IGHV. There was no significant interaction between IGHV status and the ibrutinib or venetoclax effects.

Exposure-safety analysis

The incidence of the different types of TEAEs was plotted by quartiles of the summary exposure measures. On visual inspection, liver function abnormalities, all Grade ≥3 TEAEs, all serious TEAEs, and all TEAEs leading to ibrutinib and venetoclax dose reduction, dose interruption, or drug discontinuation appear to increase with increasing exposure for both ibrutinib and venetoclax. In addition, any events of hemorrhage, diarrhea, and infection appear to increase with increasing ibrutinib exposure, and neutropenia appears to increase with increasing venetoclax exposure. These TEAEs were therefore explored further using regression analysis.

There were significant associations of both ibrutinib and venetoclax exposure on the incidence of Grade ≥3 TEAEs, with the most significant effect being venetoclax observed Ctrough. Upon fitting effects of ibrutinib observed Ctrough and venetoclax observed Ctrough simultaneously, and also the interaction of these parameters, only the venetoclax association remains significant. Ibrutinib exposure was significantly associated with the incidence of TEAEs leading to ibrutinib dose reduction, dose interruption, or drug discontinuation. Age was a significant covariate for association with TEAEs leading to ibrutinib dose reduction, dose interruption, or drug discontinuation, with the risk increasing with age. Sex was a significant covariate for association with TEAEs leading to venetoclax dose reduction, dose interruption, or drug discontinuation, with the risk found to be higher in females.

2.3.5. Discussion on clinical pharmacology

Analytical methods for ibrutinib and its metabolite JNJ-54243761 (PCI-45227) were validated and have been assessed earlier and deemed acceptable. An LC-MS/MS method for the concentration determination of venetoclax in K2EDTA anticoagulated plasma was developed. The bioanalysis is deemed acceptable.

The exposures of ibrutinib and venetoclax were assessed using non-compartmental analysis. No dedicated DDI studies are included in the current submission. The potential for a DDI between ibrutinib and venetoclax was evaluated via comparison of the ibrutinib and venetoclax pharmacokinetics from combination treatment and monotherapy (historical data). Additionally, the ibrutinib plasma concentrations were analysed using nonlinear mixed effects modelling.

The pharmacokinetics of ibrutinib and venetoclax were assessed using non-compartmental analysis. The potential for a DDI between ibrutinib and venetoclax was evaluated via comparison of historical data. Additionally, the ibrutinib plasma concentrations were analysed using nonlinear mixed effects modelling. Venetoclax observed plasma concentration at steady-state exposure (approximately 1.8-fold higher AUC, 1.7-fold higher Cmax and 2.8-fold higher Ctrough). In vitro studies suggest that ibrutinib may inhibit BCRP and P-gp transport at clinical doses. Venetoclax is a P-gp and BCRP substrate, as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. Therefore, the observed increase in venetoclax exposure, when administered with ibrutinib, may be due to a transporter-mediated interaction, which may increase the bioavailability and/or reduce the clearance of the compound.

Non-compartmental analysis indicated that Ibrutinib pharmacokinetics were generally consistent with previously reported (historical) assessments and no effect of venetoclax on ibrutinib pharmacokinetics was observed. The population pharmacokinetic analysis of ibrutinib using a previously developed model indicated that, while the model described Ctrough data well, the ibrutinib peak was under-predicted. Several sets of re-estimations of model parameters were attempted, resulting in a final model where all structural parameters were re-estimated, but the covariate effects and random effects were fixed to previous estimates. After re-estimation of parameters, tests for differences in CL and F1 of ibrutinib when administered alone or with venetoclax were not significant. The model could describe the ibrutinib plasma concentration acceptably.

ER analysis was also conducted, where clinical efficacy and safety endpoint data were considered from 253 subjects in both Studies 1142 and CLL3011. For the ER analysis of binary endpoints, a graphical exploration (incidence of endpoint by quartile of exposure) was performed and, if significant trends were observed, logistic regression (mono- [for individual compounds] and bi-variate [for both ibrutinib and venetoclax]) was performed. Kaplan-Meier curves stratified by quartiles of exposure summaries were used to explore the ER relationship for PFS.

The present clinical studies, performed at a single-dose level with along with dose adjustments based on safety, are not optimally suited for highlighting ER relationships. There is also a relatively high correlation between metrics of systemic exposure for ibrutinib and observed Ctrough of venetoclax (were still explored as the coefficient of determination is below 0.8, however, only cautious conclusion can be made). There was no monotherapy treatment arm with ibrutinib and venetoclax. The ER assessment evaluated numerous endpoints without any correction for multiplicity, so it is also possible that some of the significant ER relationships were highlighted by chance alone. The results should be interpreted with caution.

In general, increasing systemic exposures were associated with increased incidence of all Grade ≥3 TEAEs and TEAEs leading to ibrutinib or venetoclax dose reduction, dose interruption, or drug discontinuation. The observed association between systemic exposure and all Grade ≥3 TEAEs was driven primarily by the increased incidence of neutropenia and diarrhea. In interpretation of these findings, the study design and potential confounding effects of the two components of the combination, should be considered.

As the exposure of venetoclax is higher when given in combination with ibrutinib, adherence to the ibrutinib and venetoclax dose-modification guidelines is important in ensuring the safety of the combination. The dose-modification guidelines will ensure an optimal efficacious dose for most of the patients whilst providing the option for a more tolerable reduced dose for the patients who are more vulnerable for specific TEAEs.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of ibrutinib in combination with venetoclax have been adequately characterized and found to be consistent with previously reported (historical) assessments. Combination of ibrutinib and venetoclax results in an increased exposure of venetoclax (1.8-fold and 2.5-fold higher AUC24 and Cmin respectively), which has been described in the SmPC section 4.5. The clinical perspective on safety with the proposed posology is discussed in the clinical safety section.

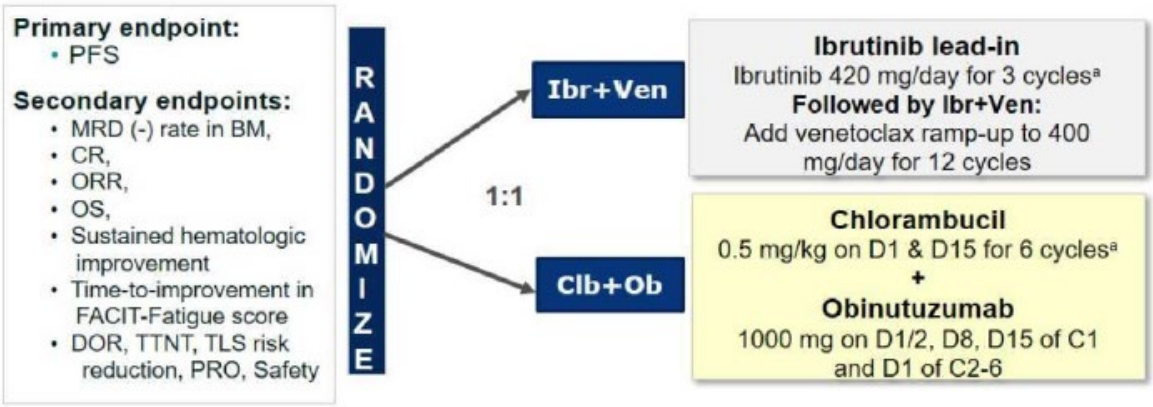
2.4. Clinical efficacy

2.4.1. Main studyies

Study CLL3011

A Randomized, Open-label, Phase 3 Study of the Combination of Ibrutinib plus Venetoclax-versus Chlorambucil plus Obinutuzumab for the First-line Treatment of Subjects with-Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL).

Figure 4 Study design



Target Enrolment: N = 200

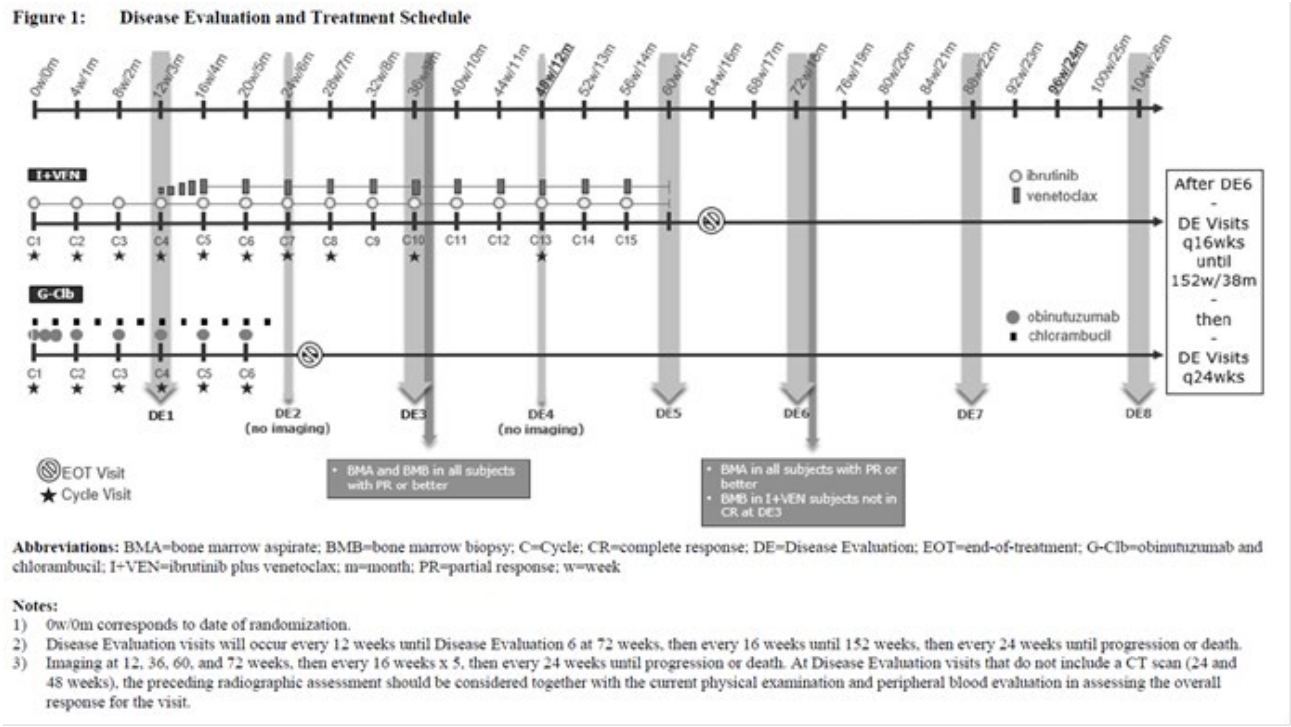
Stratification:

- *IGHV* status (mutated vs unmutated vs not available)
- del11q (yes vs no)

[a] 1 cycle=28 days

BM=bone marrow; C=cycle; CR=complete response; D=day; del11q=deletion of the long arm of chromosome 11; DOR=duration of response; Clb+Ob=obinutuzumab plus chlorambucil; FACIT=Functional Assessment of Chronic Illness Therapy; *IGHV*=immunoglobulin heavy-chain variable region; Ibr+Ven=ibrutinib plus venetoclax; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRO=patient-reported outcomes; TLS=tumor lysis syndrome; TTNT=time to next treatment

Figure 5



Methods

Study participants

Key eligibility criteria

≥65 years of age, or 18 to 64 years of age and have at least 1 of the following:

- CIRS score >6
- CrCl <70 mL/min using Cockcroft-Gault equation

Diagnosis of CLL or SLL that met iwCLL criteria
Active CLL/SLL requiring treatment per the iwCLL criteria (Hallek 2008)
Measurable nodal disease (by CT), defined as at least 1 lymph node >1.5 cm in longest-diameter
ECOG PS score of 0, 1, or 2

Key exclusion criteria
Prior anti-leukemic therapy for CLL or SLL
Presence of del17p or known TP53 mutation detected at a threshold of >10% variable allele-frequency
Central nervous system involvement or suspected Richter's syndrome

Treatments

Subjects assigned to **Treatment Arm A** (Ibr+Ven) received ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4 and contingent on completion of TLS risk assessment, venetoclax dose ramp-up (from 20 to 400 mg over 5 weeks) was initiated. Combined treatment with ibrutinib and venetoclax was administered for 12 cycles, through Cycle 15, in the absence of PD or treatment-limiting toxicity. One cycle corresponds to 28 days.

Subjects assigned to **Treatment Arm B** were to receive 6 cycles (28 days/cycle) of Clb+Ob treatment in the absence of PD or treatment-limiting toxicity. Chlorambucil was to be administered orally at a dose of 0.5 mg/kg body weight on Days 1-and 15 of Cycles 1 to 6. Obinutuzumab was to be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2-to 6. Each dose of obinutuzumab given IV was equivalent to 1000 mg except for the initial-infusion in Cycle 1 where the same total dose was to be administered over Day 1 (100 mg) and-Day 2 (900 mg).

Outcomes/endpoints

Primary endpoint: PFS by IRC based on the iwCLL 2008 GL.

Secondary endpoints tested hierarchically in the following order: MRD negativity rate in bone marrow; CR; ORR; OS; Rate of sustained platelet improvement; Rate of sustained hemoglobin improvement; Time to improvement in FACIT fatigue score.

MRD negativity rate

MRD negativity rate was defined as the proportion of subjects who reached MRD negative disease status (<1 CLL cell per 10,000 leukocytes) on or prior to initiation of subsequent anti-leukemic therapy (including subsequent single-agent ibrutinib). All randomized subjects are included in this analysis, subjects with missing MRD data are considered MRD positive. The overall MRD negativity rate in the bone marrow as assessed by NGS was the primary MRD analysis used for hierarchical testing. The MRD negativity rate by NGS in the peripheral blood was considered as the supportive analysis for this endpoint. MRD negativity rate among subjects who achieved a best overall response of CR/CRi per IRC assessment was conducted as supplementary analysis.

The MRD negativity rates in bone marrow at 3 months post-treatment (ie, end-of-treatment for each treatment arm) and in peripheral blood at 3 months and 12 months post-treatment were evaluated as supplementary analysis. The 3- and 12-month post-treatment timepoints for-Ibr+Ven correspond to DE6 and DE8; for Clb+Ob these timepoints correspond to DE3 and DE6.

Sustained hematologic improvement

Defined as hematological improvement that was sustained continuously for ≥56 days without blood transfusion or growth factors on or prior to initiation of subsequent anti-leukemic therapy (including subsequent single-agent ibrutinib):

- Hemoglobin levels increased ≥2 g/dL from baseline and lasted for at least 56 days without blood transfusion or growth factors

- Platelet counts increased ≥50% over baseline and lasted for at least 56 days without blood transfusion or growth factors

Sample size

A median PFS of 27 months is reported for the Clb+Ob when it is used to treat patients with treatment naïve CLL. It is assumed that the PFS follows an exponential distribution with a constant hazard rate. Utilizing a 1:1 randomization, this study will enroll approximately 200 subjects (100 subjects into Ibr+Ven and 100 subjects into the Clb+Ob treatment groups) to observe 71 PFS events. The study is designed to detect a hazard ratio (HR) of 0.5 for the Ibr+Ven-treatment group relative to the Clb+Ob group (corresponding to an improvement of 100% in-median PFS, e.g. from 27 months to 54 months) with 80% power at a 2-sided significance level of-0.05.

A uniform accrual rate of 20 subjects per month will result in a study duration of approximately 32 months after the first subject is randomized, with 10 months of enrollment and 22 months of-follow-up to observe 71 PFS events.

Randomisation

Central randomization was implemented; Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule, the randomization was balanced by using permuted blocks and stratified by IGHV mutational status (mutated vs. unmutated vs. not-available) and presence of del11q (yes vs. no).

Blinding (masking)

Not applicable, In this open-label study, neither the subjects nor the investigators are blinded to treatment group-assignment. However, access to efficacy data is controlled so that the Sponsor’s staff overseeing conduct of the study or analyzing/summarizing data do not have an aggregated efficacy-summary by treatment until the database is locked for primary analysis. The IRC who performs tumor assessment are required to be blinded to study treatment group assignment.

Statistical methods

No formal interim analysis for efficacy was planned, due to the small sample size and short accrual-period of the study.

All statistical tests will be performed at a 2-sided significance level of 5%, unless otherwise-specified. All interval estimation will be reported using 2-sided 95% CIs. Multiplicity incurred from testing primary and secondary endpoints will be controlled using the serial gatekeeping procedure. The

hypothesis for a secondary endpoint will be tested if and only if the null hypotheses for the primary endpoint and for the preceding secondary endpoints are rejected.

Primary analysis

No formal interim analysis for efficacy was planned, due to the small sample size and short accrual-period of the study.

All statistical tests were to be performed at a 2-sided significance level of 5%, unless otherwise-specified. All interval estimation was to be reported using 2-sided 95% CIs. Decision making will be based on the stratified log-rank test for statistical significance. Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The non-stratified Cox regression model may be used to analyze treatment effect on PFS after adjusting for covariates (selected demographics and baseline characteristics) as appropriate.

Primary analysis

Estimand Scientific Question of Interest:

What is the effect on PFS of assigning subjects to Ibr+Ven vs. Clb+Ob? This primary estimand is the main clinical quantity of interest to be estimated in this study, which is defined by the following attributes:

- Population: subjects with CLL/SLL who are treatment naïve
- Treatment: fixed duration Ibr+Ven vs. Clb+Ob
- Variable: PFS (PD is based on IRC assessment)

Population-level summary: Kaplan-Meier estimates of PFS, hazard ratio of Ibr+Ven vs. Clb+Ob

- Intercurrent events and handling strategies: treatment discontinuation, use of subsequent anticancer therapy, death due to COVID-19

Analysis methods

Assumptions

- Non-informative censoring assumed for all types of censoring.
- Distinct baseline hazard for each stratum, common proportional hazard ratio across strata.

Primary Estimator

- A stratified Cox regression model with study intervention as the sole explanatory variable will be performed, with stratification factors of IGHV gene mutational status and presence of del11q.
- Hazard ratio and its 95% CIs will be estimated.
- The treatment policy strategy is adopted for handling the intercurrent events of treatment-discontinuation, use of subsequent anti-cancer therapy and the composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19.

Supplementary Estimands

Supplementary estimands were provided:

- Subsequent anti-cancer therapy analysed according to a hypothetical strategy (Estimand 2)
- PD determined by investigator instead of IRC (Estimand 3)

– Death due to Covid -19 analysed according to a hypothetical strategy (Estimand 4)

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Treatment discontinuation (due to AE or other reasons other than AE or worsening of disease)	**Treatment policy strategy:** use time to PD or death, regardless of whether or not treatment discontinuation had occurred.
Use of subsequent anticancer therapy	**Treatment policy strategy:** use time to PD or death, regardless of whether or not used subsequent anti-cancer therapy. **Hypothetical strategy:** subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy.
Death due to COVID-19	**Composite variable strategy:** consider (pre-PD) death as a PFS event. **Hypothetical strategy:** subjects are censored at the last disease assessment before (pre-PD) death due to COVID-19.

Multiplicity incurred from testing primary and secondary endpoints was to be controlled using the serial gatekeeping procedure. The hypothesis for a secondary endpoint were to be tested if and only if the null hypotheses for the primary endpoint and for the preceding secondary endpoints are rejected. The hierarchical order of secondary endpoint for testing is specified as follows:

- MRD negativity rate in bone marrow
- CR
- ORR
- OS
- Rate of sustained platelet improvement
- Rate of sustained hemoglobin improvement
- Time to improvement in FACIT fatigue score

Subgroup analyses were planned for age, sex, Race, diagnosis, Rai stage at screening, Binet stage at screening, baseline ECOG PS, cumulative illness rating scale (CIRS) total score, bulky disease, IGHV mutation status, chromosome 11q deletion, high risk population, elevated LDH at baseline, cytopenias at baseline, Serum β2-microglobulin. Creatinine clearence, NCI-ODWG liver function classification, concomitant use of strong/moderate CYP3A inhibitor and concomitant use of strong/ CYP3A inhibitor.

Results

Participant flow

Table 2: Treatment Disposition for Fixed Duration Treatment Phase; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects ongoing	0	0	0
Completed study treatment	82 (77.4%)	100 (95.2%)	182 (86.3%)
Discontinued study treatment	24 (22.6%)	5 (4.8%)	29 (13.7%)
Reason for discontinuation			
Adverse event	11 (10.4%)	2 (1.9%)	13 (6.2%)
Subject refused further study treatment	4 (3.8%)	1 (1.0%)	5 (2.4%)
Death	4 (3.8%)	0	4 (1.9%)
Progressive disease	3 (2.8%)	1 (1.0%)	4 (1.9%)
Physician decision	2 (1.9%)	1 (1.0%)	3 (1.4%)

Table 3: Study Disposition; Intent-to-treat Analysis Set (Study 54179060CLL3011)			
	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects randomized	106 (100.0%)	105 (100.0%)	211 (100.0%)
Subjects treated	106 (100.0%)	105 (100.0%)	211 (100.0%)
Completed study participation	11 (10.4%)	11 (10.5%)	22 (10.4%)
Death	11 (10.4%)	11 (10.5%)	22 (10.4%)
Death - COVID-19 related	1 (0.9%)	4 (3.8%)	5 (2.4%)
Terminated study participation prematurely	2 (1.9%)	3 (2.9%)	5 (2.4%)
Reason for termination			
Withdrawal by subject	2 (1.9%)	3 (2.9%)	5 (2.4%)
Lost to follow-up	0	0	0

Completed study participation represents death cases before clinical cut-off.
One additional death in the Clb+Ob arm that occurred after the clinical cut and before the database lock is not counted in this table. Subject CZ10003/100033 died due to cardiac decompensation on Study Day 987. The death was not COVID-19 related

Recruitment

Study Period: 19 April 2018 (Date first subject signed informed consent) to 26 February 2021 (Date of-last observation recorded as part of the database for primary analysis). Date of data cut-off for extended-follow-up after primary analysis: 19 August 2021 (Date of last observation recorded as part of the-database for extended follow-up).

Study Center(s): Belgium (N=4); Canada (N=5); Czech Republic (N=5); Denmark (N=5); France (N=5);-Israel (N=5); Netherlands (N=4); Poland (N=5); Russia (N=6); Spain (N=8); Sweden (N=2); Turkey-(N=5); United Kingdom (N=7); United States of America (N=1).

Conduct of the study

Changes in conduct

Table 1: Summary of Protocol Amendments for Study CLL3011	
Amendment 1 (6 June 2018; substantial)	The amendment was issued to address Health Authority feedback on the initial version of the protocol and to include language informing of early pharmacokinetic results from an ongoing Phase 2 study of Ibr+Ven.
Amendment 2 (22 January 2019; substantial)	The amendment was issued primarily to implement a change in the duration of Ibr+Ven treatment based on data from an ongoing Phase 2 study of the combination.
Amendment 3 (12 August 2019; substantial)	The primary reason for the amendment was to include a Subsequent Therapy Phase within the study to allow eligible subjects who progress after completing Ibr+Ven or Clb+Ob to receive continuous treatment with single-agent ibrutinib as part of the study.
Amendment 4 (19 December 2019; substantial)	The amendment was issued to include updated safety information that is aligned with the ibrutinib Investigator's Brochure and to clarify the requirement for pulse/heart rate and blood pressure assessments.

Important changes with Amendment 1

Rationale: Clarify the threshold by which the presence of a TP53 mutation is considered exclusionary.

4.2 Exclusion Criteria; 9.1.2 Screening Phase; References	Text was added to specify that subjects with known presence of *TP53* mutations detected at a threshold of >10% variable allele frequency will be excluded from the study. New publication (Malcikova 2018) added to References and citation to this publication added.

Important changes with Amendment 2

Rationale: The protocol has been adapted to reflect recent scientific insights from relevant Phase 2 studies indicating that the removal of the last 3 cycles (cycles 16, 17, and 18) of ibrutinib monotherapy is appropriate.

Synopsis: Dosage and Administration	Update of data from relevant Phase 2 studies in which I+VEN has been investigated for the treatment of CLL.
Table 1 Time and Events Schedule for Treatment Arm A; Table 2 Time and Events Schedule for Treatment Arm B; and Table 3	For Arm A, removal of 3 additional cycles of ibrutinib monotherapy following completion of combination therapy (I+VEN) in relevant Time and Events Schedules, study overview figure, and text.

Important changes with Amendment 3

Rationale: A Subsequent Therapy Phase was added in which eligible subjects will be treated continuously with single-agent ibrutinib.

3.1 Overview of Study Design	Added statements that eligible subjects for the Subsequent Therapy Phase must have completed the treatment with I+VEN or G-Clb and subsequently develop progressive disease (as confirmed by the Independent Review Committee [IRC]) that requires treatment per International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria)
9.2.3 Response Categories	Clarified that responses will be based on assessment by the investigator during the Subsequent Therapy Phase. Noted that confirmation of responses by the IRC may be pursued by the sponsor for regulatory purposes.

Important changes with Amendment 4

Rationale: To clarify that subjects in Treatment Arm B remain eligible for subsequent therapy with single-agent ibrutinib even if they do not complete open-label therapy because this would not be expected to affect response and tolerability to ibrutinib.

Rationale: To remove specificity that a stratified analysis will be done for overall survival because the number of events may be too small in some of the strata.

11.4 Efficacy Analyses;	Deleted term "stratified" when describing the overall survival analysis. The details will be specified in the final Statistical Analysis Plan.

Changes to protocol-specified analyses

The following analyses are different from those described in the protocol:

- Additional supplementary/sensitivity analyses to mitigate the impact of the COVID-19 are-added.
- Time to next treatment is changed to be an exploratory endpoint, instead of a key secondary-endpoint.
- NGS is used as the primary method for MRD analyses, MRD by flow cytometry is used-for supplementary analyses.
- The definition for TLS risk category is updated to the following per Venetoclax USPI for CLL:
    - Low: all lymph node < 5cm AND ALC < 25x109/L
    - Medium: any lymph node 5cm to < 10cm OR ALC ≥ 25x109/L
    - High: any lymph node ≥ 10cm OR ALC ≥ 25x109/L AND any lymph node ≥ 5cm

Protocol deviations

Table 6: Summary of Subjects With Major Protocol Deviations; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Subjects With Major Protocol Deviations	6 (5.7%)	6 (5.7%)	12 (5.7%)
Received Wrong Treatment Or Incorrect Dose	5 (4.7%)	3 (2.9%)	8 (3.8%)
Other	1 (0.9%)	3 (2.9%)	4 (1.9%)
Covid-19 related	1 (0.9%)	3 (2.9%)	4 (1.9%)
Entered But Did Not Satisfy Criteria	1 (0.9%)	0	1 (0.5%)

Note: Subjects may appear in more than one category.

Four (1.9%) subjects (1 [0.9%] subject in the Ibr+Ven arm and 3 [2.9%] subjects in the Clb+Ob arm) missed a DE visit due to the COVID-19 pandemic that were considered as major protocol deviations for potentially delaying the detection of PD.

Baseline data

Table 4: Summary of Demographics and Baseline Characteristics; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Age, years			
N	106	105	211
Mean (SD)	71.0 (8.02)	72.0 (6.16)	71.5 (7.15)
Median	71.0	71.0	71.0
Range	(47; 93)	(57; 88)	(47; 93)
<65	16 (15.1%)	11 (10.5%)	27 (12.8%)
>=65-69	23 (21.7%)	27 (25.7%)	50 (23.7%)
>=70-74	32 (30.2%)	30 (28.6%)	62 (29.4%)
>=75	35 (33.0%)	37 (35.2%)	72 (34.1%)
Sex			
N	106	105	211
Female	47 (44.3%)	42 (40.0%)	89 (42.2%)
Male	59 (55.7%)	63 (60.0%)	122 (57.8%)
Race			
N	106	105	211
Asian	0	1 (1.0%)	1 (0.5%)
White	101 (95.3%)	101 (96.2%)	202 (95.7%)
Multiple	1 (0.9%)	0	1 (0.5%)
Not reported	4 (3.8%)	3 (2.9%)	7 (3.3%)
Ethnicity			
N	106	105	211
Hispanic or Latino	1 (0.9%)	3 (2.9%)	4 (1.9%)
Not Hispanic or Latino	101 (95.3%)	99 (94.3%)	200 (94.8%)
Not reported	4 (3.8%)	3 (2.9%)	7 (3.3%)

Table 5: Summary of Baseline Clinical Disease Characteristics; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Total
Analysis set: Intent-to-treat	106	105	211
Time from initial diagnosis to randomization (months)			
N	106	105	211
Mean (SD)	43.53 (41.453)	47.36 (43.409)	45.43 (42.380)
Median	35.83	35.42	35.52
Range	(0.5; 227.8)	(0.7; 178.8)	(0.5; 227.8)
Diagnosis			
N	106	105	211
CLL	96 (90.6%)	101 (96.2%)	197 (93.4%)
SLL	10 (9.4%)	4 (3.8%)	14 (6.6%)
Rai Stage (CLL only)			
N	96	101	197
0-II	41 (42.7%)	48 (47.5%)	89 (45.2%)
III-IV	55 (57.3%)	53 (52.5%)	108 (54.8%)
Binet Stage (CLL only)			
N	96	101	197
A	7 (7.3%)	8 (7.9%)	15 (7.6%)
B	46 (47.9%)	53 (52.5%)	99 (50.3%)
C	43 (44.8%)	40 (39.6%)	83 (42.1%)
Ann Arbor Stage (SLL only)			
N	10	4	14
IV	10 (100.0%)	4 (100.0%)	14 (100.0%)
ECOG Performance Status			
N	106	105	211
0	35 (33.0%)	39 (37.1%)	74 (35.1%)
1-2	71 (67.0%)	66 (62.9%)	137 (64.9%)
1	58 (54.7%)	54 (51.4%)	112 (53.1%)
2	13 (12.3%)	12 (11.4%)	25 (11.8%)
CIRS Total Score			
N	106	105	211
≤6	32 (30.2%)	44 (41.9%)	76 (36.0%)
>6	74 (69.8%)	61 (58.1%)	135 (64.0%)
7 - 12	53 (50.0%)	46 (43.8%)	99 (46.9%)
13 - 18	19 (17.9%)	14 (13.3%)	33 (15.6%)
>18	2 (1.9%)	1 (1.0%)	3 (1.4%)
Bulky Disease			
N	105	105	210
≥5cm	41 (39.0%)	38 (36.2%)	79 (37.6%)
≥10cm	0	4 (3.8%)	4 (1.9%)
Cytopenia[a]			
N	106	105	211
Yes	58 (54.7%)	65 (61.9%)	123 (58.3%)
No	48 (45.3%)	40 (38.1%)	88 (41.7%)
Anemia[a]			
N	106	105	211
Yes	45 (42.5%)	52 (49.5%)	97 (46.0%)
No	61 (57.5%)	53 (50.5%)	114 (54.0%)

Thrombocytopenia[a]			
N	106	105	211
Yes	28 (26.4%)	30 (28.6%)	58 (27.5%)
No	78 (73.6%)	75 (71.4%)	153 (72.5%)
Neutropenia[a]			
N	106	105	211
Yes	6 (5.7%)	8 (7.6%)	14 (6.6%)
No	100 (94.3%)	97 (92.4%)	197 (93.4%)
TP53 mutation			
N	106	105	211
Yes	7 (6.6%)	2 (1.9%)	9 (4.3%)
No	99 (93.4%)	103 (98.1%)	202 (95.7%)
Chromosome 11q deletion			
N	106	105	211
Yes	20 (18.9%)	18 (17.1%)	38 (18.0%)
No	86 (81.1%)	87 (82.9%)	173 (82.0%)
IGHV			
N	106	105	211
Mutated	27 (25.5%)	27 (25.7%)	54 (25.6%)
Unmutated	55 (51.9%)	54 (51.4%)	109 (51.7%)
Unavailable	24 (22.6%)	24 (22.9%)	48 (22.7%)
High risk population[b]			
N	106	105	211
Yes	63 (59.4%)	60 (57.1%)	123 (58.3%)
No	43 (40.6%)	45 (42.9%)	88 (41.7%)
Elevated LDH			
N	106	105	211
Yes (> ULN)	35 (33.0%)	51 (48.6%)	86 (40.8%)
No (≤ ULN)	71 (67.0%)	54 (51.4%)	125 (59.2%)
Serum β2 - microglobulin			
N	106	105	211
≤ 3.5 mg/L	32 (30.2%)	27 (25.7%)	59 (28.0%)
> 3.5 mg/L	74 (69.8%)	77 (73.3%)	151 (71.6%)
Missing	0	1 (1.0%)	1 (0.5%)

[a] Anemia is defined as hemoglobin ≤ 110 g/L. Thrombocytopenia is defined as platelet counts ≤ 100 * 10^9/L. Neutropenia is defined as absolute neutrophil count ≤ 1.5*10^9/L. Cytopenia is defined as yes if hemoglobin ≤ 110 g/L, platelet counts ≤ 100 * 10^9/L, or absolute neutrophil count ≤ 1.5*10^9/L is observed.
[b] High risk population: subjects with TP53 mutation, del11q, or unmutated IGHV status at baseline.

Although subjects with del17p or known TP53 mutation at baseline were excluded from the study, subjects with unknown TP53 mutation status were allowed to participate. After randomization, central laboratory testing identified 9 (4.3%) subjects with a TP53 mutation, 7 (6.6%) in the Ibr+Ven arm and 2 (1.9%) in the Clb+Ob arm.

Numbers analysed

The primary analysis included 211 subjects who were randomized and treated (106 subjects in the Ibr+Ven arm and 105 subjects in the Clb+Ob arm).

Outcomes and estimation

Primary efficacy analysis: PFS by IRC

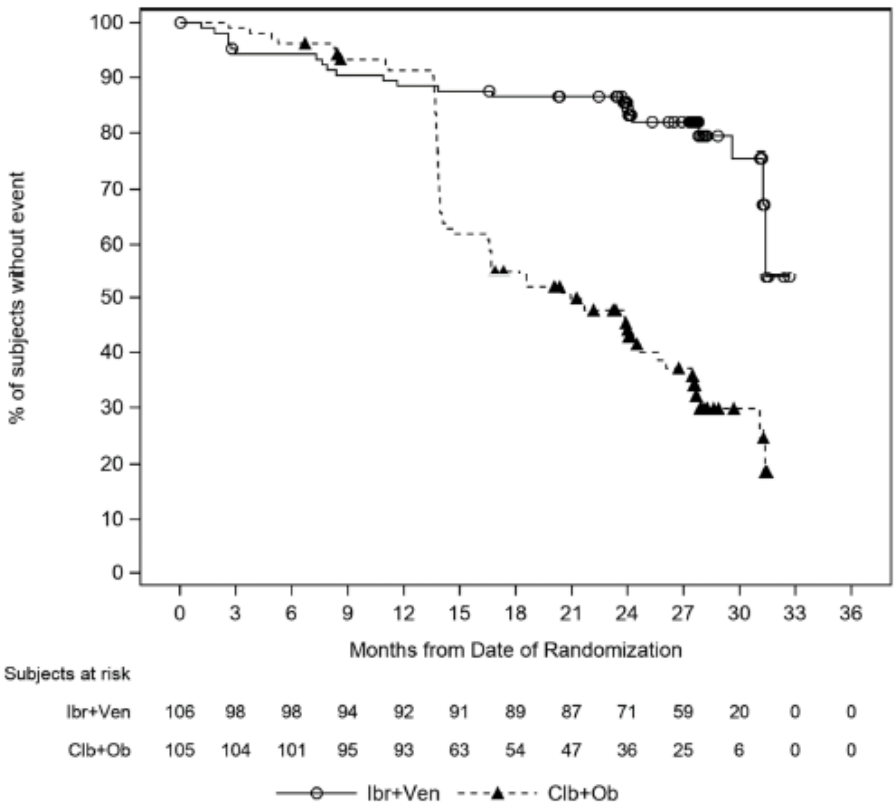
Performed 26 February 2021 with a median time on study for all subjects of 27.7 (95% CI: 27.60 to 27.89) months.

Table 9: Summary of Progression Free Survival (IRC) – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	22 (20.8%)	67 (63.8%)	
Progressive Disease	13 (12.3%)	65 (61.9%)	
Death	9 (8.5%)	2 (1.9%)	
Censored	84 (79.2%)	38 (36.2%)	
Time to event (months)			
25th percentile (95% CI)	31.24 (24.02, NE)	13.83 (13.70, 13.93)	
Median (95% CI)	NE (31.24, NE)	20.96 (16.59, 24.67)	
75th percentile (95% CI)	NE (31.41, NE)	31.08 (27.53, NE)	
Range	(0.0+, 32.7+)	(2.6, 31.5+)	
6-month event-free rate (95% CI)	0.943 (0.877, 0.974)	0.962 (0.902, 0.986)	
12-month event-free rate (95% CI)	0.885 (0.806, 0.933)	0.913 (0.840, 0.954)	
18-month event-free rate (95% CI)	0.866 (0.784, 0.918)	0.550 (0.448, 0.640)	
24-month event-free rate (95% CI)	0.844 (0.758, 0.901)	0.441 (0.342, 0.536)	
30-month event-free rate (95% CI)	0.756 (0.624, 0.848)	0.298 (0.198, 0.403)	
Hazard ratio (95% CI) [a]			0.216 (0.131, 0.357)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation. NE = not estimable.

Figure 2: Kaplan-Meier Plot of Progression Free Survival (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)



TEFPFS02: Summary of Progression Free Survival (IRC), Reason for Censoring; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Censored	84 (100.0%)	38 (100.0%)
Reason for Censoring		
Study cut off	82 (97.6%)	37 (97.4%)
Withdrew consent	2 (2.4%)	1 (2.6%)

TEFPFS14: PFS events and censoring by a period of 3 months; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven				Clb+Ob			
	PD Event	Death Event	Cumulative Sum of PFS Events	Censored	PD Event	Death Event	Cumulative Sum of PFS Events	Censored
0-3	2	4	6	2	1	0	1	0
3-6	0	0	6	0	2	1	4	0
6-9	1	3	10	0	3	0	7	3
9-12	1	1	12	0	2	0	9	0
12-15	1	0	13	0	29	1	39	0
15-18	1	0	14	1	7	0	46	2
18-21	0	0	14	2	5	0	51	2
21-24	2	0	16	14	5	0	56	6
24-27	2	0	18	10	5	0	61	6
27-30	1	1	20	37	4	0	65	15
>=30	2	0	22	18	2	0	67	4

Key: PD = progressive disease, PFS = progression-free survival.
PD events are based on Independent Review Committee (IRC) assessments.

Alternative (sensitivity) analyses of PFS

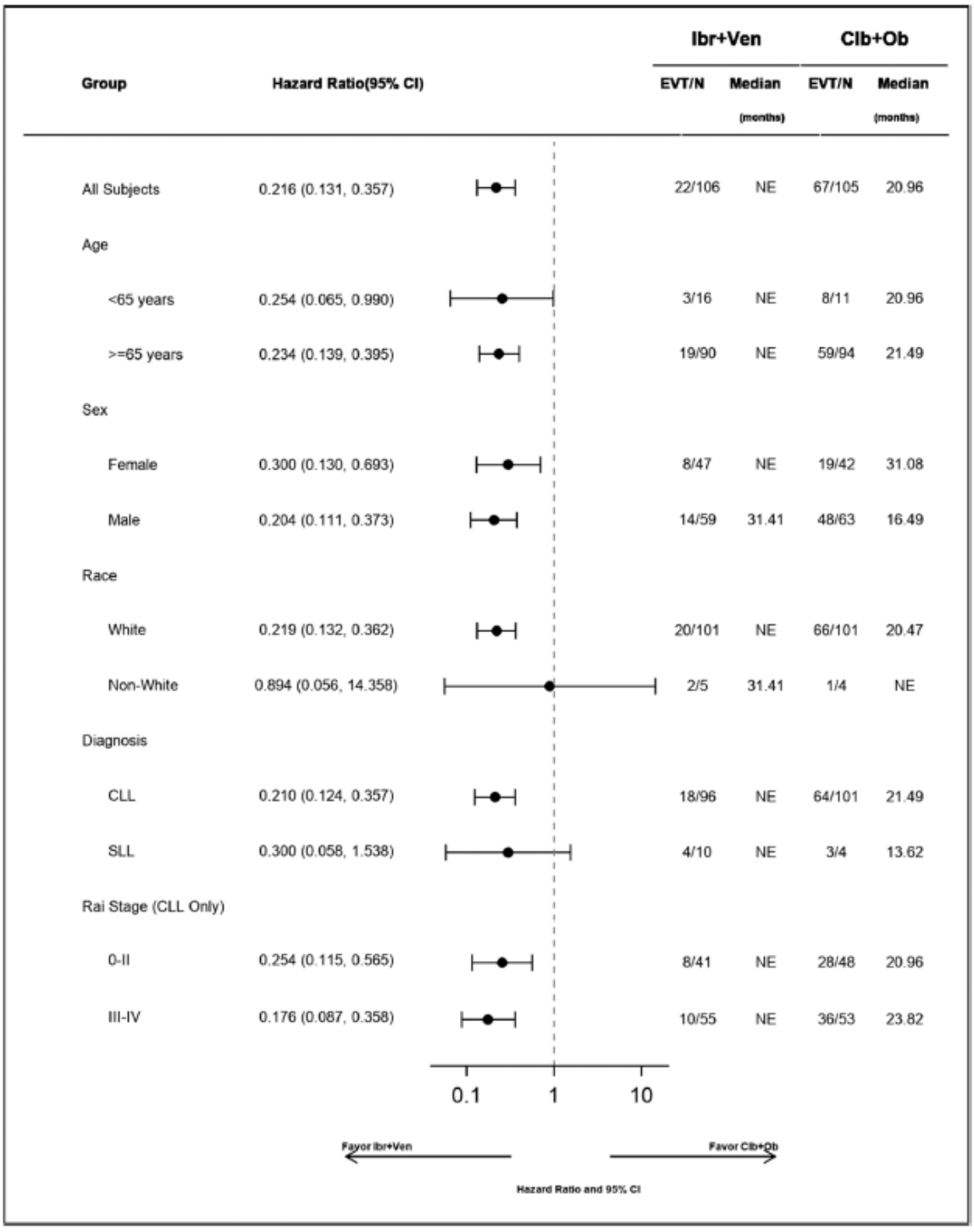
PFS by investigator: HR 0.207 (95% CI: 0.120, 0.357; nominal p<0.0001), based on event rates of 58% and 16% in the control and experimental arm, respectively. The overall concordance between IRC and investigator assessments of PD and non-PD events was 93.4% for the experimental arm and 81.0% for the control arm.

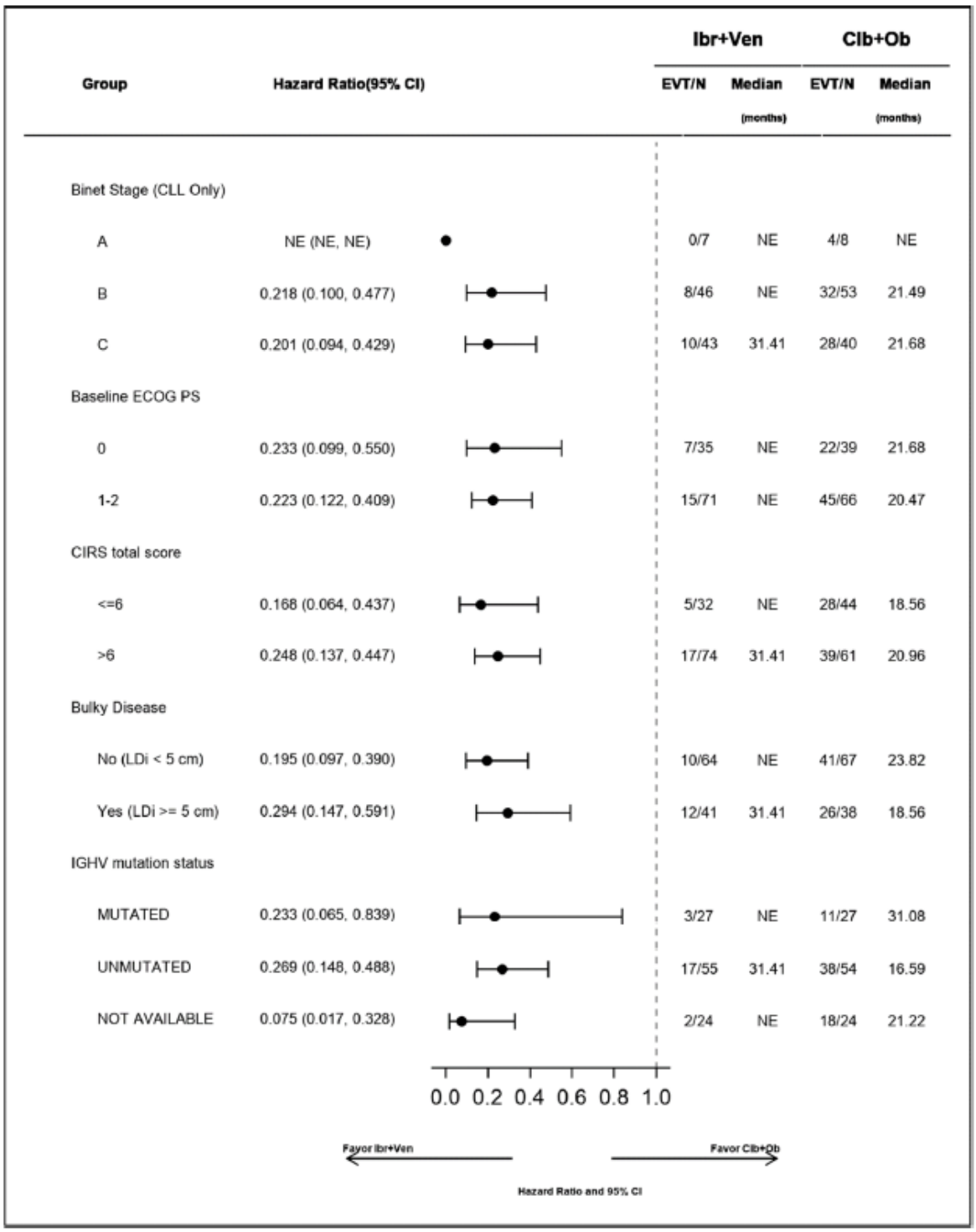
PFS analysis censoring subjects who started a subsequent anticancer therapy prior to PD: HR=0.216 (95% CI: 0.131, 0.356); p<0.0001.

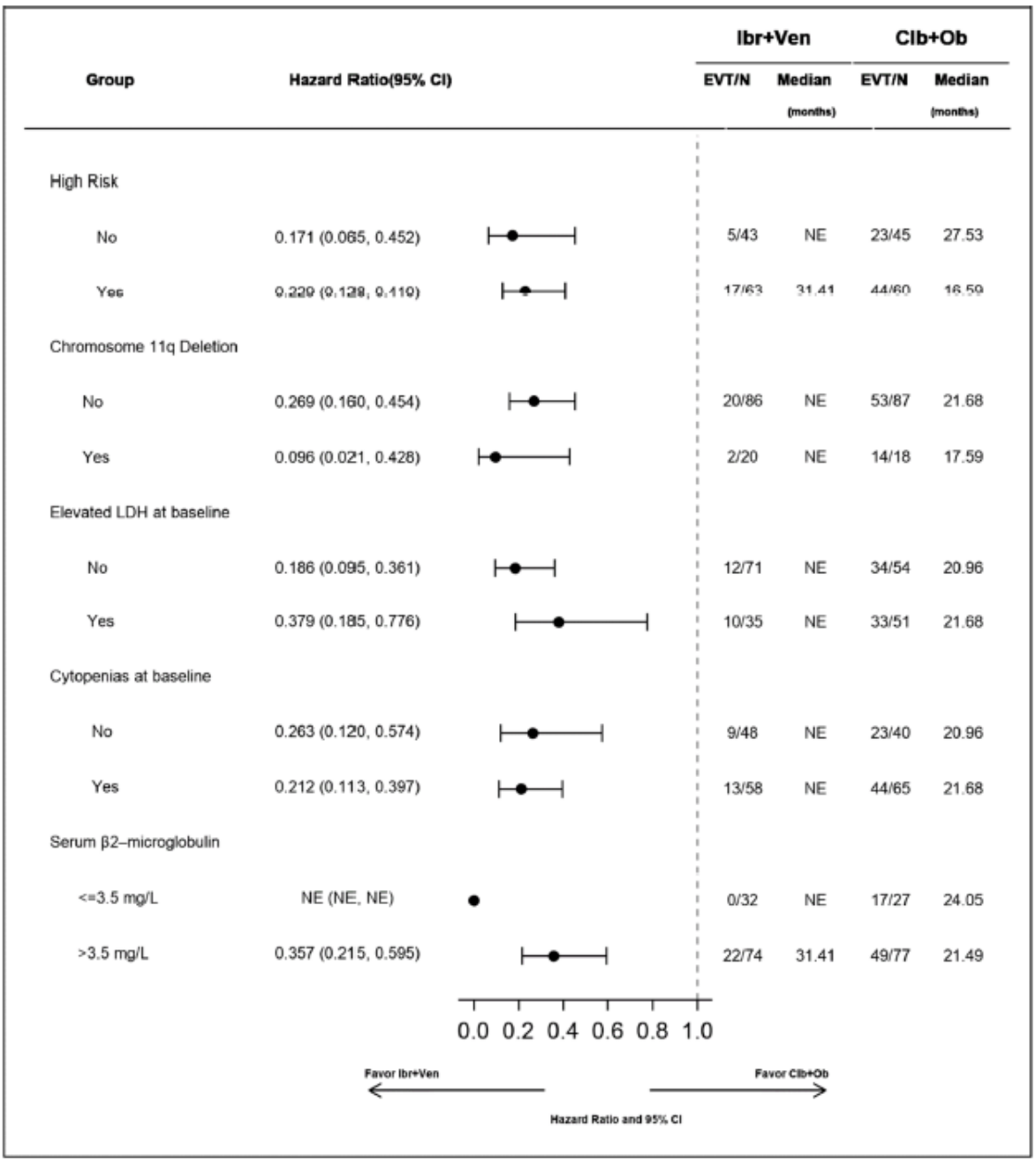
A *post-hoc* restricted mean survival time analysis was also performed: Subjects in the experimental arm, on average, were progression-free for 3 (95% CI: 1.4 to 4.6) and 5.7 (95% CI: 3.5 to 7.9) months more than subjects in the control arm at 24 and 30 months after randomization, respectively.

Subgroup analyses

Figure 4: Forest Plot of Progression Free Survival (IRC) for Subgroups Defined by Demographic Baseline Clinical Disease Characteristics; Intent-to-treat Analysis Set (Study 54179060CLL3011)




Group
Hazard Ratio(95% CI)
Ibr+Ven
Clb+Ob
EVT/N
Median (months)
EVT/N
Median (months)
Binet Stage (CLL Only)
A NE (NE, NE) 0/7 NE 4/8 NE
B 0.218 (0.100, 0.477) 8/46 NE 32/53 21.49
C 0.201 (0.094, 0.429) 10/43 31.41 28/40 21.68
Baseline ECOG PS
0 0.233 (0.099, 0.550) 7/35 NE 22/39 21.68
1-2 0.223 (0.122, 0.409) 15/71 NE 45/66 20.47
CIRS total score
<=6 0.168 (0.064, 0.437) 5/32 NE 28/44 18.56
>6 0.248 (0.137, 0.447) 17/74 31.41 39/61 20.96
Bulky Disease
No (LDi < 5 cm) 0.195 (0.097, 0.390) 10/64 NE 41/67 23.82
Yes (LDi >= 5 cm) 0.294 (0.147, 0.591) 12/41 31.41 26/38 18.56
IGHV mutation status
MUTATED 0.233 (0.065, 0.839) 3/27 NE 11/27 31.08
UNMUTATED 0.269 (0.148, 0.488) 17/55 31.41 38/54 16.59
NOT AVAILABLE 0.075 (0.017, 0.328) 2/24 NE 18/24 21.22
0.0 0.2 0.4 0.6 0.8 1.0
Favor Ibr+Ven
Favor Clb+Ob
Hazard Ratio and 95% CI



A multivariate analysis was conducted for PFS to evaluate the treatment effect when controlling for potential prognostic factors. After adjustment for selected prespecified baseline factors, the treatment effect was consistent with the primary analysis, HR=0.177 (95% CI: 0.100, 0.313); nominal p<0.0001.

Extended follow-up for PFS by IRC (data cut-off 19 August 2021)

With a median time on study for all subjects of 34.1 months the HR was 0.212 (95% CI: 0.129, 0.349); nominal p<0.0001.

A total of 3 additional IRC-assessed PD events occurred after primary analysis (2 in the experimental arm and 1 in the control arm). However, for 3 subjects in the experimental arm the assessment of PD at primary analysis was converted to maintained response by the IRC after consideration of data from additional timepoints with extended follow-up. Thus, compared with the

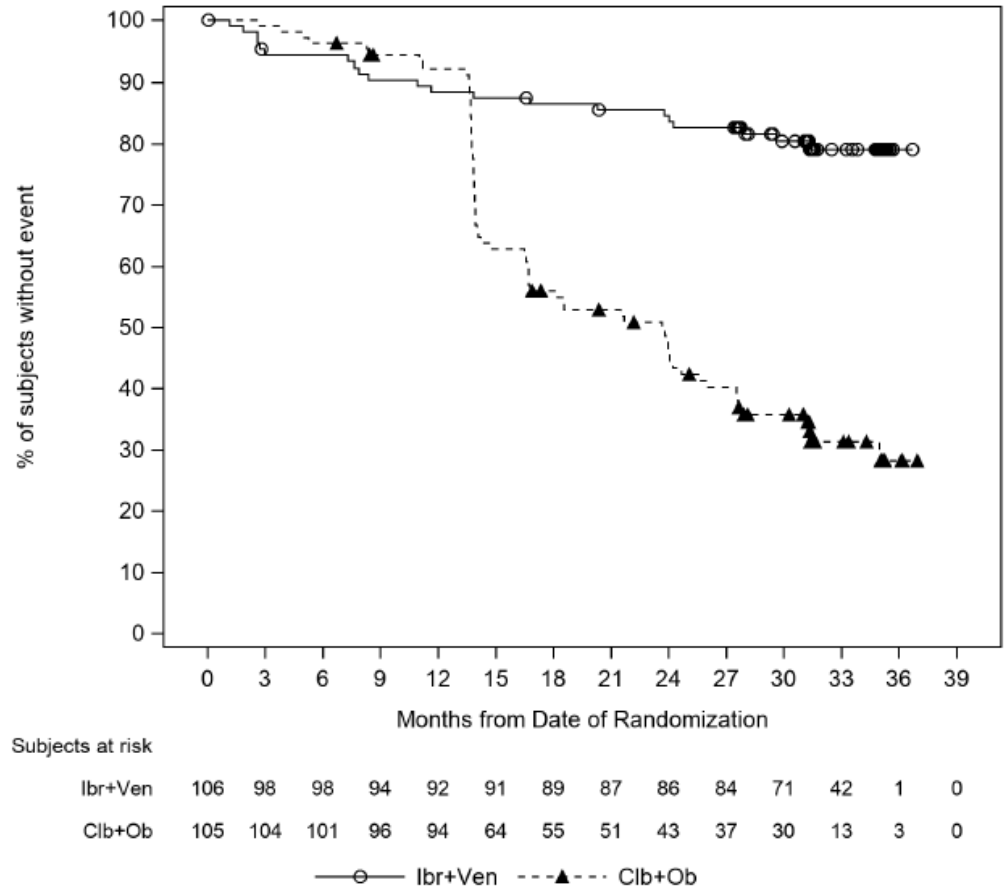
primary analysis, 1 less subject in the experimental arm and 1 additional subject in the control arm had IRC-assessed PD.

S_TEFPFS01: Summary of Progression Free Survival (IRC) – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	21 (19.8%)	68 (64.8%)	
Progressive Disease	12 (11.3%)	66 (62.9%)	
Death	9 (8.5%)	2 (1.9%)	
Censored	85 (80.2%)	37 (35.2%)	
Time to event (months)			
25th percentile (95% CI)	NE (24.02, NE)	13.83 (13.73, 13.93)	
Median (95% CI)	NE (NE, NE)	23.66 (16.62, 26.05)	
75th percentile (95% CI)	NE (NE, NE)	NE (31.34, NE)	
Range	(0.0+, 36.7+)	(2.6, 36.9+)	
6-month event-free rate (95% CI)	0.943 (0.877, 0.974)	0.962 (0.902, 0.986)	
12-month event-free rate (95% CI)	0.885 (0.806, 0.933)	0.923 (0.852, 0.961)	
18-month event-free rate (95% CI)	0.866 (0.784, 0.918)	0.560 (0.458, 0.650)	
24-month event-free rate (95% CI)	0.846 (0.761, 0.903)	0.455 (0.356, 0.550)	
30-month event-free rate (95% CI)	0.805 (0.714, 0.869)	0.358 (0.264, 0.453)	
36-month event-free rate (95% CI)	0.791 (0.698, 0.859)	0.282 (0.184, 0.389)	
Hazard ratio (95% CI) [a]			0.212 (0.129, 0.349)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.

S_GEFPFS01: Kaplan-Meier Plot of Progression Free Survival (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)



Secondary efficacy analyses

MRD negativity rate

MRD negativity rates were assessed by NGS and flow cytometry (not further discussed in this AR). The overall MRD negativity rate (best MRD response) in BM assessed by NGS was the primary analysis used in the hierarchical testing. The threshold for defining undetectable MRD (MRD negativity) in the blood and bone marrow was set at <1 CLL cell per 10,000 (10-4) leukocytes for both assays.

- **Primary analysis: MRD negativity rates assessed by NGS (best MRD response)**

Table 10: Minimal Residual Disease (MRD) Negativity Rate by NGS Data; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Rate Ratio [a]
Analysis set: Intent-to-treat	106	105	
MRD-negative disease status			
Bone marrow			
Samples obtained[c]	92 (86.8%)	84 (80.0%)	
MRD negativity, n(%)	59 (55.7%)	22 (21.0%)	2.65 (1.75, 3.99)
95% CI[d]	(46.2%, 65.1%)	(13.2%, 28.7%)	< 0.0001[b]
Peripheral blood			
Samples obtained[c]	93 (87.7%)	89 (84.8%)	
MRD negativity, n(%)	63 (59.4%)	42 (40.0%)	1.48 (1.10, 1.98)
95% CI[d]	(50.1%, 68.8%)	(30.6%, 49.4%)	0.0055[b]
Bone marrow or peripheral blood			
Samples obtained[c]	93 (87.7%)	89 (84.8%)	
MRD negativity, n(%)	66 (62.3%)	43 (41.0%)	1.52 (1.14, 2.01)
95% CI[d]	(53.0%, 71.5%)	(31.5%, 50.4%)	0.0023[b]
Bone marrow and peripheral blood			
Samples obtained[c]	92 (86.8%)	84 (80.0%)	
MRD negativity, n(%)	56 (52.8%)	21 (20.0%)	2.63 (1.71, 4.03)
95% CI[d]	(43.3%, 62.3%)	(12.3%, 27.7%)	< 0.0001[b]

Key: CI=confidence interval; BM=bone marrow; PB=peripheral blood.
[a] Rate ratio >1 in favors of Ibr+Ven.
[b] P-value is from a CMH chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).
[c] Includes MRD samples supposed to be collected per protocol only.
[d] The 95% confidence interval for MRD negativity rate is based on normal approximation to the binomial distribution.

- **MRD negativity rates assessed by NGS at 3 and 12 months post-treatment**

TEFMRD03B: MRD Negativity Rate at Selected Post-Treatment Time Points (Same Time after End of Treatment) by NGS Data; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Rate Ratio [a]
Analysis set: Intent-to-treat	106	105	
MRD-negative disease status 3-month post end of treatment			
Bone marrow			
Samples obtained[c,d]	85 (80.2%)	81 (77.1%)	
MRD negativity, n(%)	55 (51.9%)	18 (17.1%)	3.00 (1.90, 4.76)
95% CI[e]	(42.4%, 61.4%)	(9.9%, 24.4%)	< 0.0001[b]
Peripheral blood			
Samples obtained[c,d]	88 (83.0%)	88 (83.8%)	
MRD negativity, n(%)	58 (54.7%)	41 (39.0%)	1.39 (1.03, 1.89)
95% CI[e]	(45.2%, 64.2%)	(29.7%, 48.4%)	0.0259[b]
Bone marrow or peripheral blood			
Samples obtained[c,d]	88 (83.0%)	88 (83.8%)	
MRD negativity, n(%)	60 (56.6%)	42 (40.0%)	1.41 (1.05, 1.89)
95% CI[e]	(47.2%, 66.0%)	(30.6%, 49.4%)	0.0183[b]
Bone marrow and peripheral blood			
Samples obtained[c,d]	84 (79.2%)	79 (75.2%)	
MRD negativity, n(%)	52 (49.1%)	17 (16.2%)	3.00 (1.86, 4.84)
95% CI[e]	(39.5%, 58.6%)	(9.1%, 23.2%)	< 0.0001[b]
MRD-negative disease status 12-month post end of treatment			
Peripheral blood			
Samples obtained[c,d]	82 (77.4%)	52 (49.5%)	
MRD negativity, n(%)	52 (49.1%)	13 (12.4%)	3.97 (2.28, 6.90)
95% CI[e]	(39.5%, 58.6%)	(6.1%, 18.7%)	< 0.0001[b]

Key: CI=confidence interval; CR=complete response; CRi=complete response with an incomplete marrow recovery; BM=bone marrow; PB=peripheral blood.
[a] Rate ratio >1 in favors of Ibr+Ven.
[b] P-value is from a CMH chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).
[c] Includes MRD samples supposed to be collected per protocol only.
[d] Includes MRD samples not collected at prespecified but at subsequent disease evaluation.
[e] The 95% confidence interval for MRD negativity rate is based on normal approximation to the binomial distribution.

At 3 months post-treatment of the 56 subjects in the experimental arm who were MRD-negative in peripheral blood and who had a matched bone marrow specimen collected, 52 (92.9%) were MRD-negative in both peripheral blood and bone marrow. At the same timepoint, of the 39 subjects from the control arm who were MRD-negative in peripheral blood and who had a matched bone marrow specimen collected, 17 (43.6%) were MRD-negative in both peripheral blood and bone marrow.

- **MRD negativity rates by NGS at Equivalent Timepoints**

– At DE3 (9 months after randomization): MRD negativity rates for subjects in the experimental arm and the control arm were 39.6% and 17.1% in the bone marrow, respectively; 46.2% and 39.0% in the peripheral blood.

– At DE6 (18 months after randomization): MRD negativity rates for subjects in the experimental arm and the control arm were 51.9% and 9.5% in the bone marrow, respectively; 54.7% and 12.4% in the peripheral blood.

– At DE8 (26 months after randomization): MRD negativity rates for subjects in the experimental arm and the control arm were 49.1% and 3.8% in the peripheral blood, respectively.

The rate ratios of MRD negativity rates comparing experimental arm versus control arm in the peripheral blood increased over time (DE3: 1.18; DE6: 4.41; DE8: 12.84).

- **MRD negativity rates by NGS by best overall response of CR/CRi per IRC**

By use of a stratified CMH chi-square test, no statistical nominal differences were noted between study arms.

Summary of MRD negativity rates (% (n/N)) in the experimental arm

	Study CLL3011 Ibr+Ven N=106	
	NGS	FLOW Cytometry
Overall MRD negativity rate - % (n/N)		
BM	55.7 (59/106)	67.9% (72/106)
PB	59.4 (63/106)	80.2% (85/106)
MRD negativity rate at 3 months post-treatment -		
BM	51.9 (55/106)[b]	56.6 (60/106)[b]
PB	54.7 (58/106)[b]	61.3 (65/106)[b]
MRD negativity rate at 12 months post-treatment		
PB	49.1 (52/106)[c]	54.7 (58/106)[c]

[b] The time point for the Ibr+Ven group corresponds to 72 weeks after randomization, for the Clb+Ob group corresponds to 36 weeks after randomization.

[c] The timepoint for the Ibr+Ven group corresponds to 104 weeks after randomization, for the Clb+Ob group corresponds to 72 weeks after randomization.

Complete response (CR/CRi) rate

- **Primary analysis, per IRC**

Table 12: Summary of Complete Response Rate (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Complete Response Rate (CR, CRi), n(%)	41 (38.7%)	12 (11.4%)
95% CI [a]	(29.4%, 48.0%)	(5.3%, 17.5%)
Rate ratio (95% CI) [b]	3.43 (1.91, 6.15)	
p-value [c]	< 0.0001	

CR = complete response. CRi = complete response with incomplete marrow recovery.
[a] The 95% confidence interval for response rates is based on normal approximation to the binomial distribution.
[b] Rate ratio >1 favors Ibr+Ven.
[c] P-value is from Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).

TEFCR03A: Time to Complete Response (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Time to complete response (months) [a]		
N	41	12
Median (95% CI)	13.83(11.87,14.35)	8.66(8.17,13.24)
Range	(8.1; 20.0)	(8.2; 20.2)

[a] Time to complete response is calculated for subjects with CR or CRi and is defined as the interval between the date of randomization and the date of initial documentation of a CR/CRi.
Note: The above summaries are based on descriptive statistics. Analysis are based on IRC assessments.

At the cut-off, only 3/41 subjects in the experimental arm and 1/12 subjects in the control arm had lost response (including death). The 12-month landmark estimate for duration of IRC-assessed CR (CR/CRi) was 100% in the experimental arm and 91.7% in the control arm.

- **CR rate as assessed by the investigator**

Experimental arm: 45.3%

Control arm: 13.3%

The 12-month landmark estimate for duration of investigator-assessed CR (CR/CRi) was 93.9% in the experimental arm and 87.5% in the control arm.

- **CR rate per IRC: Extended follow-up**

With extended follow-up, an overall response of CR/CRi was reported for 3 additional subjects (2 subjects in the experimental arm and 1 subject in the control arm) compared with the primary analysis; CR/CRi rate 40.6% vs 12.4%.

The 18-month landmark estimate for duration of IRC-assessed CR (CR/CRi) was 97.5% in the experimental arm and 84.6% in the control arm.

Overall response rate (ORR) per IRC

Table 13: Summary of Overall Response Rate (IRC) – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Overall Response Rate (PR+nPR+CRi+CR)			
Responder	92 (86.8%)	89 (84.8%)	
95% CI	(80.3%, 93.2%)	(77.9%, 91.6%)	
Rate ratio (95% CI)[a]			1.02 (0.92, 1.14)
p-value[b]			0.6991
Best Overall Response			
Complete Response (CR)	38 (35.8%)	12 (11.4%)	
Complete Response with Incomplete Marrow Recovery (CRi)	3 (2.8%)	0	
Nodular Partial Response (nPR)	4 (3.8%)	3 (2.9%)	
Partial Response (PR)	47 (44.3%)	74 (70.5%)	
Stable Disease (SD)	8 (7.5%)	13 (12.4%)	
Progressive Disease (PD)	2 (1.9%)	2 (1.9%)	
Not Evaluable (NE)	4 (3.8%)	1 (1.0%)	

[a] Rate ratio >1 favors Ibr+Ven.
[b] P-value is from Cochran-Mantel-Haenszel chi-square test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).

Overall survival

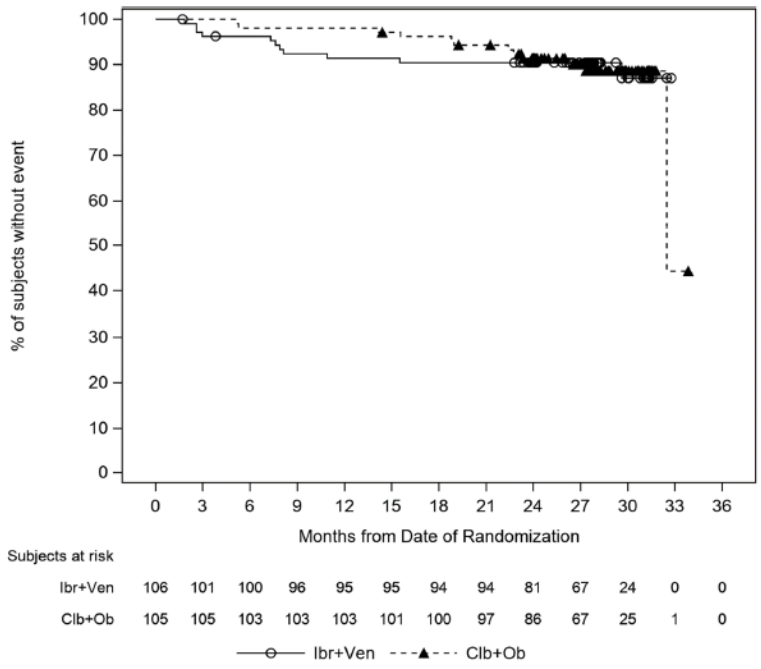
- **Primary analysis**

Table 14: Summary of Overall Survival – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	11 (10.4%)	12 (11.4%)	
Death	11 (10.4%)	12 (11.4%)	
Censored	95 (89.6%)	93 (88.6%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	32.49 (32.49, NE)	
Median (95% CI)	NE (NE, NE)	32.49 (32.49, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (32.49, NE)	
Range	(1.7+, 32.8+)	(5.1, 33.8+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.913 (0.839, 0.954)	
30-month survival rate (95% CI)	0.871 (0.757, 0.934)	0.886 (0.802, 0.936)	
Hazard ratio (95% CI) [a]			1.048 (0.454, 2.419)
p-value [b]			0.9121

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.
Includes deaths up to database lock date.

Figure 5: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Analysis Set (Study 54179060CLL3011)



Note: includes deaths up to database lock date.

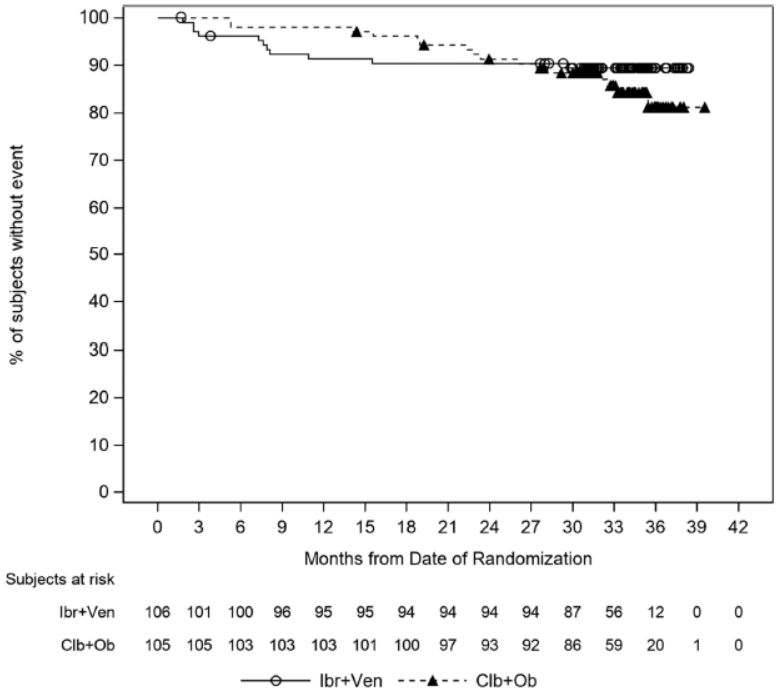
- **Extended follow-up**

Median follow-up 34.1 months. Four additional deaths reported during extended follow-up were all in the control arm. In total, 11 (10.4%) and 16 (15.2%) deaths have been reported in the experimental arm and the control arm, respectively.

S_TEFOS01A: Summary of Overall Survival – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)			
	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	11 (10.4%)	16 (15.2%)	
Death	11 (10.4%)	16 (15.2%)	
Censored	95 (89.6%)	89 (84.8%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	NE (33.22, NE)	
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.7+, 38.4+)	(5.1, 39.6+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.913 (0.840, 0.954)	
30-month survival rate (95% CI)	0.894 (0.817, 0.940)	0.884 (0.804, 0.932)	
36-month survival rate (95% CI)	0.894 (0.817, 0.940)	0.811 (0.695, 0.886)	
Hazard ratio (95% CI) [a]			0.760 (0.352, 1.642)
p-value [b]			0.4837

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.

Figure 6: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Analysis Set (Study 54179060CLL3011) – Extended Follow-up



Sustained hematologic improvement

At the primary analysis, the proportion of subjects with sustained improvement in hemoglobin was similar for the experimental arm compared with the control arm (44.3% vs. 50.5%). Also the proportion of subjects with sustained improvement in platelets was similar for experimental arm compared with the control arm (24.5% vs. 29.5%). These outcomes remained essentially similar at the extended follow-up analysis.

Time to improvement in FACIT-Fatigue score

As of the data cut-off for the primary analysis, the median time to clinically meaningful (≥3 points increase on 52-point scale) improvement in FACIT-Fatigue score was 5.59 months for subjects in the experimental arm versus 3.75 months for subjects in the control arm (HR=1.369; 95% CI: 0.959, 1.954).

Ancillary analyses

Duration of response (DOR)

As of the data cut-off for the primary analysis, with an overall median follow-up of 27.7 months, the median DOR for subjects who achieved an IRC-assessed PR or better was 28.9 months (95% CI: 28.68, NE) in the experimental arm and 21.1 months (95% CI: 15.93, 25.10) in the control arm.

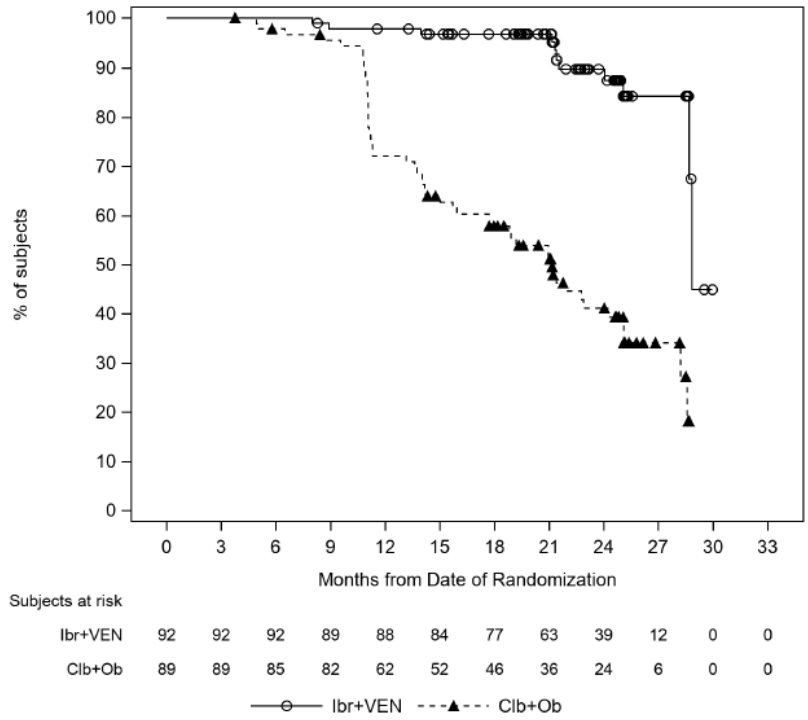
The 24-month landmark estimate for IRC-assessed DOR was 89.9% in the experimental arm and 41.2% in the control arm.

TEFDOR01A: Summary of Duration of Response (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Responders (PR or better)	92 (86.8%)	89 (84.8%)
Event	11 (10.4%)	52 (49.5%)
Progression	9 (8.5%)	51 (48.6%)
Death without documentation of progression	2 (1.9%)	1 (1.0%)
Censored	81 (76.4%)	37 (35.2%)
Duration of response (months) [a]		
25th percentile (95% CI) [b]	28.68 (25.07, NE)	11.24 (11.04, 14.16)
Median (95% CI) [b]	28.85 (28.68, NE)	21.13 (15.93, 25.10)
75th percentile (95% CI) [b]	NE (28.85, NE)	28.58 (25.10, NE)
Range	(8.0, 30.0+)	(3.7+, 28.7+)
6-month duration of response rate (95% CI) [b]	1.000 (1.000, 1.000)	0.977 (0.912, 0.994)
12-month duration of response rate (95% CI) [b]	0.978 (0.915, 0.994)	0.721 (0.614, 0.804)
18-month duration of response rate (95% CI) [b]	0.967 (0.901, 0.989)	0.580 (0.468, 0.676)
24-month duration of response rate (95% CI) [b]	0.899 (0.796, 0.951)	0.412 (0.299, 0.522)

Key: PR = partial response, PRL = partial response with lymphocytosis; CI = confidence interval.
[a] Duration of response is calculated as the number of months from first documented partial response with lymphocytosis (PRL) or better for subjects who achieved partial response (PR) or better to disease progression, death, or date of censoring
[b] Based on Kaplan-Meier estimates.
Note: + = censored observation, NE = not estimable

GEFDOR01A: Kaplan-Meier Curves for Duration of Response (IRC); Intent-to-treat Analysis Set (Study 54179060CLL3011)

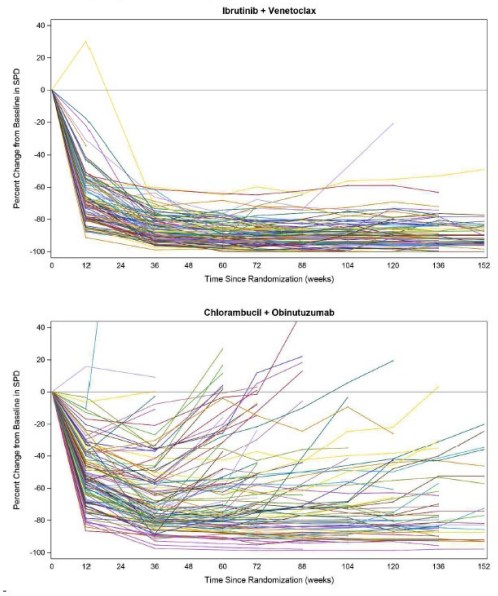


- **Extended follow-up**

With an overall median follow-up of 34.1 months, the median DOR for subjects who achieved an IRC-assessed PR or better was not reached in the experimental arm and was 21.4 months (95% CI: 18.83, 28.58) in the control arm.

The 30-month landmark estimate for IRC-assessed DOR was 86.7% in the experimental arm and 35.5% in the control arm. A graphical illustration is shown below.

Figure 7: Plot of Lymph Node Tumor Burden by Independent Review Committee (IRC) Assessment Over Time (Study 54179060CLL3011) – Extended Follow-up



Key: SPD = sum of the products of the perpendicular diameters (mm^2)

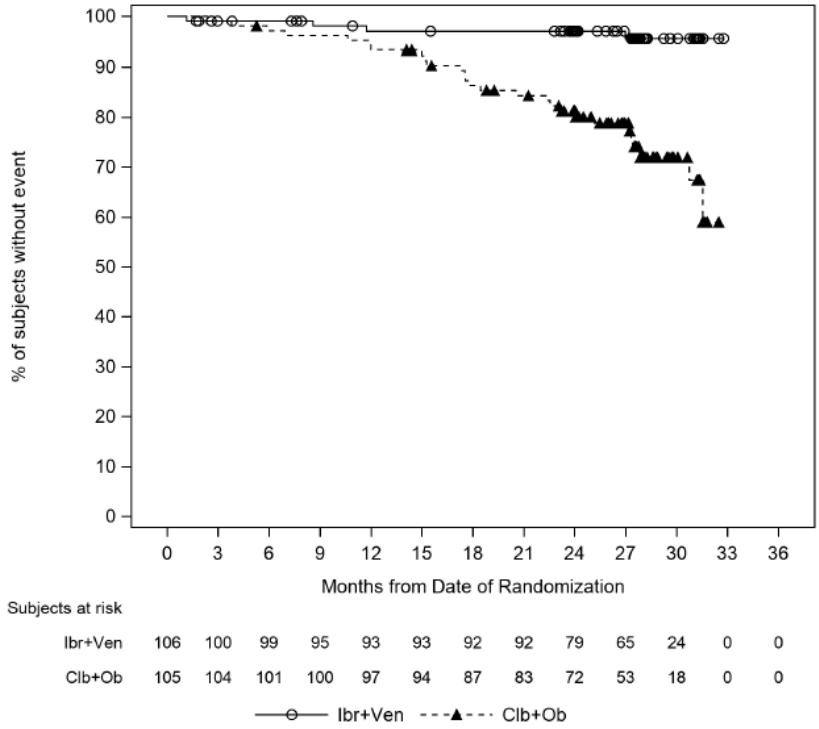
Time to next treatment

TEFSUBTX02A: Summary of Time to Subsequent Anti-cancer Therapy – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	4 (3.8%)	27 (25.7%)	
Censored	102 (96.2%)	78 (74.3%)	
Time to event (months)			
25th percentile (95% CI)	NE (NE, NE)	27.40 (22.28, NE)	
Median (95% CI)	NE (NE, NE)	NE (31.54, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.1, 32.8+)	(2.4, 32.5+)	
6-month event rate (95% CI)	0.991 (0.935, 0.999)	0.971 (0.914, 0.991)	
12-month event rate (95% CI)	0.970 (0.909, 0.990)	0.933 (0.864, 0.967)	
18-month event rate (95% CI)	0.970 (0.909, 0.990)	0.864 (0.781, 0.917)	
24-month event rate (95% CI)	0.970 (0.909, 0.990)	0.813 (0.722, 0.876)	
30-month event rate (95% CI)	0.955 (0.883, 0.983)	0.719 (0.607, 0.805)	
Hazard ratio (95% CI) [a]			0.143 (0.050, 0.410)
p-value [b]			<0.0001

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).
Note: + = censored observation, NE = not estimable.
Time to subsequent anti-cancer therapy is defined as the time interval between randomization and initiation of any subsequent anti-cancer treatment (including subsequent single-agent ibrutinib). Subjects who had not started any subsequent anti-cancer therapy are censored at the dates when the subjects were last known to be alive.

GEFSUBTX01: Kaplan Meier Curves for Time to Subsequent Anti-cancer Therapy; Intent-to-treat Analysis Set (Study 54179060CLL3011)



Subjects at risk

Ibr+Ven	106	100	99	95	93	93	92	92	79	65	24	0	0
Clb+Ob	105	104	101	100	97	94	87	83	72	53	18	0	0

TEFSUBTX01: Number of Subjects with Subsequent Anti-cancer Therapy; Intent-to-treat Analysis Set (Study 54179060CLL3011)

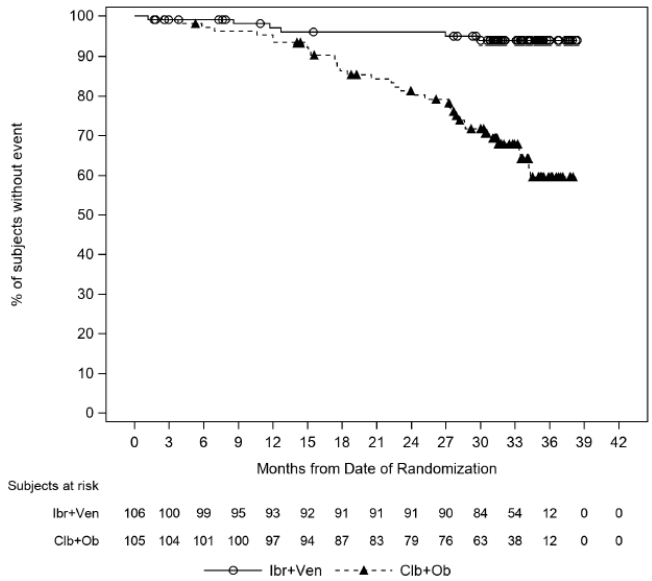
	Ibr+Ven	Clb+Ob
Analysis set: Intent-to-treat	106	105
Number of subjects with subsequent therapy	4 (3.8%)	27 (25.7%)
High-dose therapy/Stem cell transplant	0	0
Radiotherapy	1 (0.9%)	2 (1.9%)
Surgery	1 (0.9%)	1 (1.0%)
Subsequent single-agent ibrutinib per protocol	1 (0.9%)	15 (14.3%)
Systemic therapy	3 (2.8%)	11 (10.5%)
ATC Level 2/ATC Level 4/Preferred Term		
Antineoplastic Agents	3 (2.8%)	11 (10.5%)
Nitrogen Mustard Analogues	3 (2.8%)	2 (1.9%)
Cyclophosphamide	2 (1.9%)	1 (1.0%)
Chlorambucil	1 (0.9%)	0
Bendamustine	0	2 (1.9%)
Anthracyclines And Related Substances	2 (1.9%)	0
Doxorubicin	2 (1.9%)	0
Monoclonal Antibodies	2 (1.9%)	5 (4.8%)
Brentuximab Vedotin	1 (0.9%)	0
Rituximab	1 (0.9%)	5 (4.8%)
Vinca Alkaloids And Analogues	2 (1.9%)	1 (1.0%)
Vinblastine	1 (0.9%)	0
Vincristine	1 (0.9%)	0
Vincristine Sulfate	0	1 (1.0%)
Folic Acid Analogues	0	1 (1.0%)
Methotrexate	0	1 (1.0%)
Methylhydrazines	0	1 (1.0%)
Procarbazine	0	1 (1.0%)
Other Antineoplastic Agents	0	2 (1.9%)
Idelalisib	0	1 (1.0%)
Venetoclax	0	1 (1.0%)
Protein Kinase Inhibitors	0	7 (6.7%)
Acalabrutinib	0	1 (1.0%)
Ibrutinib	0	6 (5.7%)
Corticosteroids For Systemic Use	0	2 (1.9%)
Glucocorticoids	0	2 (1.9%)
Dexamethasone	0	1 (1.0%)
Prednisolone	0	1 (1.0%)

Note: Recurrent medications are counted only once per subject.
Anti-cancer Therapy are presented by decreasing frequency of ATC Level 2, ATC Level 4 and preferred term within Ibr+Ven column; those with the same frequency are presented alphabetically.

Of 4 subjects from the experimental arm and 27 subjects from the control arm who had initiated subsequent anticancer therapy, 1 and 22 subjects received subsequent anticancer therapy with a BTK inhibitor. One subject from the control arm received subsequent anticancer therapy with venetoclax.

- **Extended follow-up**

S_GEFSUBTX01: Kaplan Meier Curves for Time to Subsequent Anti-cancer Therapy; Intent-to-treat Analysis Set (Study 54179060CLL3011)



The median time to subsequent anticancer therapy was still not reached in either treatment arm with a HR of 0.147 (95% CI: 0.062, 0.350).

Of 6 and 35 subjects in the experimental and control arm, respectively, who had initiated subsequent anticancer therapy, 2 and 28 subjects received subsequent anticancer therapy with a BTK inhibitor. Four subjects from the control arm received subsequent anticancer therapy with venetoclax.

Tumor Lysis Syndrome Risk Reduction Based on Tumour Burden

Table 16: Tumor Lysis Syndrome (TLS) Risk* Reduction with 3-cycle Ibrutinib Lead-in; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven
Analysis set: Intent-to-treat	106
Baseline TLS high risk	26/106 (24.5%)
After ibrutinib lead-in	
Reduced to medium or low risk	22/26 (84.6%)
Remain high risk	2/26 (7.7%)
Missing assessment	2/26 (7.7%)
Baseline TLS medium or low risk	80/106 (75.5%)
After ibrutinib lead-in	
Increase to high risk	0/80 (0.0%)
Remain medium or low risk	77/80 (96.3%)
Missing assessment	3/80 (3.8%)

The percentage is based on number of subjects in each category divided by number of subjects with specified baseline TLS risk.
TLS risk was calculated based on protocol section 6.1.2.2. Analysis include TLS risk at baseline and the last post-baseline value on or prior to the venetoclax first dose date (cycle 4 day 1) or, for subjects never received venetoclax, the post-baseline value closest to the scheduled cycle 4 day 1, i.e. 84 days after the first dose date of ibrutinib.
Subjects do not have post-baseline assessments are categorized as missing.
*TLS risk designation of high, medium or low is based on tumor burden.

At baseline, 69 subjects in the experimental arm had an indication for hospitalization (26 due to TLS risk from high tumor burden and 43 due to TLS risk from medium tumor burden with CrCl <80 mL/min). After 3 cycles of ibrutinib lead-in, hospitalization was no longer indicated for 24 (34.8%) of these subjects.

Of 49 subjects for whom hospitalization was indicated after 3 cycles of ibrutinib, 2 subjects had TLS risk based on high tumor burden and 47 had TLS risk based on medium tumor burden but with a CrCl <80 mL/min.

Updated OS Analysis for Study CLL3011

Based on a data cut-off of 17 January 2022 (median time on study: 38.9 months [Attachment TSIDS04]), the hazard ratio (HR) for OS was estimated at 0.582 (95% confidence interval [CI]: 0.286, 1.187) (Table 9). The median OS was not reached in either treatment arm. The Kaplan-Meier OS estimates at 36 months were 89.5% and 84.3% in the Ibr+Ven and Clb+Ob arms, respectively. Thus, the positive trend observed with the August 2021 data cut favoring the experimental treatment is maintained in this updated analysis.

Table 9: Summary of Overall Survival – Stratified Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)

	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	12 (11.3%)	22 (21.0%)	
Death	12 (11.3%)	22 (21.0%)	
Censored	94 (88.7%)	83 (79.0%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	42.02 (36.50, NE)	
Median (95% CI)	NE (NE, NE)	NE (42.02, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.7+, 43.5+)	(5.1, 44.5+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.913 (0.840, 0.954)	
30-month survival rate (95% CI)	0.895 (0.818, 0.940)	0.884 (0.805, 0.932)	
36-month survival rate (95% CI)	0.895 (0.818, 0.940)	0.843 (0.757, 0.901)	
42-month survival rate (95% CI)	0.875 (0.785, 0.929)	0.764 (0.653, 0.843)	
Hazard ratio (95% CI) [a]			0.582 (0.286, 1.187)
p-value [b]			0.1319

CI=confidence interval; Clb+Ob=chlorambucil+obinutuzumab; del11q=deletion of the long arm of chromosome 11; Ibr+Ven=ibrutinib+venetoclax; IGHV=immunoglobulin heavy-chain variable region; NE=not estimable

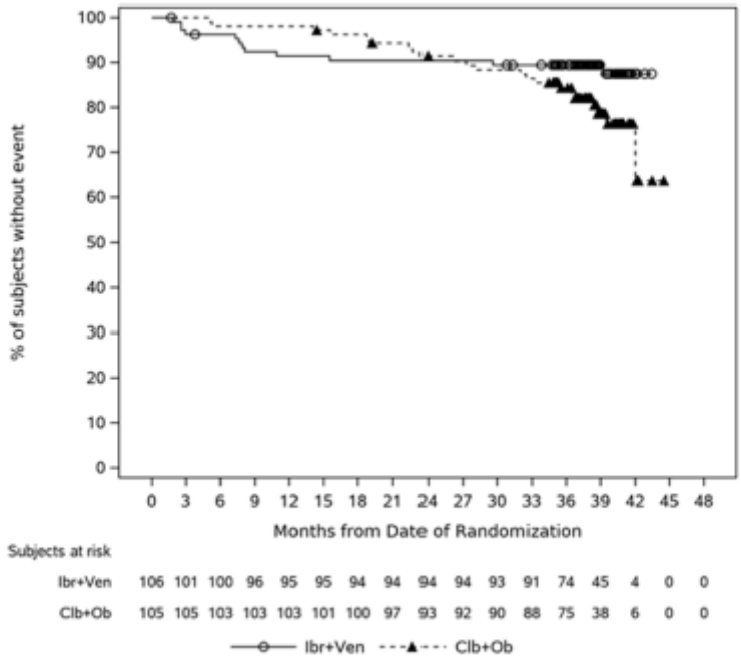
[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.

[b] p-value is from a log-rank test stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and Presence of del11q (yes vs. no).

Note: + = censored observation, NE = not estimable.

[TEFOS01A.RTF] [JNJ-54179060/54179060CLL3011/DBR_4MSU/RE_4MSU/PREPROD/TEFOS01A.SAS] 24FEB2022, 09:48

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Analysis Set (Study 54179060CLL3011)



Clb+Ob=chlorambucil+obinutuzumab; Ibr+Ven=ibrutinib+venetoclax

[GEFOS01.RTF] [JNJ-54179060/54179060CLL3011/DBR 4MSU/RE 4MSU/PREPROD/GEFOS01.SAS] 24FEB2022, 09:48

Impact of Coronavirus Disease 2019 on Efficacy Results

"As of the data cut-off for the primary analysis, there was limited impact of the COVID-19 pandemic on integrity of the study and the primary efficacy endpoint (PFS):

Six (2.8%) subjects were pending completion of the fixed duration treatment phase when the COVID-19 outbreak was declared a pandemic by WHO in March 2020.

Twenty-one (19.8%) subjects in the Ibr+Ven arm and 13 (12.4%) subjects in the Clb+Ob arm had at least 1 DE visit missed due to COVID-19. No subjects were lost to follow-up and no subject missed 2 or more consecutive DE visits due to the COVID-19 pandemic. Four subjects had missed DE visits that were considered as major protocol deviations for potentially delaying the detection of PD due to COVID-19. Sixteen (15.1%) and 23 (21.9%) subjects in the Ibr+Ven and Clb+Ob arms, respectively, had at least 1 DE visit delayed due to COVID-19.

Five deaths were reported as COVID-19 related during the study (1 in the Ibr+Ven arm and 4 in the Clb+Ob arm). All 5 deaths reported as COVID-19 related occurred post-fixed duration treatment; only 1 of these deaths occurred prior to PD. The impact of this death on the primary endpoint analysis was considered negligible.

A pre-planned supplementary PFS analysis censoring subjects who died pre-PD related to COVID-19 was not conducted because the threshold specified in the Statistical Analysis Plan was not met. A supplementary OS analysis censoring subjects who died due to COVID-19 was conducted and showed results consistent with the primary OS analysis.

A supplementary OS analysis censoring deaths related to COVID-19 at extended follow-up is inserted below by the assessor. Without such censoring, the HR was 0.760 (95% CI: 0.352, 1.642) at the cut-off for extended follow-up.

S_TEFOS03: Summary of Overall Survival – Supplementary Analysis; Intent-to-treat Analysis Set (Study 54179060CLL3011)			
	Ibr+Ven	Clb+Ob	Ibr+Ven vs. Clb+Ob
Analysis set: Intent-to-treat	106	105	
Event	10 (9.4%)	12 (11.4%)	
Death	10 (9.4%)	12 (11.4%)	
Censored	96 (90.6%)	93 (88.6%)	
Overall Survival (months)			
25th percentile (95% CI)	NE (NE, NE)	NE (35.45, NE)	
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(1.7+, 38.4+)	(5.1, 39.6+)	
6-month survival rate (95% CI)	0.962 (0.902, 0.986)	0.981 (0.926, 0.995)	
12-month survival rate (95% CI)	0.914 (0.841, 0.954)	0.981 (0.926, 0.995)	
18-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.962 (0.901, 0.985)	
24-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.932 (0.864, 0.967)	
30-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.922 (0.850, 0.960)	
36-month survival rate (95% CI)	0.904 (0.829, 0.947)	0.846 (0.727, 0.916)	
Hazard ratio (95% CI) [a]			0.893 (0.386, 2.070)
p-value [b]			0.7920

[a] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio <1 favors Ibr+Ven.
[b] p-value is from a nonstratified log-rank test.
Note: + = censored observation, NE = not estimable.
Subjects who died due to COVID-19 were censored at the death date.

The impact of the COVID-19 pandemic on the integrity of the study and the primary efficacy endpoint (PFS) remained limited with extended follow-up. One additional subject from the Clb+Ob arm had at least 1 DE visit missed due to COVID-19. Four additional subjects from the Ibr+Ven arm had at least 1 DE visit delayed due to COVID-19. No new COVID-19 infection related deaths were reported".

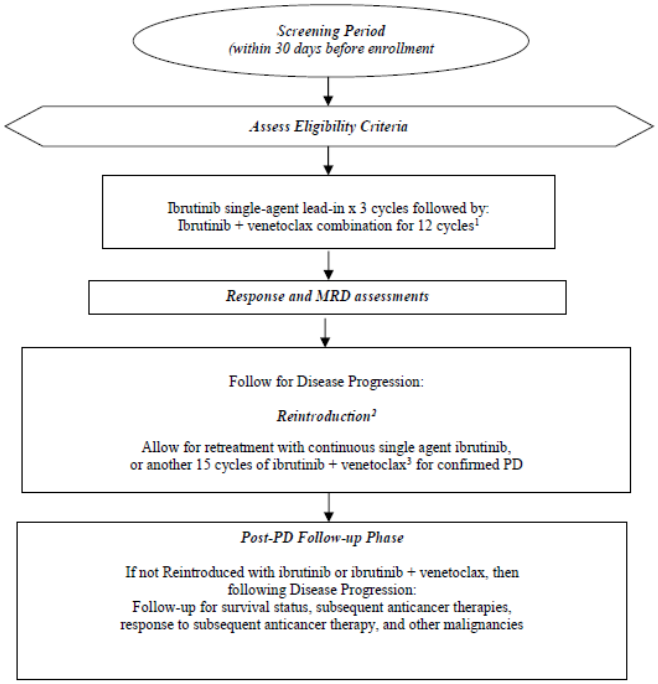
Title of Study

PHASE 2 STUDY OF THE COMBINATION OF IBRUTINIB PLUS VENETOCLAX IN SUBJECTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL LYMPHOCYTIC LYMPHOMA; PCYC-1142-CA

Methods

Study 1142 was developed to evaluate if discontinuing ibrutinib in the setting of a confirmed MRD-negative response with the combination of ibrutinib + venetoclax, allows for a treatment holiday. Encouraging early response data from investigator-initiated trials in subjects with relapsed/refractory and previously untreated CLL informed the addition of a FD cohort in which subjects received a fixed duration of Ibr+Ven. Only the FD cohort is part of this application.

3.3. Study Schema; Fixed Duration Cohort



1 Administer 12 cycles of ibrutinib + venetoclax unless discontinue for PD or toxicity. Subjects who discontinue treatment for reasons other than confirmed PD should continue participating in ongoing response follow-up visits until confirmed PD
2 Refer to Sections 3.1.3 and 5.3.3 for details regarding FD cohort Reintroduction
3 Addition of venetoclax will follow the standard dose ramp up. Venetoclax for up to 2 yrs, until PD or unacceptable toxicity, or study arm closure, whichever is first

Study participants

Key inclusion criteria

- Diagnosis of CLL/SLL that meets IWCLL diagnostic criteria (Hallek 2008).
- Active disease meeting at least 1 of the IWCLL criteria (Hallek 2008) for requiring treatment.
- Measurable nodal disease by computed tomography (CT).
- Men and women ≥18 and ≤70 years of age.
- ECOG performance status of 0-2.

Key exclusion criteria

- Any prior therapy used for treatment of CLL or SLL.
- Known or suspected history of Richter's transformation.

Treatments

The Ibr+Ven treatment schedule for the Study 1142 FD cohort was identical to that used in Study CLL3011: ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4 and contingent on completion of TLS risk assessment, venetoclax dose ramp-up (from 20 to 400 mg over 5 weeks) was initiated. Combined treatment with ibrutinib and venetoclax was administered for 12 cycles, through Cycle 15, in the absence of PD or treatment-limiting toxicity. One cycle corresponds to 28 days.

If PD per iwCLL criteria was confirmed after completion of the FD regimen, single-agent ibrutinib could be reintroduced and given continuously until PD or unacceptable toxicity. In addition, for subjects with

PD following durable efficacy after Ibr+Ven treatment (defined as time to progression after completion of fixed duration regimen of > 2 years), Ibr+Ven could be reintroduced and administered for the same 15-cycle FD period as given initially.

Outcomes/endpoints

FD Cohort
Primary Endpoint • Complete response (CR/CRi) rate
Secondary Endpoints • Duration of response • MRD negativity rate • Overall response rate • TLS risk reduction • Progression free survival • Overall survival
Safety Assessments • Safety and tolerability
Exploratory Endpoints • Sustained hemoglobin improvement rate • Sustained platelet improvement rate • Overall response rate for ibrutinib reintroduction after PD

Primary endpoint: Complete response (CR/CRi) per investigator assessment

Primary The point estimate of CRR per investigator assessment and the corresponding 95% CI based on normal approximation to the binomial distribution will be provided. In FD cohort non-del17p population, p value for testing CRR ≤ 37% vs CRR > 37% using asymptotic test for the binomial proportion will be calculated. Sensitivity CRR per IRC assessment. Supportive 1. Duration of complete response (DOCR defined as the interval between the date of initial CR or CRi until disease progression or death from any cause, whichever occurs first.) for subjects who achieved CR or CRi. 2. Durable CRR (defined as proportion of subjects with DOCR >= 336 days (12 cycles)) Subgroup (defined in table 1) The point estimate of CRR per investigator assessment and its 95% CI by normal approximation to the binomial distribution for each subgroup.

Appendix B. Schedule of Assessments for Fixed Duration Cohort

Study Visits	Screening Period	(1 cycle = 28 days)										
		Cycle 1	Cycle 2 & 3	Cycle 4					Cycle 5	Cycles 6-9	Cycle 10 & Cycle 13	Cycle 19 (3 cycles after completion of C15) C25, C28, C31 and every 6 months thereafter
				Week 1		Weeks 1-2		Wks 3-4	Wks 1 & 3			
		D1 (baseline)[g]	D1	D-3 or D-2	D-1	D1	D2	D1	D1	D1	D1	D1
Study Visit Windows	-30 days	± 3 days		± 3 days (minimum of 7 days at each dose level of venetoclax)						± 3 days		
Study Drug Administration and Dispensation												
Ibrutinib		**ibrutinib:** 420 mg PO daily[h] until completion of C15										
Venetoclax						**venetoclax:** dose ramp up[c]			**venetoclax:** 400 mg PO daily[c] until completion of C15			
Procedures												
Overall response assessment				X						X C7	X	X C19, C25, C28, C31 and every 6 months thereafter
CT/MRI scan	X[h]		X[h] C3							X C7	X	X C19, C25, C31, and annually thereafter
Bone marrow biopsy/aspirate for clinical response (local lab and Biomarker central lab)	X[i]										X[i] C10	X[i] C19
Minimal Residual Disease assessment (MRD central lab)[j]		X (PB)								X C7 (PB)	X (PB C10 and C13, BMA C10)	X (PB & BMA C19; PB C25[t], C28[t], C31, and annually thereafter)

Study Visits	Suspected CR	Suspected PD	End-of-Treatment [q]	Response Follow-Up	Post PD Follow Up
	As soon as possible after suspected CR	As soon as possible after suspected PD	30 Days	Every 3 months	Every 3 months
Study Visit Windows	Any time	Any time	± 3 days	± 14 days	± 14 days
Procedures					
Physical exam, vital signs, weight, ECOG[g]		X	X	X	
Overall response assessment		X		X	
CT/MRI scan		X		X every 6 months	
Bone marrow biopsy/aspirate for response (local lab and Biomarker central lab)[i]	X[i]	X (if clinically indicated)			
Bone marrow aspirate for biomarkers (MRD central lab)	X[s]				
MRD assessment (MRD central lab)	X (PB & BMA)		X (PB)	X every 6 months for one year, then annually thereafter	
Hematology[k]		X	X	X	

Sample size

In the FD cohort, assuming the complete response rate for Ibr + Ven is 50%, 125 subjects without del 17p will provide 83% power to ensure the rate is > 37% at 1-side alpha 0.025. A CR rate of 50% would represent meaningful improvement compared to the CR rate seen with the fixed duration combination of bendamustine + rituximab (31%), and would be an improvement over the CR rate seen with the standard of care fixed duration regimen fludarabine, cyclophosphamide and rituximab (40%) which were obtained in the CLL10 study, which included only patients without del 17p.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

This is a 2-cohort Phase 2 study assessing both MRD-guided discontinuation and fixed duration (FD) therapy with the combination of Ibr + Ven in subjects with treatment-naïve CLL or SLL. The MRD cohort is not part of this application.

FD cohort

The FD cohort was added in Protocol Amendment 1 after the completion of MRD cohort enrolment.

The primary hypothesis is that the CR rate is > 37% after 12-cycle Ibr + Ven treatment. The hypothesis was to be tested at 1-sided α level of 0.025 using asymptotic test for the binomial proportion. Since the assumption for sample size and power of this cohort is based on the historical data of subjects without del 17p, the formal hypothesis testing was to be performed on the non-del 17p population. The Non-del 17p population includes enrolled subjects who received at least 1 dose of study drug, and who are without del 17p abnormality according to non-missing baseline FISH results. All analyses for the FD cohort will be repeated on the All treated population as supportive analyses.

The primary analysis was to be based on investigator assessment and performed after the last enrolled FD subject has the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up). In addition to investigator assessment, an IRC blinded to the study treatment was to evaluate the responses for both cohorts independently.

Hypothesis testing was to be performed independently for the two cohorts (without multiplicity adjustment) for the primary endpoint only. Other endpoints were to be summarized descriptively with 95% CI whenever applicable.

Subgroup analyses were to be performed for Age, gender, race, ECOG score, Rai stage, bulky disease, Del 17p, Del 17p or TP53 mutated, FISH, IGHV per central lab, creatinine clearance and NCI ODWG Liver function classification.

No interim analysis was planned or performed.

Results

Participant flow

Table 7 Subject Disposition – FD Cohort (All-treated Population)

	FD Cohort All-treated N=159	
	Ibrutinib n (%)	Venetoclax n (%)
Treatment status		
Did not receive any study treatment	0	6 (3.8)
Ongoing	NA	NA
Completed	147 (92.5)	149 (93.7)
Discontinued	12 (7.5)	4 (2.5)
Primary reason for discontinuation of study treatment		
MRD-positive relapse	NA	NA
PD	1 (0.6)	1 (0.6)
Adverse event not related to PD	7 (4.4)	3 (1.9)
Death	1 (0.6)	0
Withdrawal of consent for treatment by subject	2 (1.3)	0
Investigator decision	1 (0.6)	0
Lost to follow-up	0	0
Subject became pregnant	0	0

FD: fixed duration; MRD: minimal residual disease; NA: not applicable; PD: progressive disease;
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

At the time of the primary analysis the median time on study was 27.9 months (range: 0.8 to 33.2 months).
The median time on study with extended follow-up was 38.7 months (range: 0.8 to 41.4 months).

Reintroduction/other subsequent anti-neoplastic therapies
At the primary analysis, 4 subjects (2.5%) had reintroduced ibrutinib post-PD; 5 subjects had received other therapy (mainly systemic therapy).

With extended follow-up, an additional 5 subjects had reintroduced ibrutinib post-PD relative to the primary analysis; 6 subjects had received other therapy (mainly systemic therapy).

Recruitment

Study Period: 28 September 2016 (date of first subject consented) to 15 December 2020 (date of database lock – primary analysis); date for database lock for extended follow-up analysis was 4 October 2021.

This study was conducted at 39 centers in the United States, Australia, New Zealand, Spain, and Italy.

Conduct of the study

Table 1 Key Changes in Protocol Amendments - Study 1142

Amendment Number and Date	Major Changes
1 25 Sep 2017	Defined MRD cohort and added a fixed duration cohort. Study to evaluate the depth of response immediately after 15 months fixed duration of therapy, in addition to the current MRD cohort assessing discontinuation based on MRD status. Included contraception up to 90 days for women of child-bearing age post-treatment in order to align with both venetoclax and ibrutinib products' current labelling. Excluded subjects with uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura. Included updates to align language with current version of the ibrutinib IB
2 29 Nov 2018	Included collection and storage of imaging for the MRD cohort in addition to the FD cohort Included collection of BM slides for the FD cohort in addition to the MRD cohort Combined endpoints for the MRD cohort pre-randomization and randomization phases Added DOR and TLS risk reduction as secondary endpoints Updated concomitant use with CYP3A inhibitor section Included updates to align language with current version of the ibrutinib IB
3 11 Sep 2019	Extended duration of study to enable extended follow-up in the FD cohort Increased frequency of efficacy assessment visits without CT scans in FD cohort Clarified duration of therapy and duration of study for the MRD cohort Clarified timing of primary analyses for FD and MRD cohorts Clarified choice and duration of reintroduction therapy for both MRD and FD cohorts Reduced frequency of both reintroduction visits and CT scans, CT assessments in response follow-up visits Clarified response to ibrutinib reintroduction as an exploratory endpoint in the MRD and FD cohorts Added an additional MRD assessment (added Cycle 28 in FD cohort) and additional biomarker assessments

Important protocol deviations (IPDs)

Table 20 Important Protocol Deviations – FD Cohort (All-treated Population)

Classification	FD Cohort All-treated N=159 n (%)
Site level	
Efficacy	4 (2.5)
Procedures/tests	2 (1.3)
Subject level	
Inclusion/exclusion	2 (1.3)
Efficacy	1 (0.6)
Safety	1 (0.6)

Site-level IPDs: for one site, CT scans were not performed at Cycle 7 for 4 subjects.

At the subject level, IPDs related to unmet eligibility criteria, efficacy, and safety were reported:

• Two subjects had IPDs related to not meeting all eligibility criteria, 1 subject was enrolled despite the need to be treated with 20 mg prednisone during the screening period to control autoimmune hemolytic anemia, while 1 subject did not have an activated partial thromboplastin time (aPTT) coagulation test performed at screening.
• One subject had an IPD impacting efficacy. 1 subject refused to have CT scans performed at multiple timepoints.

• One subject had an IPD related to safety. On 3 separate occasions, 1 subject experienced Grade 3-4 neutropenia related to venetoclax treatment, and venetoclax was not dose-reduced or withheld per protocol requirements. No IPDs were reported for the FD cohort with extended follow-up.

Study conduct during the COVID-19 pandemic (selected by the assessor)

The visit impact of logistical restrictions included subjects of the FD and MRD cohorts with virtual visits/phone calls (37.7% and 49.4%, respectively), missed visits (14.5% and 0.6%, respectively), and in-person, partial assessments (10.7% and 9.8%, respectively. Similar findings were observed after extended follow-up (virtual visits/phone calls: 41.5% and 51.2%, respectively; missed visits: 15.1% and 0.6%, respectively; partial assessments done in person: 10.7% and 11.6%, respectively.

With regard to post-treatment follow-up by investigator, most subjects in the FD cohort (> 98%) had their required assessments for overall response, radiology, hematology, and physical examination at the 3-month time point. Complete assessments for overall response, radiology, and hematology were reported for > 90% of subjects at the 12-month timepoint, but approximately 19% of subjects missed their physical examinations per lymphatic assessment due to COVID-19-related logistical restrictions.

For the evaluation of MRD negativity rate in PB at the 12-month time point in the FD cohort, a total of 39 subjects at the primary analysis and 9 subjects with extended follow-up did not have data available at the 12-month post-treatment timepoint and were thus classified as non-evaluable. For the majority of these subjects, the data were missing as a result of COVID-19 impact.

None of the deviations due to COVID-19 logistical restrictions were considered as IPDs by the MAH.

Baseline data

Table 10 Subject Demographics – FD Cohort (All-treated Population)

	FD Cohort	
	Non-del 17p N=136	All-treated N=159
Age (years)		
Mean (standard deviation)	57.9 (8.68)	58.0 (8.51)
Median	59.5	60.0
Min, max	33, 71	33, 71
Age groups – n (%)		
<65 years	97 (71.3)	114 (71.7)
≥65 years	39 (28.7)	45 (28.3)
Gender – n (%)		
Male	88 (64.7)	106 (66.7)
Female	48 (35.3)	53 (33.3)
Race – n (%)		
Asian	3 (2.2)	3 (1.9)
Black or African American	1 (0.7)	1 (0.6)
Native Hawaiian or Other Pacific Islander	1 (0.7)	1 (0.6)
White	124 (91.2)	147 (92.5)
Not reported	7 (5.1)	7 (4.4)
Ethnicity – n (%)		
Hispanic or Latino	3 (2.2)	5 (3.1)
Not Hispanic or Latino	128 (94.1)	149 (93.7)
Not reported	5 (3.7)	5 (3.1)

del 17p: deletion of the short arm of chromosome 17; FD: fixed duration
N=number of subjects in the specified population. n=number of subjects in each category. %=100*n/N.

Table 12 Baseline Disease Characteristics – FD Cohort (All-treated Population)

	FD Cohort	
	Non-del 17p N=136	**All-treated N=159**
Time from initial diagnosis (months)		
Mean (standard deviation)	46.7 (45.03)	44.4 (43.44)
Median	37.4	33.8
Min, Max	1, 284	1, 284
Baseline ECOG score		
0	97 (71.3%)	110 (69.2%)
1	39 (28.7%)	49 (30.8%)
2	0	0
Creatinine clearance rate (mL/min)		
Mean (standard deviation)	96.0 (28.29)	95.8 (27.26)
Median	89.5	90.0
Min, Max	53, 210	53, 210
< 60	6 (4.4%)	6 (3.8%)
≥ 60	130 (95.6%)	153 (96.2%)
Histology		
CLL	125 (91.9%)	146 (91.8%)
SLL	11 (8.1%)	13 (8.2%)
Rai stage		
Stage 0/I/II	100 (73.5%)	113 (71.1%)
Stage III/IV	34 (25.0%)	44 (27.7%)
Missing	2 (1.5%)	2 (1.3%)
Bulky disease[a]		
≥5 cm	44 (32.4%)	48 (30.2%)
≥10 cm	5 (3.7%)	5 (3.1%)
Cytopenia		
Hemoglobin ≤110 g/L	30 (22.1%)	37 (23.3%)
Platelets ≤100 x 10^9/L	18 (13.2%)	21 (13.2%)
Absolute neutrophil count ≤1.5 x 10^9/L	13 (9.6%)	13 (8.2%)
Any of the above	45 (33.1%)	54 (34.0%)

CLL: chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group; FD: fixed duration; 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 treatment.
[a] Bulky disease is based on the largest longest diameter of target lymph node at screening per investigator assessment.

Table 13 Baseline Genomic Characteristics – FD Cohort (All-treated Population)

	FD Cohort	
	Non-del 17p N=136 n (%)	All Subjects N=159 n (%)
Hierarchical Cytogenetics Classification[a]		
del 17p	0	20 (12.6)
del 11q	28 (20.6)	28 (17.6)
Trisomy 12	23 (16.9)	23 (14.5)
Normal	33 (24.3)	33 (20.8)
del 13q alone	52 (38.2)	54 (34.0)
Unknown	0	1 (0.6)
TP53		
Mutated	7 (5.1)	16 (10.1)
Not mutated	129 (94.9)	142 (89.3)
Unknown	0	1 (0.6)
Del 17p or TP53 mutated		
Yes	7 (5.1)	27 (17.0)
No	129 (94.9)	129 (81.1)
Unknown	0	3 (1.9)
IGHV		
Mutated	55 (40.4)	66 (41.5)
Not mutated	78 (57.4)	89 (56.0)
Unknown	3 (2.2)	4 (2.5)
Complex Karyotype[b]		
Yes	25 (18.4)	31 (19.5)
No	90 (66.2)	102 (64.2)
Unknown	21 (15.4)	26 (16.4)

CLL: chronic lymphocytic leukemia; del 11q: deletion of the long arm of chromosome 11; del 13q: deletion in chromosome 13; del 17p: deletion of the short arm of chromosome 17; FD: fixed duration; FISH: fluorescence in situ hybridization; IGHV: immunoglobulin heavy chain variable region; TP53: tumor suppressor protein 53 (p53)
N=number of subjects in the specified population. n = number of subjects in each category. %=100*n/N.

[a] Hierarchical order of cytogenetics abnormalities in CLL (Dohner et al,2000), del 17p > del 11q > trisomy 12 > normal >del 13q.

[b] Complex karyotype is defined as the presence of ≥ 3 chromosomal abnormalities (App22).

FISH results from central lab and local lab (when central lab results not available) were used. 'Normal' refers to none of del 17p, del 11q, trisomy 12 and del 13q presented. The classification is 'Unknown' when a FISH result is missing and none of the categories are abnormal.

Numbers analysed

Efficacy analyses were performed on the All-treated population.

For the FD cohort, a total of 159 subjects were analyzed for efficacy; of these subjects, 136 subjects (85.5%) did not have del 17p; 20 subjects (12.6%) had del 17p.

Outcomes and estimation

- **Primary endpoint, CRR per investigator**

Table 25 Complete and Overall Response Rates Per Investigator and IRC Assessments – FD Cohort (All-treated Population)

	Investigator Assessment				IRC Assessment			
	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)		Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)	Non-del 17p N=136 n (%)	All-treated N=159 n (%)
Complete Response Rate (CR, CRi)	76 (55.9)	88 (55.3)	79 (58.1)	91 (57.2)	83 (61.0)	95 (59.7)	87 (64.0)	99 (62.3)
95% CI[a]	47.5, 64.2	47.6, 63.1	49.8, 66.4	49.5, 64.9	52.8, 69.2	52.1, 67.4	55.9, 72.0	54.7, 69.8
Durable Complete Response Rate[c]	66 (48.5)	78 (49.1)	73 (53.7)	85 (53.5)	70 (51.5)	81 (50.9)	79 (58.1)	90 (56.6)
95% CI[a]	40.1, 56.9	41.3, 56.8	45.3, 62.1	45.7, 61.2	43.1, 59.9	43.2, 58.7	49.8, 66.4	48.9, 64.3
Overall Response Rate (CR, CRi, nPR, or PR)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)	130 (95.6)	153 (96.2)
95% CI[a]	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2	92.1, 99.0	93.3, 99.2
Best overall response								
Complete response (CR)	74 (54.4)	83 (52.2)	79 (58.1)	88 (55.3)	81 (59.6)	92 (57.9)	86 (63.2)	97 (61.0)
Complete response with incomplete bone marrow recovery (CRi)	2 (1.5)	5 (3.1)	0	3 (1.9)	2 (1.5)	3 (1.9)	1 (0.7)	2 (1.3)
Nodular partial response (nPR)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)	2 (1.5)	2 (1.3)	2 (1.5)	2 (1.3)
Partial response (PR)	53 (39.0)	64 (40.3)	50 (36.8)	61 (38.4)	45 (33.1)	56 (35.2)	41 (30.1)	52 (32.7)
Stable disease (SD)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)	2 (1.5)	2 (1.3)	2 (1.5)	2 (1.3)
Non-progressive disease	NA	NA	NA	NA	3 (2.2)	3 (1.9)	3 (2.2)	3 (1.9)
Progressive disease	0	0	0	0	0	0	0	0
Unknown/No assessment	5 (3.7)	5 (3.1)	5 (3.7)	5 (3.1)	1 (0.7)	1 (0.6)	1 (0.7)	1 (0.6)

CI: confidence interval; CRi: complete response with incomplete bone marrow recovery; CRR: complete response rate; del 17p: deletion in the short arm of chromosome 17; FD: fixed duration; IRC: independent review committee; NA: not applicable

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

[a] The 95% confidence interval for response rates based on normal approximation to the binomial distribution.

[b] One-sided P value from asymptotic test for the binomial proportion (CRR≤ 37% vs CRR > 37%).

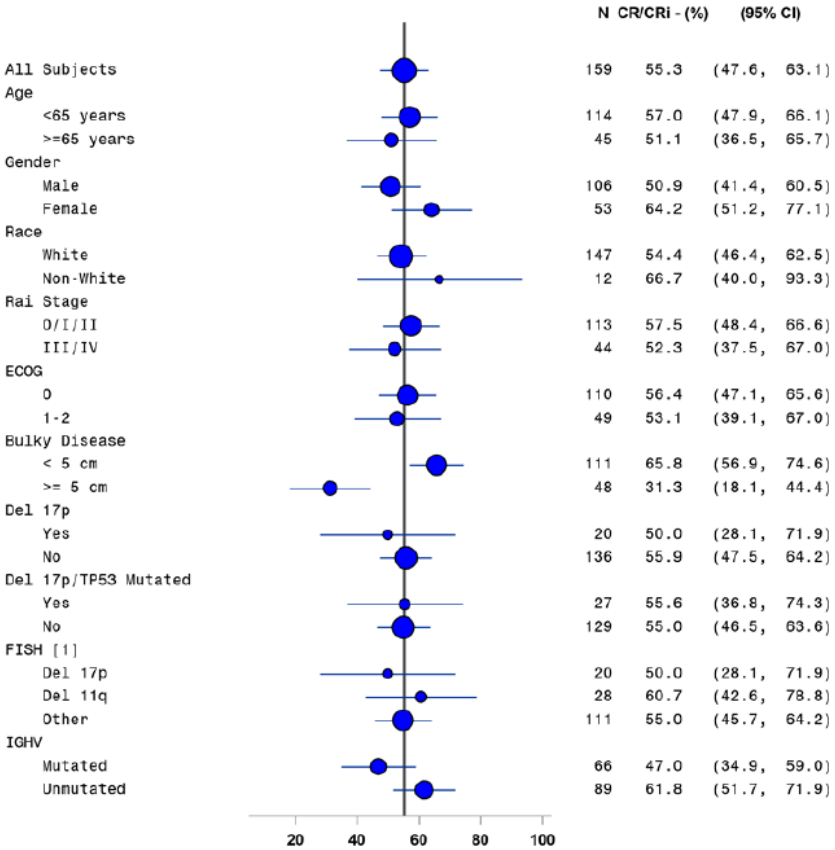
[c] Durable complete response rate defined as proportion of subjects with duration of complete response (CR/CRi) for 1 year (12 cycles). This table is based on all response assessments performed on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Table 14.2.2.1.1a Complete Response Rate (CRR) and Overall Response Rate (ORR) Based on Investigator Assessment by Del17p/TP53
FD Cohort - All Treated Population

	Del17p/TP53 Status	
	Yes (N=27) n (%)	No (N=129) n (%)
Complete Response Rate (CR, CRi)	15 (55.6)	71 (55.0)
95% CI [1]	(36.8, 74.3)	(46.5, 63.6)
Durable Complete Response Rate [2]	13 (48.1)	63 (48.8)
95% CI [1]	(29.3, 67.0)	(40.2, 57.5)
Overall Response Rate (CR, CRi, nPR, or PR)	26 (96.3)	124 (96.1)
95% CI [1]	(89.2, 100.0)	(92.8, 99.5)
Best Overall Response		
CR	14 (51.9)	69 (53.5)
CRi	1 (3.7)	2 (1.6)
nPR	0	1 (0.8)
PR	11 (40.7)	52 (40.3)
SD	0	1 (0.8)
PD	0	0
No assessment	1 (3.7)	4 (3.1)

N = number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.
CR = complete response. CRi = CR with incomplete blood count recovery. nPR = nodular partial response. PR = partial response.
SD = stable disease. PD = progressive disease.
[1] 95% confidence interval based on normal approximation to the binomial distribution.
[2] Durable complete response rate was defined as the proportion of subjects with duration of complete response (CR/CRi) for 1 year (defined as at least 12 cycles).
This table is based on response assessments performed on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Figure 1 **Complete Response Rate Based on Investigator Assessment At Primary Analysis – Subgroup Analysis for FD Cohort (All-treated Population)**



- **ORR**

At the primary analysis, the ORR per investigator assessment as well as IRC was 96.2% for all subjects and 95.6% for subjects without del 17p. For subjects with del 17p/TP53 mutated, the ORR was 96.3% per investigator assessment as well as IRC. No change in ORR per investigator assessment was observed after extended follow-up.

- **DOR**

At the primary analysis, the median durations of response per investigator assessment for the FD cohort were not reached for all subjects or for subjects without del 17p; the 24-month landmark estimates were 94.7% for all subjects and 96.1% for subjects without del 17p based on an overall median follow-up of 27.9 months.

With extended follow-up, similar outcomes in DOR were observed for all subjects and subjects without del 17p (median not reached for both populations; 30-month landmark estimates of 88.6% and 89.8%, respectively) based on a median follow-up of 38.7 months.

- **MRD-negativity rate**

Table 26 MRD-negativity Rate – FD Cohort (All-treated Population)

	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p	All-treated	Non-del 17p	All-treated
Overall MRD Negativity Rate	N=136	N=159	N=136	N=159
Bone marrow– n (%)	84 (61.8)	95 (59.7)	84 (61.8)	95 (59.7)
Peripheral blood – n (%)	104 (76.5)	122 (76.7)	104 (76.5)	122 (76.7)
MRD Negativity Rate 3 Months Post-Treatment[a]	N=136	N=159	N=136	N=159
Bone marrow– n (%)	74 (54.4)	83 (52.2)	74 (54.4)	83 (52.2)
Peripheral blood – n (%)	78 (57.4)	90 (56.6)	78 (57.4)	90 (56.6)
MRD Negativity Rate in Subjects with CR/CRi Based on Investigator Assessment	N=76	N=88	N=79	N=91
Bone marrow– n (%)	53 (69.7)	63 (71.6)	56 (70.9)	66 (72.5)
Peripheral blood – n (%)	67 (88.2)	79 (89.8)	70 (88.6)	82 (90.1)
MRD Negativity Rate in Subjects with CR/CRi Per Investigator 3 Months Post-Treatment[b]				
Subjects with CR/CRi - N	N=66	N=77	N=66	N=77
Bone marrow– n (%)	42 (63.6)	50 (64.9)	42 (63.6)	50 (64.9)
Peripheral blood – n (%)	43 (65.2)	51 (66.2)	43 (65.2)	51 (66.2)

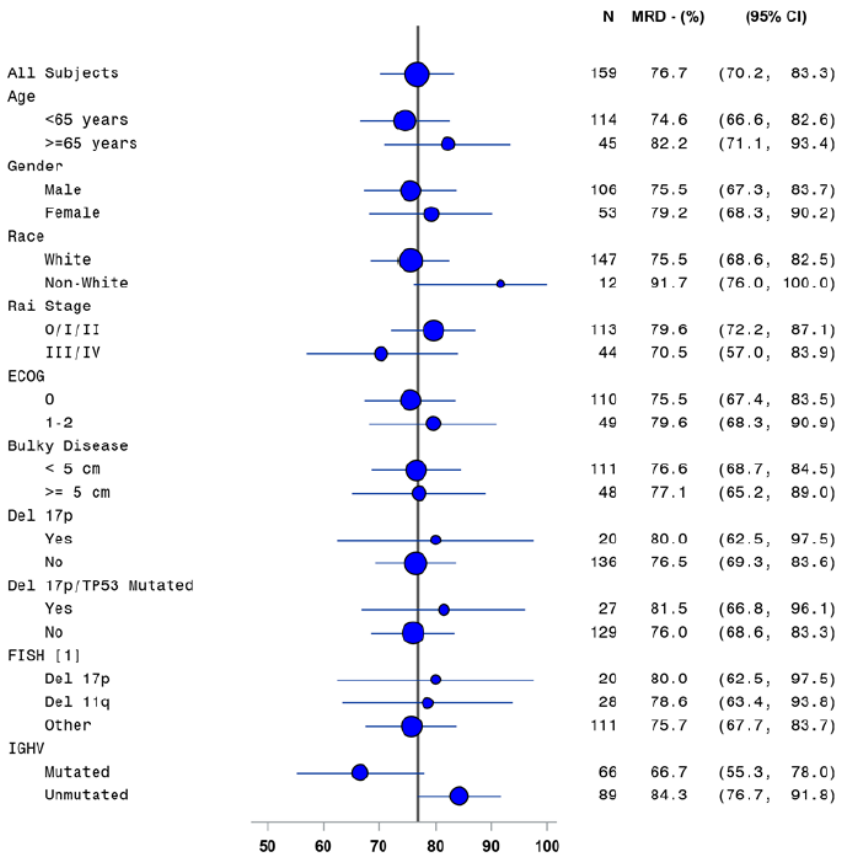
BM: bone marrow; CR: complete response; CRi: complete response with incomplete bone marrow recovery; del 17p: deletion of the short arm of chromosome 17; FD: fixed duration; MRD: minimal residual disease; PB: peripheral blood

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

[a] MRD assessment in BM and PB was scheduled at Cycle 19 Day 1 for the FD cohort. The first valid MRD result > 2 cycles(56 days) after the last dose date was used in this summary.

[b] The summary for 3 months post-treatment is based on overall response and MRD at first assessment > 2 cycles (56 days) after last dose and on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.

Figure 3 **Subgroup Analysis of MRD Negativity Rates in Peripheral Blood at Primary Analysis – FD Cohort (All-treated Population)**



<u>12 months post-treatment</u>

At 12 months post-treatment, the MRD negativity rate in PB was 35.2% for all subjects and 34.6% for subjects without del 17p. The majority of the 39 non-evaluable subjects did not have valid MRD results due to COVID-19 impact (ie, 18 subjects with non-evaluable samples plus 21 subjects with no sample taken within the required time window). At the 12-month time point, in an analysis based on evaluable subjects (ie, those with valid MRD results > 11 cycles after the last dose date or had no sample taken within the time window due to PD, initiation of subsequent antineoplastic therapy, death, or study exit), the MRD negativity rate in the PB was 46.7% for all subjects and 46.1% for subjects without del 17p at the primary analysis.

With extended follow-up, the MRD negativity rate in PB at 12 months post-treatment was 42.8% in all subjects and 43.4% for subjects without del 17p. Only 9 non-evaluable subjects remained as more MRD samples had been collected. Similar MRD negativity rates were observed with extended follow-up and collection of addition of additional samples from subjects previously not evaluable due to COVID-19 compared to primary-analysis rates in the evaluable population (all subjects: 45.3%; subjects without del 17p: 45.7%).

- **PFS**

Table 27 Progression-free Survival Based on Investigator Assessment – FD Cohort (All-treated Population)

	Primary Analysis (12 November 2020)		Extended Follow-up (04 August 2021)	
	Non-del 17p N=136	All-treated N=159	Non-del 17p N=136	All-treated N=159
Events - n (%)	16 (11.8)	20 (12.6)	23 (16.9)	28 (17.6)
PD- n	14	18	21	26
Death – n	2	2	2	2
Censored - n (%)	120 (88.2)	139 (87.4)	113 (83.1)	131 (82.4)

At the primary analysis, the median PFS per investigator assessment for the FD cohort was not reached for all subjects or for subjects without del 17p based on an overall median follow-up of 27.9 months. The Kaplan-Meier point estimates at 24 months were 94.8% for all subjects and 96.2% for non-del 17p subjects. For subjects with del 17p/TP53 mutated, the median PFS was not reached, and the Kaplan-Meier point estimate at 24 months was 84.1%.

At extended follow-up (overall median follow-up: 38.7 months), the median PFS per investigator assessment was not reached for all subjects or for subjects without del 17p, and the Kaplan-Meier point estimates at 36 months were 88.1% for all subjects, 89.1% for non-del 17p subjects, and 79.9% for subjects with del 17p/TP53 mutated.

- **OS**

At the primary analysis, the median OS for the FD cohort was not reached for all subjects or for subjects without del 17p based on an overall median follow-up of 27.9 months. A total of 3 deaths were reported (2 deaths due to cardiac events [including 1 death due treatment-emergent sudden death] and 1 death due to intracranial hemorrhage), with all the deaths occurring in subjects without del 17p. The Kaplan-Meier point estimates at 24 months were 98.1% for all subjects and 97.7% for non-del 17p subjects. For subjects with del 17p/TP53 mutated, the median OS was not reached, and the Kaplan-Meier point estimate at 24 months was 96.2%.

Analysis of OS with extended follow-up (overall median follow-up: 38.7 months indicated no change in the findings observed at the primary analysis for all subjects and subjects without del 17p as well as for subjects with del 17p/TP53 mutated with no additional deaths reported.

- **TLS risk reduction**

Table 29 Tumor Lysis Syndrome Risk at Baseline and after 3-Cycle Ibrutinib Lead-in – FD Cohort (All-treated Population)

TLS Risk	Baseline n (%)	After Ibrutinib Lead-in n (%)
High	34 (21.4)	1 (0.6)
LDi ≥ 10 cm	4 (2.5)	0
LDi ≥ 5 cm and ALC ≥ 25 x 10^9/L	30 (18.9)	1 (0.6)
Medium	97 (61.0)	106 (66.7)
Low	28 (17.6)	46 (28.9)
Missing	0	6 (3.8)

ALC: absolute lymphocyte count; LDi: the largest diameter of target lymph nodes. FD: fixed duration; TLS: tumor lysis syndrome

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

TLS risk was assessed by investigator per criteria specified on App1, Protocol Amendment 3, Appendix H. Analysis include TLS risk at baseline and the last post-baseline value on or prior to the venetoclax first dose date (Cycle 4 Day 1) or, for subjects never received venetoclax, the post-baseline value closest to the scheduled Cycle 4 Day 1, ie, 84 days after the first dose date of ibrutinib.

At baseline, hospitalization indicated per the VENCLEXTA® USPI, 2020 and VENCLYXTO® SmPC, 2020 (based upon TLS risk and creatinine clearance) was observed for 39.6% of subjects and 17.6% of subjects after 3 cycles of single-agent ibrutinib lead-in therapy. For all subjects, 54.0% of subjects indicated for hospitalization due to TLS risk at baseline were no longer indicated for hospitalization after the 3-cycle ibrutinib lead-in.

Ancillary analyses

- **Rate of sustained hemoglobin improvement**

At the primary analysis, the proportion of subjects achieving a sustained improvement in hemoglobin was 41.5% for all subjects in the FD Cohort. For those subjects with anemia at baseline, the proportion of subjects achieving a sustained improvement in hemoglobin was 86.5%. Similar trends were observed after extended follow-up (ie, sustained improvement in hemoglobin observed for 45.9% of all subjects and 91.9% of subjects with baseline anemia.

- **Rate of sustained platelet improvement**

At the primary analysis, the proportion of subjects achieving a sustained improvement in platelet count was 17.6% for all subjects in the FD Cohort. For those subjects with thrombocytopenia at baseline, the proportion of subjects achieving a sustained improvement in platelet count was 57.1%. Similar trends were observed after extended follow-up (ie, sustained improvement in platelet count observed for 19.5% of all subjects and 61.9% of subjects with baseline thrombocytopenia).

Summary of main study(ies)

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 1. Summary of Efficacy for pivotal studies CLL3011 and 1142

	Study CLL3011				Study 1142 FD Cohort	
	Ibr+Ven N=106		**Clb+Ob N=105**		**Ibr+Ven N=159**	
Median time on study (months)	27.7		27.9		27.9	
Median PFS by IRC (months)	**NE**		**21.0**		**NE**	
Min, Max	0.03+, 32.7+		2.6, 31.5+		0.8, 33.2+	
24-mo landmark estimate (%)	84.4		44.1		88.9	
p-value	<0.0001				NA	
HR (95% CI)	0.216 (0.131, 0.357)				NA	
MRD						
Overall MRD negativity rate (%)	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	55.7	59.4	21.0	40.0	Not applicable	
Flow cytometry	67.9	80.2	22.9	46.7	59.7	76.7
MRD negativity, 3 mo post- treatment	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	51.9	54.7	17.1	39.0	NA	NA
Flow cytometry	56.6	61.3	16.2	41.0	52.2	56.6
MRD negativity, 12 mo post-treatment	***BM***	***PB***	***BM***	***PB***	***BM***	***PB***
NGS	-	49.1	-	12.4	Not applicable	
Flow cytometry	-	54.7	-	16.2	-	42.8 [a]
ORR (CR, CRi, nPR, PR)	86.8		84.8		96.2	
95% CI	80.3, 93.2		77.9, 91.6		93.3, 99.2	
Rate ratio (95% CI)	1.02 (0.92, 1.14)				NA	
p-value	0.6991				NA	
CR rate	38.7		11.4		59.7	
95% CI	29.4, 48.0		5.3, 17.5		52.1, 67.4	
Rate ratio (95% CI)	3.43 (1.91, 6.15)				NA	
p-value	<0.0001				NA	
OS						
Median OS (months)	NE		32.5		NE	
24-mo landmark estimate (%)	90.4		91.3		98.1	
p-value	0.9121				NA	
HR (95% CI)	1.048 (0.454, 2.419)				NA	
Extended follow-up: 30-mo landmark estimate (%)	89.4		88.4		98.1	
p-value	0.4837				NA	
HR (95% CI)	0.760 (0.352, 1.642)				NA	

Analysis performed across trials

Evaluation of the Individual Contributions of Ibrutinib and Venetoclax to the Overall Profile of Combination Treatment

Given the lack of FD single-agent ibrutinib and venetoclax CLL/SLL study data to assess the contribution of each agent to the overall activity of the FD Ibr+Ven treatment, cross-study comparisons of clinical data from ibrutinib and venetoclax single-agent, continuous therapy with Ibr+Ven combination therapy were conducted as an alternative approach to address this point. Of note, there are no available single-agent venetoclax data in the previously untreated disease setting. Therefore, key efficacy results from Ibr+Ven combination studies were compared with single-agent continuous ibrutinib and venetoclax studies in the relapsed/refractory setting to evaluate the efficacy contribution of both agents in the combination therapy.

The following table provides an overview of the clinical studies used for the cross-study analyses.

Table 12: Overview of Studies Selected for Cross-study Comparisons

Relapsed/Refractory CLL/SLL			
	Study	**Subject Population (n)**	**Phase**
IBRUTINIB			
Single-agent	**Continuous Treatment**		
	Study 1112 (RESONATE)	Older, frail subjects (inc. del17p); (n=195)	3
	Study1102/1103	Broad subject population (inc. del17p); (n=85)	2
	Study 1117 (RESONATE-17)	Limited to subjects with del17p only; (n=144)	2
VENETOCLAX			
Single-agent	**Continuous Treatment**		
	Study M12-175	Broad subject population (inc. del17p); (n=116)[a]	1
	Study M13-982	Limited to subjects with del17p only; (n=158)	2
	Study M14-032	Broad subject population (inc. del17p); (n=127)	2
IBR+VEN			
Combination Therapy	**MRD-guided discontinuation**		
	Study CLARITY[b]	Broad subject population (inc. del17p); (n=54)	2
	Study HO-141 (VISION/HOVON 141)[c]	Broad subject population (inc. del17p); (n=51)	2

BM=bone marrow; CLL=chronic lymphocytic leukemia; del17p=deletion of the short arm of chromosome 17; inc.=including; MRD=minimal residual disease; MRD4=eradication of MRD to <1 CLL cell in 10,000 leukocytes according to the iwCLL guidelines [Hallek 2008]; n=number; PB=peripheral blood; SLL=small lymphocytic lymphoma; Ven=venetoclax; Ven+Ob=venetoclax + obinutuzumab; Ven+R=venetoclax + rituximab

[a] Study M12-175: A total of 116 subjects were enrolled in 8 groups in dose-escalation cohort; subsequent subjects started with a test dose of 50 mg or 20 mg and in the absence of TLS underwent a ramp-up in dose to designated daily doses of 150 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, and 1200 mg. Sixty-seven subjects had the 400 mg/day dose, which is referenced in the VENCLEXTA® USPI

[b] CLARITY: Duration of therapy defined by confirmed MRD response with 3 possibilities: MRD level $<1 \times 10^{-4}$ in both PB and BM at Month 8 to stop Ibr and Ven at Month 14; MRD detectable at Month 8 but MRD level $<1 \times 10^{-4}$ in both PB and BM at Month 14 and/or Month 26 to stop Ibr and Ven at Month 26; and MRD detectable at Month 26 to stop Ven but continue Ibr until progression.

[c] VISION: Results of interim analyses, total enrollment N=230. Subjects achieving MRD negativity (MRD $<1 \times 10^{-4}$ level by flow cytometry) on Day 15 of Cycle 15 in PB+BM randomized 1 : 2 between continuous Ibr treatment until toxicity or progression and treatment-free observation. Subjects not achieving MRD negativity in PB and/or BM at Day 15 of Cycle 15 continue Ibr treatment until toxicity or progression (non-randomized subjects).

Table S1: Tabular Comparison of Key Baseline and Efficacy Data in Studies with Ibr+Ven, Single-agent Ibrutinib, and Single-agent Venetoclax Based on Comparable Follow-up

	Fixed Duration Ibr+Ven[a]		Continuous Single-agent Ibrutinib			Continuous Single-agent Venetoclax			
	CLARITY[b]	VISION	Study 1112 (RESONATE)	Study 1117 (RESONATE-17)	Study 1102/1103	M12-175	M13-982	M14-032	
Number of subjects - N	**54**	**51**	**195**	**144**	**85[c]**	**116[d]**	**158[e]**	**91[f] (prior Ibr tx)**	**36[g] (prior Idel tx)**
Median age (range) – years	64 (31-83)	67 (40-83)	67 (30-86)	64.0 (IQR 57-72)	66 (37-82)	66 (36-86)	67 (29-85)	66 (28-81)	68 (56-85)
Subjects with del17p - % (n/N)	22 (11/50)	--	32 (63/195)	100 (144/144)	34 (29/85)	30 (31/102)	100 (158/158)	47 (42/90)	22 (8/36)
Unmutated *IGHV* - % (n/N)	74 (40/54)	57 (NA)	73 (98/134)	67 (97/144)	76 (65/85)	45 (46/102)	78 (45/58)	75 (50/67)	88 (22/25)
Median prior therapies (range) - n	1 (1-6)	--	3 (1-12)	2 (1-7)	4 (1-12)	3 (1-11)	2 (0-10)	4 (1-15)	3 (1-11)
Median treatment duration (range) - months	--	--	18.3 (0.2-25.3)	24.9 (0.4-31.1)	19.3 (0.3, 28.7)	17.0 (<1-44.0)	23.1 (0-44.2)	--	14 (1-29)
Median follow-up (range) – months	21.1 (NA)	--	19.0 (0.33+, 26.2)	27.6 (0.5+, 31.1+)	22.1 (0.7, 28.7)	17.0 (1.0-44.0)	26.6 (0-44.2)	14 (IQR 8-18)	14 (NA)
Median PFS (95% CI) - months	NR (NA)	--	NR (NA)	NR (27.7, NE)	NR (NE, NE)	22 (17, 29)[h]	27.2 (21.9, NR)[i]	24.7 (19.2, NR)	NR (NA)
Landmark estimates - %									
12 months	100	--	83.8	80.0	85.0	--	--	75	79
18 months	100	--	76.2	70.1	78.8	69 (15 mo)	--	--	--
24 months	--	--	--	62.5	73.6	49	54	--	--
Median OS (95%CI) - months	NR (NA)	--	NR (NA)	NR (29.5, NE)	NR (NE, NE)	NA	NA	NR (27.8, NR)	NR (NA)
Landmark									

	CLARITY[b]	VISION	Study 1112 (RESONATE)	Study 1117 (RESONATE-17)	Study 1102/1103	M12-175	M13-982	M14-032	
12 months	100	--	90.2	84.1	91.5	--	--	91	94
18 months	100	--	86.1	78.9	83.1	89 (15 mo)	--	--	--
24 months	--	--	--	75.0	77.5	84	73	--	--
ORR (CR, CRi, nPR, PR) - %	89 (47/53)	82	90.3	83	75.3	79	77	65	67
CR + CRi (%)	51 (27/53)	57	6.7	10	2.4	20	20	9	8
MRD negativity rate - % (n/N)[j]									
Bone Marrow	36 (19/53)	39 (NA)	--	--	--	5 (6/116)	71 (20/28 with PB MRD neg)[k]	38.4 (5/13 with PB MRD neg)[l]	--
Peripheral Blood	53 (28/53)	55 (NA)	--	--	--	--	30 (48/158)	26 (24/91)	22 (8/36)

BM=bone marrow; CI=confidence interval; CR=complete response; CRi=complete response with incomplete bone marrow recovery; del17p=deletion of the short arm of chromosome 17; Ibr+Ven=ibrutinib + venetoclax; idel=idelalisib; IGHV=immunoglobulin heavy chain variable region; IQR=interquartile range; MRD=minimal residual disease; NA=not available; NE=not estimable; nPR=nodular partial response; NR=not reached; ORR=overall response rate; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; tx=treatment; Ven+R=venetoclax + rituximab.

a. Two-cycle lead-in with ibrutinib followed by 12 cycles of Ibr+Ven.

b. A total of 54 subjects were allocated to intervention (ie, non-randomized) and reported upon for baseline characteristics. Fifty subjects received Ibr+Ven intervention and were analyzed (ie, N at risk at time zero per K-M). Minimal residual disease negativity and response data was obtained from 53 subjects.

c. This total contains relapsed/refractory subjects who received 1 of 2 dosing regimens for ibrutinib (ie, 420 mg/day and 840 mg/day).

d. A total of 116 subjects were enrolled in 8 groups in dose-escalation cohort; subsequent subjects started with a test dose of 50 mg or 20 mg and in the absence of TLS underwent a ramp-up in dose to designated daily doses of 150 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, and 1200 mg. Sixty-seven subjects had the 400 mg/day dose, which is referenced in the Venclexta® USPI.

e. Study includes 5 of 158 subjects who were previously untreated.

f. Data in this column are from 91 subjects who had received ibrutinib as the last B-cell receptor pathway inhibitor therapy before enrollment.

g. Data in this column are from 36 subjects who had received idelalisib as the last B-cell receptor pathway inhibitor therapy before enrollment.

h. Estimate may be unstable as limited number of patients followed to an event beyond 21 months.

i. Median PFS was not reached for patients with CR/CRi.

j. MRD negativity rates assessed by flow cytometry.

k. Contemporaneous BM assessment was available for 28 of 48 subjects with blood MRD $<10^{-4}$, 20 of whom were MRD negative in the BM.

1. Fifty-seven subjects were assessed for MRD in PB from Week 24 after treatment initiation; 5 of 13 subjects subsequently assessed for MRD in BM were negative.

Note: n/N provided when the number of subjects evaluable did not correspond to the overall number of subjects for a study.
For all studies, response data shown in this table are per investigator assessment.
Data from Study M14-032 is included with a median follow up time of 14 months as the best available data source for this comparison.
PFS and OS landmark estimates are provided only for time points that are included within the median follow up time for a given study.

Table S2: Tabular Comparison of Key Baseline and Efficacy Data in Studies with Ibr+Ven, Single-agent Ibrutinib, and Single-agent Venetoclax Based on Longest Follow-up

	Fixed Duration Ibr+Ven[a]		Continuous Single-agent Ibrutinib			Continuous Single-agent Venetoclax			
	CLARITY[b]	VISION	Study 1112 (RESONATE)	Study 1117 (RESONATE-17)	Study 1102/1103	M12-175	M13-982	M14-032	
Number of subjects - N	**54**	**51**	**195**	**144**	**101[c]**	**116[d]**	**158[e]**	**91[f] (prior Ibr tx)**	**36[g] (prior Idel tx)**
Median age (range) – years	64 (31-83)	67 (40-83)	67 (30-86)	64.0 (IQR 57-72)	64 (37-82)	66 (36-86)	67 (29-85)	66 (28-81)	68 (56-85)
Subjects with del17p - % (n/N)	22.0 (11/50)	--	32 (63/195)	100 (144/144)	34 (34/101)	30 (31/102)	100 (158/158)	47 (42/90)	22 (8/36)
Unmutated *IGHV* - % (n/N)	74 (40/54)	57 (NA)	73 (98/134)	67 (97/144)	78 (79/101)	45 (46/102)	78 (45/58)	75 (50/67)	88 (22/25)
Median prior therapies (range) - n	1 (1-6)	--	3 (1-12)	2 (1-7)	4 (1-12)	3 (1-11)	2.5 (0-10)	4 (1-15)	3 (1-11)
Median treatment duration (range) - months	--	--	41.0 (0.2-71.1)	24.9 (0.4-31.1)	39 (0.3-98)	17.0 (<1-44.0)	23.1 (0-44.2)	--	14 (1-29)
Median follow-up (range) – months	21.1 (NA)	--	65.3 (0.3, 71.6)	27.6 (0.5+, 31.1+)	82.0 (0.7, 98)	17.0 (1.0-44.0)	26.6 (0-44.2)	14 (IQR 8-18)	14 (NA)
Median PFS (95% CI) - months	NR (NA)	--	44.1 (38.5, 56.2)	NR (27.7, NE)	52 (37.3, 69.7)	22 (17, 29)[h]	27.2 (21.9, NR)[i]	24.7 (19.2, NR)	NR (NA)
Landmark estimates - %									
18 months	100	--	76.2	70.1	80.6	69 (15 mo)	--	--	--
24 months	--	--	74.0	62.5	72.7	49	54	--	--
30 months	--	--	--	57.2	68.0	--	--	--	--
36 months	--	--	58.8	--	63.4	--	--	--	--
48 months	--	--	46.8	--	51.3	--	--	--	--
Median OS (95%CI) - months	NR (NA)	--	67.7 (61.0, NE)	NR (29.5, NE)	92 (65.6, NE)	NA	NA	NR (27.8, NR)	NR (NA)
Landmark estimates - %									
12 months	100	--	90.2	84.1	92.8	--	--	91	94
18 months	100	--	86.1	78.9	86.1	89 (15 mo)	--	--	--
24 months	--	--	83.4	75.0	80.3	84	73	--	--
30 months	--	--	77.0	62.7	76.7	--	--	--	--
36 months	--	--	73.2	--	75.4	--	--	--	--
ORR (CR, CRi, nPR, PR) - %	89 (47/53)	82	91	83	89	76	80	65	67
CR + CRi (%)	51 (27/53)	57	11	10	10	10	8	9	8
MRD negativity rate - % (n/N)[j]									
Bone Marrow	36 (19/53)	39 (NA)	--	--	--	5 (6/116)	71 (20/28 with PB MRD neg)[k]	38.4 (5/13 with PB MRD neg)[l]	--
Peripheral Blood	53 (28/53)	55 (NA)	--	--	--	--	30 (48/158)	26 (24/91)	22 (8/36)

BM=bone marrow; CI=confidence interval; CR=complete response; CRi=complete response with incomplete bone marrow recovery; del17p=deletion of the short arm of chromosome 17; Ibr+Ven=ibrutinib + venetoclax; idel=idelalisib; IGHV=immunoglobulin heavy chain variable region; IQR=interquartile range; MRD=minimal residual disease; NA=not available; NE=not estimable; nPR=nodular partial response; NR=not reached; ORR=overall response rate; OS=overall survival; PB=peripheral blood; PFS=progression-free survival; tx=treatment; Ven+R=venetoclax + rituximab.

a. Two-cycle lead-in with ibrutinib followed by 12 cycles of Ibr+Ven.

b. A total of 54 subjects were allocated to intervention (ie, non-randomized) and reported upon for baseline characteristics. Fifty subjects received Ibr+Ven intervention and were analyzed (ie, N at risk at time zero per K-M). Minimal residual disease negativity and response data was obtained from 53 subjects.

c. This total contains relapsed/refractory subjects who received 1 of 2 dosing regimens for ibrutinib (ie, 420 mg/day and 840 mg/day).

d. A total of 116 subjects were enrolled in 8 groups in dose-escalation cohort; subsequent subjects started with a test dose of 50 mg or 20 mg and in the absence of TLS underwent a ramp-up in dose to designated daily doses of 150 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, and 1200 mg. Sixty-seven subjects had the 400 mg/day dose, which is referenced in the Venclexta® USPI.

e. Study includes 5 of 158 subjects who were previously untreated.

f. Data in this column are from 91 subjects who had received ibrutinib as the last B-cell receptor pathway inhibitor therapy before enrollment.

g. Data in this column are from 36 subjects who had received idelalisib as the last B-cell receptor pathway inhibitor therapy before enrollment.

h. Estimate may be unstable as limited number of patients followed to an event beyond 21 months.

i. Median PFS was not reached for patients with CR/CRi.

j. MRD negativity rates assessed by flow cytometry.

k. Contemporaneous BM assessment was available for 28 of 48 subjects with blood MRD $<10^{-4}$, 20 of whom were MRD negative in the BM.

l. Fifty-seven subjects were assessed for MRD in PB from Week 24 after treatment initiation; 5 of 13 subjects subsequently assessed for MRD in BM were negative.

Note: n/N provided when the number of subjects evaluable did not correspond to the overall number of subjects for a study.
For all studies, response data shown in this table are per investigator assessment.
Data from Study M14-032 is included with a median follow up time of 14 months as the best available data source for this comparison.
PFS and OS landmark estimates are provided only for time points that are included within the median follow up time for a given study.

Propensity score analysis

A propensity score analysis (PSA) was conducted among selected relapsed CLL/SLL clinical studies. The efficacy endpoints CRR, ORR, PFS and OS were compared between Ibr+Ven and single agent ibrutinib, and between Ibr+Ven and single-agent venetoclax in the relapsed setting.

CRR and ORR were compared by Pearson's chi-squared test. The 95% confidence interval (CI) for the rate differences were provided. PFS and OS rates were compared by Log-Rank test. Hazard ratio and its 95% CI were calculated based on Cox regression model. Landmark estimates of 30-month PFS and OS rates were estimated by Kaplan-Meier method. The 30-month landmark was selected according to the median follow-up time of treatment groups for PSA (in the analysis population consisting of CLL subjects with 1 to 6 prior lines of therapy only):

- VISION 34 months
- Ibr+Ven Pool 36 months
- PCYC-1112 66 months
- Ven Pool 33 months

Propensity scores were estimated using a logistic regression with the binary treatment assignment (T=1~Ibr+Ven and T=0~single-agent) as a dependent variable and selected prognostic factors as covariates. Similarity in the subjects between the treatment arm and the control arm are measured using the overlap coefficient defined as the overlapping area of the estimated marginal propensity score density curves per arm.

Four PSA methods were used. Inverse Probability of Treatment Weighting on the Average Treatment Effect (IPTW-ATE), Average Effect of the Treatment on the Treated (ATT) Weighting, Overlap Weighting (OW) and Propensity Score Matching (PSM). IPTW-ATE was treated as the primary method for analyses while ATT Weighting, OW, and PSM were treated as sensitivity analyses.

Multiplicities were adjusted by Holm's procedure within each paired treatment comparison for each endpoint at 2-sided 0.05 alpha level.

Table XX: Summary of Propensity Score Methods Used for the Propensity Score Analysis

PSA Method	Target Population	Estimand	Subject Weight (Ibr+Ven, single-agent)
IPTW-ATE (Stabilized Weights) – Primary Analysis	Combined (Ibr+Ven and single-agent)	ATE	(PT/PS, (1-PT)/(1-PS))
ATT Weighting	Treated (Ibr+Ven)	ATT	(1, PS/(1-PS))[a]
Overlap Weighting	Overlap	ATO	(1-PS, PS)*
Matching (GNNM)	Cohort formed by the matched sample	ATM	

ATE=Average Treatment Effect; ATM=Average Treatment Effect of the Matched Sample; ATO=Average Treatment Effect of the Overlap; ATT=Average Effect of the Treatment on the Treated; GNNM= Greedy Nearest Neighbor Matching; Ibr+Ven=ibrutinib + venetoclax; PS=propensity score;
PT - the proportion of subjects in the Ibr+Ven arm
PS - the propensity score is the conditional probability that a subject is in Ibr+Ven given the clinical covariates.
a. To allow for comparison between weighting methods, weights were normalized so that the mean weight per treatment arm is 1.

Table XX: Summary of propensity score models

Baseline variables	Strata[a]	Model 1	Model 2	Model 3
Age	≥65 vs <65	Y	Y	Y
Gender	Male vs Female	Y	Y	Y
ECOG	≥1 vs 0	Y	Y	Y
Prior lines	1 to 4[b] as continuous variable	Y	Y	Y
Binet stage	Stage C vs Stage A or B	Y	N	Y
Hemoglobin	≤110 g/L vs >110 g/L	N	Y	N
Platelet	≤100 x 10^9/L vs >100 x1 0^9/L	N	Y	N
Bulky disease	≥5 cm vs <5 cm	N	Y	N
ALC	≥25 x 10^9/L vs <25 x 10^9/L	Y	Y	Y
del17p	Yes vs No	Y	Y	N
del11q	Yes vs No	Y	Y	N
High Risk Population (del17p/*TP53*/del11q/u*IGHV*)	Yes vs No	N	N	Y
Beta-2 microglobulin[c]	>3.5 mg/L vs ≤3.5 mg/L	Y - Ibr	Y - Ibr	Y - Ibr
Creatinine Clearance	<60 mL/min vs ≥60 mL/min	Y	Y	Y

ALC=absolute lymphocyte count; del11q= deletion of the long arm of chromosome 11; del17p=deletion of the short arm of chromosome 17; ECOG=Eastern Cooperative Oncology Group; Ibr=ibrutinib; u*IGHV*=unmutated immunoglobulin heavy chain variable region; N=no; vs=versus; Y=yes

a. All baseline variables but prior lines were dichotomized. In these binary variables, subjects with missing or unknown values were included in the second strata (after 'vs').
b. Prior lines were analyzed as continuous variable with values 1, 2, 3, 4. The '4' included prior lines 4 to 6.
c. Only for comparisons with ibrutinib (Study PCYC-1112). The venetoclax studies had ~ 40% missing beta-2 microglobulin.

The MAH used 4 different computational methods for the PSA, Inverse Probability of Treatment Weighting on the Average Treatment Effect (IPTW-ATE) as the primary method for analysis. Analyses are performed both including and excluding the single arm study Clarity. Also, three different models were used for baseline variables. The statistical methodology is considered appropriate, but substantial residual bias cannot be excluded, especially since data for the different treatment arms were from different data sources.

Results

Key efficacy results following IPTW-ATE (primary analysis method) for Model 1 (primary model) are as follows:

- The CR rate (per investigator assessment) was statistically significantly higher in Ibr+Ven in VISION compared with single-agent ibrutinib: rate difference 70.4% (95% CI: 63.3, 77.5, adjusted p<0.0001); and compared with single agent venetoclax pool: rate difference 68.3% (95% CI: 60.8, 75.9, adjusted p<0.0001). Similar significantly higher CR rates were also observed for the Ibr+Ven pool relative to single-agent ibrutinib and the single-agent venetoclax pool.
- The ORR (per investigator assessment) was similar in Ibr+Ven in VISION compared with single-agent ibrutinib (92.1% vs. 92.6%, respectively), rate difference -0.5 (95% CI: -5.9, 4.9); while it was higher compared with single-agent venetoclax pool (91.8% vs. 80.6%, adjusted p=0.0017), rate difference 11.2% (95% CI: 4.0, 18.5). The results of the Ibr+Ven pool versus single-agent ibrutinib and single-agent venetoclax pool were similar to the results of the comparison using Ibr+Ven in VISION.
- PFS (per investigator assessment) was significantly improved with the Ibr+Ven combination in VISION versus single-agent ibrutinib with a hazard ratio of 0.265 (95% CI: 0.153, 0.457, adjusted p=0.0001); this improvement represents a 74% reduction in the risk of PD or death with the Ibr+Ven combination compared with single-agent ibrutinib. The Kaplan-Meier 30-month progression-free rate for Ibr+Ven in VISION was 91.5% and 70.9% for single-agent ibrutinib. Similarly, PFS was significantly improved with the Ibr+Ven combination in VISION versus single-agent venetoclax pool; with a hazard ratio of 0.191 (95% CI: 0.113, 0.324, adjusted p<0.0001); this improvement represents an 81% reduction in the risk of PD or death with the Ibr+Ven combination compared with single-agent venetoclax. The Kaplan-Meier 30-month progression-free rate for Ibr+Ven was 90.5% and 69.2% for single-agent venetoclax pool. Similar statistically significant improvements in PFS were also observed for the comparison of the Ibr+Ven pool relative to single-agent ibrutinib and the single-agent venetoclax pool.
- The hazard ratio for OS for the Ibr+Ven combination in VISION versus single-agent ibrutinib was 0.275 (95% CI: 0.144, 0.525; adjusted p=0.0014), indicating a significant benefit in OS for Ibr+Ven. The Kaplan-Meier OS rate at 30-months was 94.2% for Ibr+Ven in VISION and 83.0% for single-agent ibrutinib. The PSA results did not reveal a significant improvement in OS for Ibr+Ven in the comparison of VISION versus single-agent venetoclax pool, while the HR showed a beneficial trend (HR: 0.469; 95% CI: 0.237, 0.927; adjusted p=0.1907). The Kaplan-Meier OS rate at 30-months was 93.1% for Ibr+Ven in VISION and 85.9% for single-agent venetoclax pool. Similar results were observed for the comparison of Ibr+Ven pool versus single-agent ibrutinib and venetoclax pool.

Persistance of efficacy and/or tolerance effects

- **PFS rates were maintained after treatment completion**

In Study CLL3011, with a median follow-up of 27.7 months at the primary analysis, PFS was significantly improved with FD Ibr+Ven compared with Clb+Ob (HR: 0.216; 95% CI: 0.131, 0.357; p<0.0001). Kaplan-Meier PFS rate estimates per IRC at 24 months (ie 10 months after treatment completion of Ibr+Ven and Clb+Ob) were 84.4% for the Ibr+Ven arm and 44.1% for the Clb+Ob arm.

With extended follow up (median follow-up of 34.1 months), the improvement in PFS for Ibr+Ven was maintained with a HR of 0.212 (95% CI: 0.129, 0.349). The median PFS was not reached for the Ibr+Ven arm and was 23.7 months for the Clb+Ob arm. The Kaplan-Meier PFS rate estimate at 30 months was 80.5% for the Ibr+Ven arm and 35.8% for the Clb+Ob arm, demonstrating persistence of Ibr+Ven of PFS benefit at least 15 months after the end of treatment with Ibr+Ven.

Results from Study 1142 corroborate these observations with a Kaplan-Meier PFS rate estimate per IRC at 24 months of 88.9% for all subjects and 90.8% for subjects without del17p at a median follow-up of 27.9 months at the primary analysis.

With extended follow-up (median follow-up of 38.7 months), Kaplan-Meier PFS rate estimates at 36 months (22 months post-treatment) were 85.5% for all subjects and 86.0%, for subjects without del17p.

- **MRD Negativity Rates Sustained from 3 to 12 Months Post-treatment**

The MRD negativity rates at 3 months post-treatment as assessed by NGS in Study CLL3011 were substantially higher with Ibr+Ven arm versus Clb+Ob in both the BM (51.9% vs 17.1%; respectively) and PB (54.7% vs 39.0%; respectively).

At 12 months post-treatment, the MRD negativity rates in PB in the Ibr+Ven arm and the Clb+Ob arms were 49.1% vs 12.4%, respectively. Similar sustained results for Ibr+Ven were observed by flow cytometry with MRD negativity rates of 61.3% for Ibr+Ven and 41.0% for Clb+Ob in PB at 3 months post-treatment and 54.7% for Ibr+Ven and 16.2% for Clb+Ob at 12 months post-treatment. These data indicate that the MRD negativity was sustained with Ibr+Ven throughout the first year after treatment completion while substantially decreased for subjects in the Clb+Ob arm.

In the FD cohort of Study 1142, at 3 months post-treatment, the MRD negativity rates were 52.2% in the BM and 56.6% in the PB. With extended follow-up and the collection of additional samples, the MRD negativity rate in the PB at 12-months post treatment was 42.8% (9 subjects still had missing samples primarily due to the COVID-19 pandemic).

- **Duration of CR after treatment is completed**

In Study CLL3011 at the primary analysis, FD Ibr+Ven resulted in significantly higher CR rates (CR or CRi) per IRC assessment compared with Clb+Ob (38.7% vs. 11.4%, respectively; $p<0.0001$). The 12-month landmark estimate for IRC-assessed duration of CR was 100% in the Ibr+Ven arm and 91.7% in the Clb+Ob arm. At extended follow-up, the 18-month landmark estimates for IRC-assessed duration of CR were 97.5% in the Ibr+Ven arm and 84.6% in the Clb+Ob arm.

Similar results were observed for the FD cohort in Study 1142. At the primary analysis, the CR rate per IRC assessment for all subjects was 59.7% (95% CI: 52.1, 67.4) and 61.0% (95% CI: 52.8, 69.2) for subjects without del17p. With a median follow-up of 27.9 months, the 18-month landmark estimates were 95.2% for all subjects and 95.7% without del17p. With extended follow-up (median: 38.7 months), the 30-month landmark estimates were 83.0% for all subjects and 81.6%, for subjects without del17p.

Supportive studies

Table 1: Key Study Design Characteristics for Pivotal and Supportive Studies Providing Efficacy Data in Previously Untreated Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Study	Study Design and Duration of Treatment	Study Population	Efficacy Endpoints	Region	No. of Subjects	Median Time on Study
CLL3011 (GLOW)	Phase 3, randomized, open-label, multicenter, international, safety and efficacy study of Ibr+Ven vs Clb+Ob Ibr up to 15 cycles + Ven up to 12 cycles (started from Cycle 4 Day 1) Clb up to 6 cycles + Ob up to 6 cycles	Previously untreated CLL/SLL Age ≥65 years or 18 to 64 years or <65 years of age with CIRS score >6 or CrCl <70 mL/min ECOG PS 0-2 No del17p or known *TP53* mutation	Primary: PFS by IRC Secondary: MRD negativity rate, CR rate by IRC, ORR per IRC, OS, sustained hematologic improvement, time to improvement in FACIT-Fatigue Score [a], TLS risk reduction, TTNT, PRO and PK	Belgium, Canada, Czech Republic, Denmark, France, Israel, Netherlands, Poland, Russia, Spain, Sweden, Turkey, UK, US	Randomized: 211 (Ibr+Ven: 106 Clb+Ob: 105)	Primary analysis 27.7 months Extended follow-up 34.1 months
1142 FD cohort	Phase 2, open-label, multicenter, international, safety and efficacy study of Ibr up to 15 cycles + Ven up to 12 cycles (started from Cycle 4 Day 1)	All Subjects: Previously untreated CLL/SLL Active disease requiring treatment per iwCLL criteria ≥18 and ≤70 years ECOG PS 0-2 Included del17p and *TP53* mutation	Primary: CR rate by investigator Secondary: DOR by investigator, MRD negativity rate, ORR by investigator, TLS risk reduction, PFS by investigator, OS	Australia, Italy, New Zealand, Spain, US	All-Treated: 159	Primary analysis 27.9 months Extended follow-up 38.7 months
CLL14	Phase 3, randomized, open-label, multicenter, international, safety and efficacy study of Ven+Ob vs Clb+Ob Ven up to 12 cycles (started from Cycle 1 Day 22) + Ob up to 6 cycles Clb up to 12 cycles + Ob up to 6 cycles	Previously untreated CLL and coexisting conditions Age ≥18 years CIRS score of >6, or CrCl <70 mL/min Included del17p	Primary: PFS by investigator Secondary: PFS per IRC, MRD negativity, ORR and CR rate 3 months after treatment completion per investigator assessment, MRD negativity in PB and BM in subjects with CR 3 months after treatment completion, OS, DOR, EFS, time to new antileukemic treatment	Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Italy, Mexico, New Zealand, Poland, Rumania, Russian Federation, Spain, Switzerland, UK, US	Randomized: 432 (Ven+Ob: 216, Clb+Ob: 216)	28.1 months
1130	Phase 3, randomized, open-label, multicenter, international, safety and efficacy study of 420 mg/day Ibr+Ob vs Clb+Ob Ibr continuous therapy + Ob up to 6 cycles Clb+Ob up to 6 cycles	Previously untreated CLL/SLL ≥18 years of age ECOG 0-2 Included del17p	Primary: PFS by IRC. Secondary: PFS for high-risk subpopulation (ie, del17p/*TP53* mutation, del11q or unmutated *IGHV*)[b], ORR by IRC, 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.	Australia, Austria, Belgium, Canada, Czech Republic, France, Israel, Italy, New Zealand, Poland, Russian Federation, Spain, Sweden, Turkey, UK, US	Randomized: 229 (Ibr+Ob: 113, Clb+Ob: 116)	31.3 months
E1912	Phase 3, randomized, open-label, multicenter, safety and efficacy study of 420 mg/day Ibr+R vs FCR Ibr continuous therapy + R up to 6 cycles FCR up to 6 cycles	Previously untreated CLL/SLL ≥18 and ≤70 years ECOG 0-2 No del17p	Primary: PFS by ECOG-ACRIN case evaluation. Secondary: OS, PFS in high-risk population (*TP53* mutation, del11q, or unmutated *IGHV*) by ECOG-ACRIN case evaluation; change in FACT-Leu TOI score at 12 months after beginning of therapy, ORR by investigator	US	Randomized: 529 (Ibr+R: 354, FCR: 175)	36.6 months
1115	Phase 3, randomized, open-label, multicenter, international, safety and efficacy study of 420 mg/day ibrutinib vs chlorambucil Ibr continuous therapy Clb up to 12 cycles	Previously untreated CLL/SLL ≥65 years of age ECOG 0-2 No del17p	Primary: PFS by IRC Secondary: ORR by IRC, OS, EFS by IRC, sustained hematological improvement, rate of MRD negative response, improvement in fatigue as measured by FACIT-Fatigue Score	Australia, Belgium, Canada, China, Czech Republic, Ireland, Israel, Italy, New Zealand, Poland, Russia, Spain, Turkey, Ukraine, UK, US	Randomized: 269 (Ibr: 136, Clb: 133)	18.4 months

CIRS=cumulative illness rating scale; Clb= chlorambucil; Clb+Ob=chlorambucil+obinutuzumab; CLL=chronic lymphocytic leukemia; CR=complete response (CR/CRi); CrCl=creatinine clearance; CRi=complete response with incomplete bone marrow recovery; del11q=deletion of long arm of chromosome 11; del17p=deletion in the short arm of chromosome 17; DOR=duration of response; ECOG-ACRIN=Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; ECOG PS=Eastern Cooperative Oncology Group-Performance Status; 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; FD=fixed duration; Ibr=ibrutinib; Ibr+Ob=ibrutinib+obinutuzumab; Ibr+R=ibrutinib+rituximab; Ibr+Ven=ibrutinib+venetoclax; *IGHV*=immunoglobulin heavy chain variable region; IRC=independent review committee; iwCLL=International Workshop on Chronic Lymphocytic Leukemia; MRD=minimal residual disease; NGS=next generation sequencing; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PRO=patient-reported outcomes, SLL=small lymphocytic lymphoma; SCE=Summary of Clinical Efficacy; TLS=tumor lysis syndrome; TOI=Trial Outcome Index; TTNT=time to next treatment; *TP53*=tumor protein P53 gene; UK=United Kingdom; US=United States; vs=versus

Note: Only subjects with CLL were included in Study CLL14. Only Study 1142 FD cohort is included in this SCE. Ibrutinib was to be administered for the period stated or until PD or unacceptable toxicity.

[a] For Study CLL3011 secondary efficacy endpoints were tested in hierarchal manner at the nominal 0.05 significance level (2-sided) in the following order: MRD negativity rate by NGS in bone marrow, CR rate, ORR, OS, rate of sustained platelet improvement, rate of sustained hemoglobin improvement, and time to improvement in FACIT-Fatigue score.

[b] For Study 1130, an additional analysis for IRC-assessed PFS was performed in the high-risk population (ie, del17p/*TP53* mutation, del11q, or unmutated *IGHV*).

Table 5: Demographic and Baseline Characteristics

	Study CLL3011		Study 1142 FD cohort	Ibr+Ven pool[a]	Study CLL14		Study 1130		Study E1912		Study 1115	
	Ibr+Ven N=106	Clb+Ob N=105	Ibr+Ven N=159	Ibr+Ven N=265	Ven+Ob N=216	Clb+Ob N=216	Ibr+Ob N=113	Clb+Ob N=116	Ibr+R N=354	FCR N=175	Ibr N=136	Clb N=133
Age (years)												
Median	71.0	71.0	60.0	65.0	72	71	70.0	72.0	58.0	57.0	73.0	72
Min, Max	47, 93	57, 88	33, 71	33, 93	43, 89	41, 89	47, 87	40, 86	31, 70	28, 70	65, 89	65, 90
del17p/*TP53* mutated (%)[f]												
Yes	6.6	1.9	17.0	12.8	UR	UR	15.9	19.8	7.6	2.3	8.8	3.0
No	93.4	98.1	81.1	86.0	UR	UR	84.1	80.2	76.8	74.3	91.2	97.0
Unknown	0	0	1.9	1.1	UR	UR	0	0	15.5	23.4	UR	UR

Table 6: Progression-free Survival per IRC Assessment Based on Primary Analyses of Pivotal and Supportive Studies

	Pivotal Studies				Supportive Studies							
	Study CLL3011		Study 1142 FD cohort	Ibr+Ven pool[a]	Study CLL14		Study 1130		E1912[b]		Study 1115	
	Ibr+Ven N=106	Clb+Ob N=105	Ibr+Ven N=159	Ibr+Ven N=265	Ven+Ob N=216	Clb+Ob N=216	Ibr+Ob N=113	Clb+Ob N=116	Ibr+R N=354	FCR N=175	Ibr N=136	Clb N=133
Median time on study (months)	27.7	27.9	27.9	27.8	28.1		30.9	31.3	37.7	33.7	18.4	18.4
Median PFS[c] (months)	NE	21.0	NE	NE	NE	NE	NE	19.0	NE	NE	NE	18.9
Min, Max	0.03+, 32.7+	2.6, 31.5+	0.8, 33.2+	0.03+, 33.2+	NA	NA	0.2, 35.3+	0.03+, 35.2+	0.03+, 51.2+	0.03+, 51.3+	0.03+, 24.7	0.03+, 24.0+
Landmark estimates (%)[c]												
12 months	88.5	91.3	97.4	93.8	NA	NA	91.9	74.4	97.4	93.2	93.2	61.7
18 months	86.6	55.0	92.2	89.9	NA	NA	86.3	52.3	96.3	86.0	89.9	51.5
24 months	84.4	44.1	88.9	87.1	88.6	63.7	79.5	34.3	93.1	83.3	83.9[f]	--
p-value[d]	<0.0001		NA	NA	<0.0001		<0.0001		<0.0001		<0.0001	
HR (95% CI)[e]	0.216 (0.131, 0.357)		NA	NA	0.33 (0.22, 0.51)		0.231 (0.145, 0.367)		0.340 (0.222, 0.522)		0.161 (0.091, 0.283)	

CI=confidence interval; Clb=chlorambucil; Clb+Ob=chlorambucil + obinutuzumab; FCR=fludarabine + cyclophosphamide + rituximab; HR=hazard ratio; Ibr=ibrutinib; Ibr+Ob=ibrutinib + obinutuzumab; Ibr+R=ibrutinib + rituximab; Ibr+Ven=ibrutinib + venetoclax; max=maximum; min=minimum; N=number of subjects in the specified population; NA=not available; NE=not estimable; Ob=obinutuzumab; PFS=progression-free survival; Ven=venetoclax; Ven+Ob=venetoclax + obinutuzumab; + indicates censored observation.

[a] This summary is based on ITT population for CLL3011 and all treated population for study 1142 FD cohort.

[b] PFS assessed by Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN)

[c] Estimated by Kaplan-Meier method. See Table 4 for further details.

[d] p-value is based on log rank test.

[e] HR is based on Cox regression model. HR<1 favors Ibr and/or Ven containing regimen.

[f] for Study 1115, the median follow-up was 18.4 months, therefore the PFS rate estimate at 24 months is not a reliable estimate.

Table 8: Tabular Summary of MRD negativity Rates for Pivotal Studies CLL3011 and 1142 and Supportive Studies[a]

	Study CLL3011 Ibr+Ven N=106		Study 1142 FD Cohort Ibr+Ven N=159	CLL14 Ven+Ob (N=216)		Study 1130 Ibr+Ob (N=113)	Study E1912 Ibr+R (N=354	Study 1115 Ibr (N=136)
	NGS	FLOW Cytometry	FLOW Cytometry	ASO-PCR	FLOW Cytometry	FLOW Cytometry	FLOW Cytometry	FLOW Cytometry
Overall MRD negativity rate - % (n/N)								
BM	55.7 (59/106)	67.9% (72/106)	59.7 (95/159)	NA	NA	20.4 (23/113)	NA	0 (0/136)
PB	59.4 (63/106)	80.2% (85/106)	76.7 (122/159)	NA	NA	30.1 (34/113)	8.3 (23/276)	
MRD negativity rate at 3 months post-treatment - % (n/N)								
BM	51.9 (55/106)[b]	56.6 (60/106)[b]	52.2 (83/159)[b]	56.9 (123/216)	NA	NA	NA	-
PB	54.7 (58/106)[b]	61.3 (65/106)[b]	56.6 (90/159)[b]	75.5 (163/216)	61.1 (132/216)	NA	NA	-
MRD negativity rate at 12 months post-treatment - % (n/N)								
PB	49.1 (52/106)[c]	54.7 (58/106)[c]	42.8 (68/159)[c,d]	58.3 (126/216)	NA	NA	NA	-

ASO-PCR=allele-specific oligonucleotide polymerase chain reaction; BM=bone marrow; CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with incomplete hematologic recovery; FD=fixed duration; ibr=ibrutinib; Ibr+Ven=ibrutinib + venetoclax; Ibr+R=ibrutinib + rituximab; IRC=independent review committee; MRD=minimal residual disease; NA=not available; NGS=next generation sequencing; PB=peripheral blood; Ven+Ob=venetoclax + obinutuzumab
N=number of subjects in the specified population.

[a] MRD negativity was defined as <1 CLL cell per 10,000 leukocytes ($<1 \times 10^{-4}$).

[b] In the Study1142 FD cohort, MRD assessment in BM and PB was scheduled at Cycle 19 Day 1, 3 cycles (84 days) after the last dose date. In Study CLL3011 the time point for the Ibr+Ven group corresponds to 72 weeks after randomization, for the Clb+Ob group corresponds to 36 weeks after randomization.

[c] In the Study 1142 FD cohort, MRD assessment in PB test was scheduled at Cycle 28 Day 1 and/or Cycle 31 Day 1. In Study CLL3011 the timepoint for the Ibr+Ven group corresponds to 104 weeks after randomization, for the Clb+Ob group corresponds to 72 weeks after randomization.

[d] For Study 1142 the MRD negativity rate by flow cytometry in PB was 35.2% at primary analyses. However, with extended follow-up and the collection of additional samples, the MRD negativity rate in the PB at 12 months post-treatment was 42.8% (9 subjects still had missing samples at extended follow-up primarily due to the COVID-19 pandemic).

Table 9: Response Rates Based on Primary Analyses of Pivotal and Supportive Studies

	Study CLL3011		Study 1142 FD cohort	Ibr+Ven pool[a]	Study CLL14		Study 1130		Study E1912		Study 1115	
	Ibr+Ven N=106	Clb+Ob N=105	Ibr+Ven N=159	Ibr+Ven N=265	Ven+Ob N=216	Clb+Ob N=216	Ibr+Ob N=113	Clb+Ob N=116	Ibr+R N=354	FCR N=175	Ibr N=136	Clb N=133
Time on study (months)												
Median	27.7	27.9	27.9	27.8	28.1		30.9	31.3	37.7	33.7	18.4	18.4
Response rates – (%)												
ORR (CR, CRi, nPR, PR)	86.8	84.8	96.2	92.5	84.7	71.3	88.5	73.3	96.9	85.7	82.4	35.3
95% CI[b]	80.3, 93.2	77.9, 91.6	93.3, 99.2	89.3, 95.6	NA	NA	NA		NA	NA	NA	NA
Rate ratio[d] (95% CI)	1.02 (0.92, 1.14)				NA		1.208 (1.062, 1.373)		1.130 (1.061, 1.204)		2.32 (1.82, 2.95)	
p-value	0.6991		NA	NA	0.0007		0.0035		<0.0001		<0.0001	
CR rate (CR, CRi)[c]	38.7	11.4	59.7	51.3	49.5	23.1	19.5	7.8	54.5	58.3	4.4	1.5
95% CI[b]	29.4, 48.0	5.3, 17.5	52.1, 67.4	45.3, 57.3	NA	NA	NA	NA	NA	NA	NA	NA
Rate ratio[d] (95% CI)	3.43 (1.91, 6.15)		NA	NA	NA		2.509 (1.208, 5.212)		NA		NA	
p-value	<0.0001		NA	NA	<0.0001		0.0096		NA		NA	

CI=confidence interval; Clb=chlorambucil; Clb+Ob=chlorambucil + obinutuzumab; CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with incomplete bone marrow recovery; FCR=fludarabine + cyclophosphamide + rituximab; FD=fixed duration; Ibr=ibrutinib; Ibr+Ob=ibrutinib + obinutuzumab; Ibr+R=ibrutinib + rituximab; Ibr+Ven=ibrutinib + venetoclax; IRC=independent review committee; NA=not available; nPR=nodular partial response; ORR=overall response rate; PR=partial response; ITT=intent-to-treat; Ven+Ob=venetoclax + obinutuzumab
N=number of subjects in the specified population.
Note: Only subjects with CLL were included in study CLL14. Response assessment was based on IRC assessments for all studies except Studies CLL14 and E1912, which was based on investigator assessment.

[a] This summary is based on ITT population for CLL3011 and all treated population for study 1142 FD cohort.

[b] 95% confidence interval based on normal approximation to the binominal distribution.

[c] CR rate is defined as the proportion of subjects with a best overall response of CR or CRi.

[d] Rate ratio >1 favors Ibr and/or Ven containing regimen.

Table 10: Summary of Overall Survival Based on Primary Analyses of Pivotal and Supportive Studies

	Study CLL3011		Study 1142 FD cohort	Ibr+Ven pool[a]	Study CLL14		Study 1130		Study E1912		Study 1115	
	Ibr+Ven N=106	Clb+Ob N=105	Ibr+Ven N=159	Ibr+Ven N=265	Ven+Ob N=216	Clb+Ob N=216	Ibr+Ob N=113	Clb+Ob N=116	Ibr+R N=354	FCR N=175	Ibr N=136	Clb N=133
Median time on study (months)	27.7	27.9	27.9	27.8	28.1		30.9	31.3	37.7	33.7	18.4	18.4
Median OS[b] (months)	NE	32.5	NE	NE	NE		NE	NE	NE	NE	NE	NE
Min, Max	1.7+, 32.8+	5.1, 33.8+	0.8, 33.2+	0.8, 33.2+	NA		0.2, 36.6+	1.1, 36.9+	0.03+, 52.3+	0.07+, 51.4+	0.10+, 24.8	0.10+, 24.3+
Landmark estimates[b] (%)												
12 months	91.4	98.1	99.4	96.2	NA	NA	94.6	93.1	99.7	98.8	97.8	91.5
18 months	90.4	96.2	98.1	95.0	NA	NA	91.0	89.6	99.4	98.1	97.8	87.2
24 months	90.4	91.3	98.1	95.0	91.8	93.3	87.3	87.8	99.1	96.1	97.8[e]	85.3[e]
p-value[c]	0.9121		NA	NA	0.52		0.8057		0.0007		0.0010	
HR[d] (95% CI)	1.048 (0.454, 2.419)		NA	NA	1.24 (0.64, 2.40)		0.921 (0.479, 1.772)		0.170 (0.053, 0.541)		0.163 (0.048, 0.558)	

CI=confidence interval; Clb=chlorambucil; Clb+Ob=chlorambucil + obinutuzumab; FCR=fludarabine + cyclophosphamide + rituximab; FD=fixed duration; HR=hazard ratio; Ibr=ibrutinib; Ibr+Ob=ibrutinib + obinutuzumab; Ibr+R=ibrutinib + rituximab; Ibr+Ven=ibrutinib + venetoclax; IRC=independent review committee; max=maximum; min=minimum; OS=overall survival; NA=not available; NE=not estimable; Ven+Ob=venetoclax + obinutuzumab

\+ Indicates censored observation.

N=number of subjects in the specified population.

[a] This summary is based on ITT population for CLL3011 and all treated population for study 1142 FD cohort.

[b] Estimated by Kaplan-Meier method.

[c] p-value is based on log-rank test.

[d] HR is based on Cox regression model. HR <1 favors Ibr and/or Ven containing regimen.

[e] For Study 1115, the median follow-up was 18.4 months, therefore the OS rate estimate at 24 months is not a reliable estimate.

2.4.2. Discussion on clinical efficacy

To support an unrestricted indication of FD ibr+ven in previously untreated CLL the outcomes of 2 main studies were reported:

- The randomized open study 3011 comparing FD ibr+ven (n=106) with clb+obi (n=105) in subjects ≥65 years of age or younger with comorbidities, excluding del17p/TP53 mutated disease. The primary outcome was IRC-assessed PFS.
- The FD cohort of study 1142, a SAT investigating FD ibr+ven in fit patients (n=159 whereof 27 with del17p/TP53 mutated disease). The primary endpoint was investigator-assessed CRR.

Design and conduct of clinical studies

Regarding the 3011 study, the study entry criteria define a population appropriate for treatment with the control regimen. Venetoclax, chlorambucil and obinutuzumab were administrated according to EU label in untreated disease.

The statistical methods are generally considered acceptable. The assumption that all types of censoring are considered non-informative might be disputable. However, as further discussed below, censoring due to other reasons than study cut off were rare in the primary analysis.

The primary estimand had a treatment policy strategy for handling the intercurrent events of treatment discontinuation, use of subsequent anti-cancer therapy and a composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19. This is considered appropriate. Supplementary analyses with hypothetical strategies for subsequent anti-cancer therapy and death due to Covid-19 were provided. The clear presentation of methods within the estimand framework, provided by the MAH, is appreciated.

The statistical methods are generally considered acceptable. Censoring due to other reasons than study cut off were rare in the primary analysis. The primary estimand had a treatment policy strategy for handling the intercurrent events of treatment discontinuation, use of subsequent anti-cancer therapy and a composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19. This is considered appropriate. Supplementary analyses with hypothetical strategies for subsequent anti-cancer therapy and death due to Covid-19 were provided. The clear presentation of methods within the estimand framework, provided by the MAH, is appreciated. Multiplicity was controlled using a serial gatekeeping procedure, which is acceptable. No interim analysis was performed. The primary estimator is stratified on the randomisation stratification variables, which is supported.

Regarding the FD cohort of the 1142 study, enrolment criteria are acceptable. Previously untreated subjects 18-70 93

with CLL/SLL in ECOG PS 0-2 with or without del 17p or TP53 mutation were recruited. The treatment was identical to the experimental regimen in study 3011.

Efficacy data and additional analyses

Study 3011

In the control arm, 6 cycles of treatment were received, corresponding to ≈168 days or a little less than 6 months. In the experimental arm, ibrutinib was administrated for a total of 15 cycles (15x28=420 days, corresponding to approximately 14 months) and venetoclax was introduced after 3 cycles of ibrutinib monotherapy as an attempt to reduce frequency/severity of tumour lysis syndrome (TLS). This means that a SOC treatment of ≈6 months duration is compared to an experimental regimen of ≈14 months duration.

The amendments and changes to protocol-specified analyses are not considered to challenge the integrity of the study, and numbers of subjects with major protocol deviations were similar in the study arms and deemed unlikely to have a major impact on study outcomes. The potential impact of the COVID-19-related missed/delayed DE visits on study integrity and outcomes is difficult to dissect but with the large effect size noted with the primary analysis it is deemed unlikely that these have substantially altered the outcome estimations.

The primary analysis was event-driven, planned after 71 observed events, and based on a cut-off on 26 February 2021 with a median follow-up of ~28 months. An analysis with extended follow-up was also provided, cut-off 19 August 2021 with a median follow-up of ~34 months.

The experimental regimen was statistically superior over control in terms of PFS, HR=0.216 (95% CI: 0.131, 0.357); p<0.0001, at the primary analysis by IRC, with an event rate of 64% for the control arm, and supported by presented alternative analyses, and a generally consistent treatment effect is noted in the predefined subgroups. By an additional follow-up of 6 months, the outcome remains stable.

Best MRD response in bone marrow (assessed by NGS showed a response rate of 55.7% in the experimental arm and 21.0% in the control arm, rate ratio 2.65 (95% CI: 1.75, 3.99); p<0.0001.

The CR (CR and CRi) rate was significantly higher in the experimental arm, 38.7% vs 11.4% in the control arm; rate ratio 3.42 (95% CI: 2.01, 5.82); p<0.0001.

Based on a data cut-off of 17 January 2022 for Study CLL3011 with a median time on study of 39 months and a maturity of 21% in the control arm and 11% in the experimental arm, the HR for OS was estimated at 0.582 (95% CI: 0.286, 1.187). At the August 2021 cut-off, the HR for OS was 0.760

(0.352, 1.642). Thus, with 5 months further follow-up after the August 2021 cut-off, the positive trend observed with the August 2021 data cut favouring the experimental treatment is maintained in this updated analysis and no longer-term detrimental effect on OS is noted.

FD cohort of study 1142

The amendments are not considered to challenge the integrity of the study. At confirmed PD, ibrutinib monotherapy or, if >2 years since completion of study therapy, ibrutinib+venetoclax for 15 cycles FD could be (re)introduced.

The primary analysis was planned when the last enrolled subject had the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up) and based on a data extract on 12 November 2020, with a median follow-up of ~28 months. An analysis with extended follow-up was also provided, cut-off 4 August 2021 with a median follow-up of ~39 months.

At the primary analysis, the CRR per investigator for all subjects was 55.9% (95% CI: 47.5, 64.2) for subjects without del 17p (the primary analysis set). The CR rate for subjects without del 17p was significantly higher than the study-assumed minimum rate of 37% (1-sided p-value < 0.0001) as well as the 40% rate achieved in this population with FCR. CRR in del 17p/TP53 mutated disease (n=27) was similar to the complement, 56%. With extended follow-up, CRR was 58% per investigator and 64% per IRC in the non-del17 population.

The median DOR per investigator assessment was not reached for all subjects or for subjects without del 17p.

With MRD assessed by flow cytometry in the all-treated population, the overall negativity rate was 60% in BM and 77% in PB.

2.4.3. Conclusions on the clinical efficacy

The broad indication sought in previously untreated CLL is, from an efficacy perspective considered supported by sufficiently robust data, as well as by precedent decision in the field of CLL.

The following measures are considered necessary to address issues related to efficacy:>

2.5. Clinical safety

Introduction

The safety data in support of this application is derived from 2 studies, as follows:

- Study CLL3011 (N=211) is a Phase 3, randomized, open-label, multicenter, international, efficacy and safety study of Ibr+Ven (N=106) versus Clb+Ob (N=105) in subjects with treatment-naïve CLL/SLL without del17p or known TP53 mutation.
- Study 1142 (N=323) is a Phase 2, multicenter, international, efficacy and safety study assessing Ibr+Ven in subjects with treatment-naïve CLL/SLL (with or without del17p/TP53 mutation) in a FD treatment cohort (FD cohort) and an MRD-guided treatment discontinuation cohort (MRD cohort) that included a pre-randomization and randomization phase. In the pre-randomization phase of the MRD cohort, subjects received ibrutinib and venetoclax as described above for the FD cohort plus an additional cycle of Ibr+Ven (Cycle 16) before

proceeding with randomization and further treatment. Safety data from the FD cohort (N=159) were pooled with safety data from the pre-randomization phase of the MRD cohort (N=164) with 16 cycles of treatment, as these treatments and TEAE collection periods were similar.

Safety data are presented based on the primary analysis data cut-off date for each study (Study CLL3011: 26 February 2021; Study 1142: 12 November 2020). Where applicable, safety data from an extended follow-up analysis are presented with data cut-off dates as follows: study CLL3011: 19 August 2021, representing an additional 6 months of follow-up; study 1142: 04 August 2021, representing an additional 9 months of follow-up.

Alongside the safety data from both studies, the MAH has provided safety data for the so-called Current Label Pool, representing integrated safety data for 1552 patients treated with ibrutinib as monotherapy or in combination therapy across the 10 studies that form the basis of the currently authorized indications for ibrutinib (MCL, CLL, and WM) in the ibrutinib EU SmPC:

- CLL: Studies 1102, 1112, 1115, 1130, E1912, and CLL3001
- WM: Studies 1118E and 1127 (arms A [Ibr+R] and C [ibrutinib monotherapy])
- MCL: Studies 1104 and MCL3001.

Considering the heterogeneity in the Current Label Pool in terms of therapeutic setting and treatment (ibrutinib as monotherapy or in combination therapy) and the difference in treatment duration (fixed duration in the current data set vs. treatment until progressive disease or unacceptable toxicity in the Current Label Pool), a comparison of safety data is not considered informative and will not be further discussed.

Patient exposure

In Study CLL3011 and in the FD cohort of Study 1142, single-agent ibrutinib 420 mg/day was administered for 3 cycles followed by TLS risk assessment and subsequent Ibr+Ven combination treatment for 12 cycles (with a 5 week venetoclax dose titration to 400 mg/day once daily as described in the Venclyxto SmPC), using the approved doses of both medicinal products for subjects with previously untreated CLL/SLL (Imbruvica SmPC; Venclyxto SmPC). In the pre-randomization phase of the MRD cohort of Study 1142, this was followed by 1 cycle (Cycle 16) of Ibr+Ven, during which MRD status was assessed and confirmed prior to the randomization phase of the MRD cohort. In study CLL3011, subjects randomly assigned to Clb+Ob treatment received 6 cycles (28 days/cycle) of in the absence of PD or treatment-limiting toxicity.

Table 5. Patient exposure

Table 2: Extent of Exposure - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Treatment duration (months)				
N	106	105	323	1552
Mean (SD)	11.9 (3.84)	5.2 (0.69)	13.8 (2.78)	19.2 (12.18)
Median	13.8	5.1	14.1	17.4
Range	(1; 15)	(2; 8)	(0; 25)	(0; 52)
0 - < 3 months	9 (8.5%)	4 (3.8%)	11 (3.4%)	126 (8.1%)
3 - < 6 months	3 (2.8%)	94 (89.5%)	6 (1.9%)	85 (5.5%)
6 - < 9 months	9 (8.5%)	7 (6.7%)	0	148 (9.5%)
9 - < 12 months	8 (7.5%)	0	0	137 (8.8%)
12 - < 15 months	77 (72.6%)	0	290 (89.8%)	169 (10.9%)
15 - < 18 months	0	0	13 (4.0%)	137 (8.8%)
18 - < 24 months	0	0	2 (0.6%)	271 (17.5%)
>= 24 months	0	0	1 (0.3%)	479 (30.9%)
Cumulative total dose received (g)				
WM				
N	NA	NA	NA	169
Mean (SD)				249.0 (121.24)
Median				260.0
Range				(3; 467)
CLL/SLL				
N	106	NA	323	1133
Mean (SD)	140.2 (51.66)		167.7 (36.62)	247.5 (156.93)
Median	170.5		176.4	212.9
Range	(6; 185)		(5; 258)	(1; 665)
MCL				
N	NA	NA	NA	250
Mean (SD)				188.3 (127.73)
Median				182.0
Range				(1; 452)
Average dose level per administration				
WM (mg/day for Ibrutinib)				
N	NA	NA	NA	169
Mean (SD)				394.5 (49.14)
Median				414.0
Range				(158; 420)
CLL/SLL (mg/day for Ibrutinib)				
N	106	NA	323	1133
Mean (SD)	382.3 (58.88)		398.8 (40.36)	391.8 (48.52)
Median	410.2		415.0	411.9
Range	(144; 420)		(163; 420)	(90; 456)
MCL (mg/day for Ibrutinib)				
N	NA	NA	NA	250
Mean (SD)				531.8 (52.80)
Median				556.2
Range				(170; 567)
Relative dose intensity (%)				
N	106	NA	323	1552
Mean (SD)	91.0 (14.02)		95.0 (9.61)	93.6 (11.26)
Median	97.7		98.8	98.4
Range	(34; 100)		(39; 100)	(21; 109)
< 75%	17 (16.0%)		19 (5.9%)	123 (7.9%)
75% - < 90%	8 (7.5%)		29 (9.0%)	169 (10.9%)
≥ 90%	81 (76.4%)		275 (85.1%)	1260 (81.2%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: CLL/SLL = Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, MCL = Mantle Cell Lymphoma, WM = Waldenstrom's Macroglobulinemia.
Results in Ibrutinib groups are for Ibrutinib only.

[TSIEXP01.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSIEXP01.SAS] 22NOV2021, 11:20

Demographic and Other Characteristics of Study Population

Table 6. Demographics and baseline characteristics

Table 3: Demographics and Baseline Characteristics - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Region				
N	106	105	323	1552
North America	9 (8.5%)	12 (11.4%)	147 (45.5%)	794 (51.2%)
Europe	97 (91.5%)	93 (88.6%)	78 (24.1%)	667 (43.0%)
ROW	0	0	98 (30.3%)	91 (5.9%)
Age (years)				
N	106	105	323	1552
Mean (SD)	71.0 (8.02)	72.0 (6.16)	57.7 (8.44)	64.6 (10.21)
Median	71.0	71.0	59.0	65.0
Range	(47; 93)	(57; 88)	(28; 71)	(30; 90)
< 65 years	16 (15.1%)	11 (10.5%)	237 (73.4%)	744 (47.9%)
≥ 65 years	90 (84.9%)	94 (89.5%)	86 (26.6%)	808 (52.1%)
≥ 70 years	67 (63.2%)	67 (63.8%)	3 (0.9%)	524 (33.8%)
≥ 75 years	35 (33.0%)	37 (35.2%)	0	271 (17.5%)
Sex				
N	106	105	323	1552
Male	59 (55.7%)	63 (60.0%)	209 (64.7%)	1045 (67.3%)
Female	47 (44.3%)	42 (40.0%)	114 (35.3%)	507 (32.7%)
Race				
N	106	105	323	1552
White	101 (95.3%)	101 (96.2%)	294 (91.0%)	1389 (89.5%)
Black or African American	0	0	3 (0.9%)	54 (3.5%)
Asian	0	1 (1.0%)	8 (2.5%)	42 (2.7%)
American Indian or Alaska Native	0	0	1 (0.3%)	1 (0.1%)
Native Hawaiian or other Pacific Islander	0	0	1 (0.3%)	2 (0.1%)
Other	1 (0.9%)	0	0	10 (0.6%)
Multiple	0	0	0	0
Unknown/not reported	4 (3.8%)	3 (2.9%)	16 (5.0%)	54 (3.5%)
Ethnicity				
N	106	105	323	1552
Hispanic or Latino	1 (0.9%)	3 (2.9%)	16 (5.0%)	49 (3.2%)
Not Hispanic or Latino	101 (95.3%)	99 (94.3%)	299 (92.6%)	1450 (93.4%)
Unknown/not reported	4 (3.8%)	3 (2.9%)	8 (2.5%)	53 (3.4%)
ECOG performance status				
N	106	105	323	1552
0	35 (33.0%)	39 (37.1%)	215 (66.6%)	782 (50.4%)
1	58 (54.7%)	54 (51.4%)	108 (33.4%)	722 (46.5%)
2	13 (12.3%)	12 (11.4%)	0	47 (3.0%)
> 2	0	0	0	1 (0.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: ECOG = Eastern Cooperative Oncology Group.

[TSIDEM01.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSIDEM01.SAS] 30JUN2021, 15:34

Patient disposition

Table 7. Patient disposition

Table 4: Subject Disposition and Treatment Withdrawal Information - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Still on treatment	0	0	0	1080 (69.6%)
Completed treatment	82 (77.4%)	100 (95.2%)	297 (92.0%)	35 (2.3%)
Discontinued treatment	24 (22.6%)	5 (4.8%)	26 (8.0%)	437 (28.2%)
Reason for discontinuation				
Progressive disease or relapse	3 (2.8%)	1 (1.0%)	3 (0.9%)	170 (11.0%)
Adverse event	11 (10.4%)	2 (1.9%)	17 (5.3%)	146 (9.4%)
Death	4 (3.8%)	0	1 (0.3%)	35 (2.3%)
Lost to follow-up	0	0	0	2 (0.1%)
Pregnancy	0	0	0	0
Investigator or sponsor decision	2 (1.9%)	1 (1.0%)	2 (0.6%)	13 (0.8%)
Subject refuses further treatment	4 (3.8%)	1 (1.0%)	3 (0.9%)	49 (3.2%)
Non-compliance	0	0	0	1 (0.1%)
Other	0	0	0	21 (1.4%)
Discontinued Ibrutinib due to adverse event	17 (16.0%)	NA	17 (5.3%)	142 (9.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator.
The last row summarizes the number/percentage of subjects in Ibrutinib group d/c treatment reason = adverse event.
For subjects from PCYC-1142-CA, the treatment disposition are based on Ibrutinib only.
Subjects from 1142 MRD cohort who entered randomization phase are considered as completed study treatment.

[T]SIDS01.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSIDS01.SAS]
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Primary analysis

In Study CLL3011, the median time on study was 27.6 months for the Ibr+Ven arm and 27.8 months for the Clb+Ob arm.

In Study 1142, the median time on study was 27.9 months in the FD cohort and 14.8 months in the pre-randomization phase (ie, first 16 cycles) of the MRD cohort.

Extended follow-up

The treatment disposition profile remained the same with extended follow-up for both Study CLL3011 and FD cohort of Study 1142 (all subjects were off treatment before the primary analysis), as well as the first 16 cycles of the MRD cohort of Study 1142 (all subjects had completed the pre-randomization phase before the primary analysis).

Adverse events

Table 8. Overall summary of TEAEs

Table 5: Overall Summary of Treatment-emergent Adverse Events - CLL3011, PCYC-1142-CA and Current Label Events Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Any TEAE	105 (99.1%)	99 (94.3%)	322 (99.7%)	1537 (99.0%)
Grade >= 3	80 (75.5%)	73 (69.5%)	209 (64.7%)	1162 (74.9%)
Drug related	89 (84.0%)	97 (92.4%)	307 (95.0%)	1360 (87.6%)
Grade >= 3	61 (57.5%)	68 (64.8%)	181 (56.0%)	775 (49.9%)
Any TESAE	49/106 (46.2%)	29/105 (27.6%)	70/323 (21.7%)	574/1200 (47.8%)
Grade >= 3	41/106 (38.7%)	23/105 (21.9%)	59/323 (18.3%)	506/1200 (42.2%)
Drug related	26/106 (24.5%)	20/105 (19.0%)	39/323 (12.1%)	261/1200 (21.8%)
TEAE leading to Ibrutinib discontinuation	21 (19.8%)	NA	19 (5.9%)	185 (11.9%)
TEAE leading to Ibrutinib dose reduction	19 (17.9%)	NA	39 (12.1%)	162 (10.4%)
TEAE with outcome death	7 (6.6%)	2 (1.9%)	1 (0.3%)	82 (5.3%)
Deaths within 30 days after last dose of study treatment [1]	7 (6.6%)	0	1 (0.3%)	83 (5.3%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[1] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 23.1.
Study 1126e is excluded from SAE summary.

[TSFAE01.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE01.SAS] 30JUN2021, 14:54

Common TEAEs

Table 9. Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects

Table 6: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA			Current Label Pool		
		Ibr+Ven			Clb+Ob			Ibr+Ven				
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any TEAE	105 (99.1%)	73 (68.9%)	7 (6.6%)	99 (94.3%)	71 (67.6%)	2 (1.9%)	322 (99.7%)	208 (64.4%)	1 (0.3%)	1537 (99.0%)	1080 (69.6%)	82 (5.3%)
System Organ Class Preferred Term												
Gastrointestinal disorders	71 (67.0%)	14 (13.2%)	0	43 (41.0%)	4 (3.8%)	0	289 (89.5%)	25 (7.7%)	0	1151 (74.2%)	132 (8.5%)	2 (0.1%)
Diarrhoea	54 (50.9%)	11 (10.4%)	0	13 (12.4%)	1 (1.0%)	0	215 (66.6%)	13 (4.0%)	0	659 (42.5%)	51 (3.3%)	0
Nausea	28 (26.4%)	0	0	27 (25.7%)	0	0	142 (44.0%)	2 (0.6%)	0	442 (28.5%)	11 (0.7%)	0
Vomiting	15 (14.2%)	1 (0.9%)	0	14 (13.3%)	0	0	70 (21.7%)	4 (1.2%)	0	217 (14.0%)	10 (0.6%)	0
Constipation	11 (10.4%)	0	0	7 (6.7%)	0	0	52 (16.1%)	0	0	255 (16.4%)	5 (0.3%)	0
Dyspepsia	10 (9.4%)	0	0	3 (2.9%)	0	0	57 (17.6%)	0	0	156 (10.1%)	1 (0.1%)	0
Mouth ulceration	8 (7.5%)	0	0	0	0	0	38 (11.8%)	0	0	26 (1.7%)	0	0
Abdominal pain	2 (1.9%)	0	0	5 (4.8%)	1 (1.0%)	0	40 (12.4%)	1 (0.3%)	0	177 (11.4%)	27 (1.7%)	0
Stomatitis	2 (1.9%)	0	0	3 (2.9%)	0	0	45 (13.9%)	2 (0.6%)	0	154 (9.9%)	9 (0.6%)	0
Gastrooesophageal reflux disease	0	0	0	1 (1.0%)	0	0	41 (12.7%)	0	0	103 (6.6%)	1 (0.1%)	0
Infections and infestations	64 (60.4%)	16 (15.1%)	2 (1.9%)	51 (48.6%)	11 (10.5%)	1 (1.0%)	225 (69.7%)	27 (8.4%)	0	1068 (68.8%)	296 (19.1%)	23 (1.5%)
Urinary tract infection	17 (16.0%)	2 (1.9%)	0	5 (4.8%)	2 (1.9%)	0	23 (7.1%)	0	0	145 (9.3%)	26 (1.7%)	0
Upper respiratory tract infection	13 (12.3%)	0	0	14 (13.3%)	0	0	85 (26.3%)	0	0	314 (20.2%)	18 (1.2%)	0
Pneumonia	11 (10.4%)	5 (4.7%)	2 (1.9%)	10 (9.5%)	5 (4.8%)	1 (1.0%)	12 (3.7%)	6 (1.9%)	0	187 (12.0%)	102 (6.6%)	4 (0.3%)
Blood and lymphatic system disorders	56 (52.8%)	36 (34.0%)	0	72 (68.6%)	58 (55.2%)	0	202 (62.5%)	116 (35.9%)	0	926 (59.7%)	509 (32.8%)	1 (0.1%)
Neutropenia	36 (34.0%)	30 (28.3%)	0	56 (53.3%)	47 (44.8%)	0	136 (42.1%)	110 (34.1%)	0	363 (23.4%)	307 (19.8%)	0
Anaemia	19 (17.9%)	3 (2.8%)	0	19 (18.1%)	2 (1.9%)	0	21 (6.5%)	6 (1.9%)	0	479 (30.9%)	89 (5.7%)	0
Thrombocytopenia	12 (11.3%)	6 (5.7%)	0	28 (26.7%)	21 (20.0%)	0	51 (15.8%)	10 (3.1%)	0	246 (15.9%)	118 (7.6%)	0
Increased tendency to bruise	0	0	0	0	0	0	70 (21.7%)	0	0	60 (3.9%)	0	0
Skin and subcutaneous tissue disorders	52 (49.1%)	10 (9.4%)	0	27 (25.7%)	1 (1.0%)	0	215 (66.6%)	9 (2.8%)	0	858 (55.3%)	67 (4.3%)	0
Rash	18 (17.0%)	4 (3.8%)	0	7 (6.7%)	0	0	24 (7.4%)	0	0	139 (9.0%)	7 (0.5%)	0
Petechiae	5 (4.7%)	0	0	0	0	0	37 (11.5%)	0	0	89 (5.7%)	0	0
Dry skin	4 (3.8%)	0	0	1 (1.0%)	0	0	35 (10.8%)	0	0	98 (6.3%)	2 (0.1%)	0
Rash maculo-papular	1 (0.9%)	0	0	0	0	0	50 (15.5%)	4 (1.2%)	0	219 (14.1%)	26 (1.7%)	0
Metabolism and nutrition disorders	45 (42.5%)	16 (15.1%)	0	25 (23.8%)	11 (10.5%)	0	118 (36.5%)	14 (4.3%)	0	665 (42.8%)	155 (10.0%)	0
Decreased appetite	14 (13.2%)	1 (0.9%)	0	6 (5.7%)	1 (1.0%)	0	23 (7.1%)	0	0	185 (11.9%)	9 (0.6%)	0
Hyperphosphataemia	11 (10.4%)	1 (0.9%)	0	0	0	0	17 (5.3%)	3 (0.9%)	0	11 (0.7%)	0	0
Hyperuricaemia	6 (5.7%)	4 (3.8%)	0	3 (2.9%)	2 (1.9%)	0	21 (6.5%)	1 (0.3%)	0	156 (10.1%)	21 (1.4%)	0
General disorders and administration site conditions	42 (39.6%)	5 (4.7%)	2 (1.9%)	44 (41.9%)	3 (2.9%)	0	166 (51.4%)	7 (2.2%)	1 (0.3%)	997 (64.2%)	101 (6.5%)	14 (0.9%)
Fatigue	16 (15.1%)	1 (0.9%)	0	10 (9.5%)	0	0	85 (26.3%)	5 (1.5%)	0	580 (37.4%)	39 (2.5%)	0

Table 6: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Oedema peripheral	16 (15.1%)	0	0	3 (2.9%)	0	0	24 (7.4%)	0	0	274 (17.7%)	10 (0.6%)	0
Pyrexia	7 (6.6%)	0	0	20 (19.0%)	1 (1.0%)	0	42 (13.0%)	0	0	334 (21.5%)	22 (1.4%)	0
Chills	2 (1.9%)	0	0	12 (11.4%)	1 (1.0%)	0	15 (4.6%)	0	0	108 (7.0%)	2 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	38 (35.8%)	3 (2.8%)	0	30 (28.6%)	2 (1.9%)	0	157 (48.6%)	4 (1.2%)	0	774 (49.9%)	64 (4.1%)	8 (0.5%)
Epistaxis	12 (11.3%)	0	0	3 (2.9%)	0	0	42 (13.0%)	0	0	125 (8.1%)	1 (0.1%)	0
Cough	9 (8.5%)	0	0	11 (10.5%)	0	0	55 (17.0%)	0	0	350 (22.6%)	2 (0.1%)	0
Dyspnoea	7 (6.6%)	0	0	9 (8.6%)	1 (1.0%)	0	25 (7.7%)	1 (0.3%)	0	201 (13.0%)	25 (1.6%)	1 (0.1%)
Oropharyngeal pain	3 (2.8%)	0	0	4 (3.8%)	0	0	45 (13.9%)	0	0	126 (8.1%)	1 (0.1%)	0
Investigations	36 (34.0%)	18 (17.0%)	0	27 (25.7%)	12 (11.4%)	0	101 (31.3%)	21 (6.5%)	0	660 (42.5%)	354 (22.8%)	0
Neutrophil count decreased	11 (10.4%)	9 (8.5%)	0	9 (8.6%)	7 (6.7%)	0	20 (6.2%)	11 (3.4%)	0	228 (14.7%)	147 (9.5%)	0
Blood creatinine increased	5 (4.7%)	0	0	3 (2.9%)	0	0	19 (5.9%)	0	0	176 (11.3%)	6 (0.4%)	0
Platelet count decreased	3 (2.8%)	1 (0.9%)	0	1 (1.0%)	1 (1.0%)	0	15 (4.6%)	2 (0.6%)	0	253 (16.3%)	31 (2.0%)	0
Lymphocyte count increased	0	0	0	0	0	0	0	0	0	275 (17.7%)	210 (13.5%)	0
Musculoskeletal and connective tissue disorders	36 (34.0%)	8 (7.5%)	0	27 (25.7%)	0	0	214 (66.3%)	13 (4.0%)	0	842 (54.3%)	84 (5.4%)	0
Arthralgia	15 (14.2%)	1 (0.9%)	0	8 (7.6%)	0	0	109 (33.7%)	6 (1.9%)	0	345 (22.2%)	32 (2.1%)	0
Back pain	10 (9.4%)	1 (0.9%)	0	7 (6.7%)	0	0	47 (14.6%)	4 (1.2%)	0	223 (14.4%)	19 (1.2%)	0
Muscle spasms	9 (8.5%)	0	0	2 (1.9%)	0	0	79 (24.5%)	0	0	213 (13.7%)	2 (0.1%)	0
Myalgia	7 (6.6%)	0	0	1 (1.0%)	0	0	47 (14.6%)	0	0	244 (15.7%)	10 (0.6%)	0
Pain in extremity	6 (5.7%)	1 (0.9%)	0	8 (7.6%)	0	0	43 (13.3%)	1 (0.3%)	0	175 (11.3%)	14 (0.9%)	0
Nervous system disorders	32 (30.2%)	4 (3.8%)	1 (0.9%)	21 (20.0%)	2 (1.9%)	0	143 (44.3%)	10 (3.1%)	0	652 (42.0%)	68 (4.4%)	0
Headache	7 (6.6%)	0	0	5 (4.8%)	1 (1.0%)	0	86 (26.6%)	2 (0.6%)	0	292 (18.8%)	14 (0.9%)	0
Dizziness	3 (2.8%)	0	0	3 (2.9%)	0	0	52 (16.1%)	0	0	184 (11.9%)	3 (0.2%)	0
Vascular disorders	27 (25.5%)	9 (8.5%)	0	24 (22.9%)	2 (1.9%)	0	72 (22.3%)	24 (7.4%)	0	425 (27.4%)	133 (8.6%)	1 (0.1%)
Hypertension	14 (13.2%)	8 (7.5%)	0	5 (4.8%)	2 (1.9%)	0	51 (15.8%)	22 (6.8%)	0	277 (17.8%)	116 (7.5%)	0
Cardiac disorders	26 (24.5%)	13 (12.3%)	2 (1.9%)	14 (13.3%)	3 (2.9%)	0	70 (21.7%)	11 (3.4%)	0	307 (19.8%)	111 (7.2%)	7 (0.5%)
Atrial fibrillation	15 (14.2%)	7 (6.6%)	0	2 (1.9%)	0	0	19 (5.9%)	5 (1.5%)	0	116 (7.5%)	58 (3.7%)	0
Palpitations	6 (5.7%)	0	0	3 (2.9%)	0	0	36 (11.1%)	0	0	63 (4.1%)	0	0
Injury, poisoning and procedural complications	25 (23.6%)	6 (5.7%)	0	36 (34.3%)	6 (5.7%)	0	116 (35.9%)	3 (0.9%)	0	552 (35.6%)	49 (3.2%)	3 (0.2%)
Contusion	5 (4.7%)	0	0	0	0	0	55 (17.0%)	0	0	230 (14.8%)	0	0
Infusion related reaction	0	0	0	31 (29.5%)	3 (2.9%)	0	0	0	0	141 (9.1%)	8 (0.5%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
[TSFAE04.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE04.SAS] 30JUN2021, 14:57

In Study CLL3011, the most common TEAEs (≥20% of subjects) in the Ibr+Ven arm were diarrhea (50.9%), neutropenia (34.0%), and nausea (26.4%). The most common TEAEs (≥20% of subjects) in the Clb+Ob arm were neutropenia (53.3%), infusion-related reaction (29.5%), thrombocytopenia (26.7%), and nausea (25.7%). Adverse events that were reported more frequently (≥10% difference) in the Ibr+Ven arm versus the Clb+Ob arm were diarrhea (50.9% vs. 12.4%, respectively), rash (17.0% vs. 6.7%), urinary tract infections (16.0% vs. 4.8%), peripheral edema (15.1% vs. 2.9%), atrial fibrillation (14.2% vs. 1.9%), and hyperphosphatemia (10.4% vs. 0%). Adverse events that were reported more frequently (≥10% difference) in the Clb+Ob arm versus the Ibr+Ven arm were neutropenia (53.3% vs. 34.0%, respectively), thrombocytopenia (26.7% vs. 11.3%), infusion-related reaction (29.5% vs. 0%), and pyrexia (19.0% vs. 6.6%).

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, the most common TEAE (≥20% of subjects) were diarrhea (66.6%), nausea (44.0%), neutropenia (42.1%), arthralgia (33.7%), headache (26.6%), upper respiratory tract infection, fatigue (26.3% each), muscle spasms (24.5%), increased tendency to bruise, and vomiting (21.7% each).

Common TEAEs by 3-month Intervals

In Study CLL3011, the prevalence rates for common TEAEs were generally stable or decreased over the 3-month time intervals during the study. In the Ibr+Ven arm, increased prevalence rates from the Day 1-90 interval to the Day 91-180 interval were observed, with the addition of venetoclax to ibrutinib, for diarrhea (22.9% vs 38.2%), nausea (12.5% vs 21.3%), and neutropenia (6.3% vs 23.6%). The prevalence rate for hypertension increased over time from 6.3% at the Day 1-90 interval to 9.7% at the Day ≥366 interval.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, the prevalence rates for common TEAEs were generally stable or decreased over the 3-month time intervals during the study. Increased

prevalence rates from the Day 1-90 interval to the Day 91-180 interval were observed, with the addition of venetoclax to ibrutinib, for diarrhea (33.1% vs 50.6%), nausea (19.3% vs 31.1%), and neutropenia (8.9% vs 33.0%). The prevalence rate increased over time for gastroesophageal reflux disease (5.9% at the Day 1-90 interval to 9.5% at the Day ≥366 interval) and hypertension (4.3% at the Day 1-90 interval to 11.0% at the Day ≥366 interval).

The prevalence rates for common TEAEs over the 3-month time intervals of Ibr+Ven subjects in Study CLL3011 and the FD cohort + the first 16 cycles of the MRD cohort of Study 1142 were generally similar to those of the Current Label Pool, with stable or decreasing rates over time. Of note, the clinically meaningful increases in prevalence rates with the addition of venetoclax to ibrutinib (ie, from the Day 1-90 interval to the Day 91-180 interval) observed in the Ibr+Ven arm of Study CLL3011 and the FD cohort + first 16 cycles of the MRD cohort of Study 1142 were not observed for the Current Label Pool (diarrhea: 32.2% [Day 1-90] and 18.4% [Day 91-180]; nausea: 21.2% [Day1-90] and 11.8% [Day 91-180]; neutropenia 18.8% [Day 1-90] and 21.0% [Day 91-180]). Consistent with the Ibr+Ven arm of Study CLL3011 and the FD cohort + first 16 cycles of the MRD cohort of Study 1142, the prevalence rate for hypertension increased over time from 3.7% at the Day 1-90 interval to 10.6% at the Day ≥366 interval for the Current Label Pool.

Grade 3 or 4 TEAEs

Table 10. Incidence of grade 3 or 4 TEAEs

Table 7: Incidence of Treatment-emergent Adverse Events Occurring in 5% or More Subjects for Grade 3 or 4 by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA			Current Label Pool		
	Ibr+Ven			Clb+Ob			Ibr+Ven					
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any TEAE	105 (99.1%)	73 (68.9%)	7 (6.6%)	99 (94.3%)	71 (67.6%)	2 (1.9%)	322 (99.7%)	208 (64.4%)	1 (0.3%)	1537 (99.0%)	1080 (69.6%)	82 (5.3%)
System Organ Class Preferred Term												
Gastrointestinal disorders	71 (67.0%)	14 (13.2%)	0	43 (41.0%)	4 (3.8%)	0	289 (89.5%)	25 (7.7%)	0	1151 (74.2%)	132 (8.5%)	2 (0.1%)
Diarrhoea	54 (50.9%)	11 (10.4%)	0	13 (12.4%)	1 (1.0%)	0	215 (66.6%)	13 (4.0%)	0	659 (42.5%)	51 (3.3%)	0
Infections and infestations	64 (60.4%)	16 (15.1%)	2 (1.9%)	51 (48.6%)	11 (10.5%)	1 (1.0%)	225 (69.7%)	27 (8.4%)	0	1068 (68.8%)	296 (19.1%)	23 (1.5%)
Pneumonia	11 (10.4%)	5 (4.7%)	2 (1.9%)	10 (9.5%)	5 (4.8%)	1 (1.0%)	12 (3.7%)	6 (1.9%)	0	187 (12.0%)	102 (6.6%)	4 (0.3%)
Blood and lymphatic system disorders	56 (52.8%)	36 (34.0%)	0	72 (68.6%)	58 (55.2%)	0	202 (62.5%)	116 (35.9%)	0	926 (59.7%)	509 (32.8%)	1 (0.1%)
Neutropenia	36 (34.0%)	30 (28.3%)	0	56 (53.3%)	47 (44.8%)	0	136 (42.1%)	110 (34.1%)	0	363 (23.4%)	307 (19.8%)	0
Anaemia	19 (17.9%)	3 (2.8%)	0	19 (18.1%)	2 (1.9%)	0	21 (6.5%)	6 (1.9%)	0	479 (30.9%)	89 (5.7%)	0
Thrombocytopenia	12 (11.3%)	6 (5.7%)	0	28 (26.7%)	21 (20.0%)	0	51 (15.8%)	10 (3.1%)	0	246 (15.9%)	118 (7.6%)	0
Metabolism and nutrition disorders	45 (42.5%)	16 (15.1%)	0	25 (23.8%)	11 (10.5%)	0	118 (36.5%)	14 (4.3%)	0	665 (42.8%)	155 (10.0%)	0
Hyponatraemia	6 (5.7%)	6 (5.7%)	0	1 (1.0%)	0	0	10 (3.1%)	5 (1.5%)	0	89 (5.7%)	30 (1.9%)	0
Tumour lysis syndrome	0	0	0	6 (5.7%)	6 (5.7%)	0	1 (0.3%)	1 (0.3%)	0	15 (1.0%)	14 (0.9%)	0
Investigations	36 (34.0%)	18 (17.0%)	0	27 (25.7%)	12 (11.4%)	0	101 (31.3%)	21 (6.5%)	0	660 (42.5%)	354 (22.8%)	0
Neutrophil count decreased	11 (10.4%)	9 (8.5%)	0	9 (8.6%)	7 (6.7%)	0	20 (6.2%)	11 (3.4%)	0	228 (14.7%)	147 (9.5%)	0
Lymphocyte count increased	0	0	0	0	0	0	0	0	0	275 (17.7%)	210 (13.5%)	0
Vascular disorders	27 (25.5%)	9 (8.5%)	0	24 (22.9%)	2 (1.9%)	0	72 (22.3%)	24 (7.4%)	0	425 (27.4%)	133 (8.6%)	1 (0.1%)
Hypertension	14 (13.2%)	8 (7.5%)	0	5 (4.8%)	2 (1.9%)	0	51 (15.8%)	22 (6.8%)	0	277 (17.8%)	116 (7.5%)	0
Cardiac disorders	26 (24.5%)	13 (12.3%)	2 (1.9%)	14 (13.3%)	3 (2.9%)	0	70 (21.7%)	11 (3.4%)	0	307 (19.8%)	111 (7.2%)	7 (0.5%)
Atrial fibrillation	15 (14.2%)	7 (6.6%)	0	2 (1.9%)	0	0	19 (5.9%)	5 (1.5%)	0	116 (7.5%)	58 (3.7%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
[TSFAE03.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE03.SAS] 30JUN2021, 14:56

In Study CLL3011, the proportion of subjects with Grade 3 or higher TEAEs was similar in the Ibr+Ven and Clb+Ob arms (75.5% and 69.5% respectively). The most common events (≥5% of subjects) in the Ibr+Ven arm were neutropenia (28.3%), diarrhea (10.4%), neutrophil count decreased (8.5%), hypertension (7.5%), atrial fibrillation and pneumonia (6.6% each), and hyponatremia and thrombocytopenia (5.7% each). For the Clb+Ob arm, the most commonly occurring Grade 3 or higher TEAEs were neutropenia (44.8%), thrombocytopenia (20.0%), neutrophil count decreased (6.7%), and pneumonia and TLS (5.7% each).

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, Grade 3 or higher TEAEs occurred in 64.7% of subjects; the most common events (≥5% of subjects) were neutropenia (34.1%), and hypertension (6.8%).

Serious adverse event/deaths/other significant events

Serious adverse events

Table 11. Incidence of SAEs

Table 10: Incidence of Treatment-emergent Serious Adverse Events Occurring in 2% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1200		
Subjects with Any TESAE	49 (46.2%)	34 (32.1%)	7 (6.6%)	29 (27.6%)	21 (20.0%)	2 (1.9%)	70 (21.7%)	58 (18.0%)	1 (0.3%)	574 (47.8%)	428 (35.7%)	78 (6.5%)
System Organ Class Preferred Term												
Cardiac disorders	14 (13.2%)	11 (10.4%)	2 (1.9%)	3 (2.9%)	3 (2.9%)	0	13 (4.0%)	10 (3.1%)	0	90 (7.5%)	69 (5.8%)	7 (0.6%)
Atrial fibrillation	7 (6.6%)	5 (4.7%)	0	0	0	0	6 (1.9%)	5 (1.5%)	0	40 (3.3%)	35 (2.9%)	0
Cardiac failure	3 (2.8%)	2 (1.9%)	1 (0.9%)	0	0	0	1 (0.3%)	1 (0.3%)	0	5 (0.4%)	5 (0.4%)	0
Infections and infestations	13 (12.3%)	9 (8.5%)	2 (1.9%)	9 (8.6%)	6 (5.7%)	1 (1.0%)	26 (8.0%)	24 (7.4%)	0	254 (21.2%)	208 (17.3%)	23 (1.9%)
Pneumonia	6 (5.7%)	4 (3.8%)	2 (1.9%)	6 (5.7%)	5 (4.8%)	1 (1.0%)	6 (1.9%)	6 (1.9%)	0	94 (7.8%)	82 (6.8%)	4 (0.3%)
General disorders and administration site conditions	6 (5.7%)	1 (0.9%)	2 (1.9%)	2 (1.9%)	1 (1.0%)	0	3 (0.9%)	2 (0.6%)	1 (0.3%)	73 (6.1%)	34 (2.8%)	12 (1.0%)
Pyrexia	1 (0.9%)	0	0	2 (1.9%)	1 (1.0%)	0	0	0	0	29 (2.4%)	13 (1.1%)	0
Blood and lymphatic system disorders	5 (4.7%)	2 (1.9%)	0	5 (4.8%)	4 (3.8%)	0	7 (2.2%)	6 (1.9%)	0	88 (7.3%)	86 (7.2%)	1 (0.1%)
Anaemia	3 (2.8%)	0	0	2 (1.9%)	0	0	1 (0.3%)	1 (0.3%)	0	15 (1.3%)	12 (1.0%)	0
Febrile neutropenia	1 (0.9%)	1 (0.9%)	0	3 (2.9%)	3 (2.9%)	0	4 (1.2%)	4 (1.2%)	0	44 (3.7%)	44 (3.7%)	0
Gastrointestinal disorders	4 (3.8%)	4 (3.8%)	0	2 (1.9%)	2 (1.9%)	0	7 (2.2%)	5 (1.5%)	0	65 (5.4%)	48 (4.0%)	2 (0.2%)
Diarrhoea	3 (2.8%)	2 (1.9%)	0	1 (1.0%)	1 (1.0%)	0	1 (0.3%)	1 (0.3%)	0	12 (1.0%)	10 (0.8%)	0
Injury, poisoning and procedural complications	4 (3.8%)	4 (3.8%)	0	7 (6.7%)	4 (3.8%)	0	1 (0.3%)	1 (0.3%)	0	56 (4.7%)	35 (2.9%)	3 (0.3%)
Infusion related reaction	0	0	0	3 (2.9%)	1 (1.0%)	0	0	0	0	6 (0.5%)	2 (0.2%)	0
Metabolism and nutrition disorders	2 (1.9%)	0	0	3 (2.9%)	3 (2.9%)	0	4 (1.2%)	4 (1.2%)	0	27 (2.3%)	23 (1.9%)	0
Tumour lysis syndrome	0	0	0	3 (2.9%)	3 (2.9%)	0	0	0	0	7 (0.6%)	7 (0.6%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130.
Key: TESAE = Treatment-emergent serious adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Study 1126e is excluded.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
[TSFAE08.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE08.SAS] 30JUN2021, 14:59

In Study CLL3011, the proportion of subjects with treatment-emergent serious adverse events was higher in the Ibr+Ven arm compared with the Clb+Ob arm (46.2% vs. 27.6%, respectively). Within the first 6 months after the start of study treatment, which approximates the treatment duration for Clb+Ob, serious adverse events were reported in 34.0% and 26.7% of subjects in the Ibr+Ven and Clb+Ob arms, respectively.

The proportion of subjects with Grade 3 or 4 serious adverse events was 32.1% in the Ibr+Ven arm and 20.0% in the Clb+Ob arm. Overall, the most commonly occurring serious adverse events (≥2% of subjects) were atrial fibrillation (6.6%), pneumonia (5.7%), anemia (2.8%), cardiac failure (2.8%), and diarrhea (2.8%) in the Ibr+Ven arm and pneumonia (5.7%), febrile neutropenia (2.9%), infusion-related reaction (2.9%), and TLS (2.9%) in the Clb+Ob arm. As of the data cut off for extended follow-up, 2 additional treatment-emergent serious adverse events (MDS and MPN) were reported in 1 subject in the Clb+Ob arm.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, treatment-emergent serious adverse events were reported in 21.7% of subjects; the proportion of subjects with Grade 3 or 4 serious adverse events was 18.0%. Overall, the most commonly occurring treatment-emergent serious adverse events (≥ 1% of subjects) were pneumonia, atrial fibrillation (1.9% each), cellulitis and febrile neutropenia (1.2% each).

Deaths

Table 12. Summary of all deaths

TSFDTH02: Summary of All Deaths - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Summary of all deaths	11 (10.4%)	12 (11.4%)	3 (0.9%)	183 (11.8%)
Primary cause of death				
Adverse event	7 (6.6%)	5 (4.8%)	0	40 (2.6%)
Progressive disease	1 (0.9%)	0	0	88 (5.7%)
Other	3 (2.8%)	7 (6.7%)	3 (0.9%)	27 (1.7%)
Unknown	0	0	0	28 (1.8%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator.
[TSFDTH02.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFDTH02.SAS] 30JUN2021, 15:31

Table 13. Deaths within 30 days of last dose

TSFDTH01: Death Within 30 Days After Last Dose of Study Treatment - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Death within 30 days after last dose	7 (6.6%)	0	1 (0.3%)	83 (5.3%)
Primary cause of death				
Adverse event	7 (6.6%)	0	0	31 (2.0%)
Progressive disease	0	0	0	33 (2.1%)
Other	0	0	1 (0.3%)	14 (0.9%)
Unknown	0	0	0	5 (0.3%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Death after the first dose of crossover Ibrutinib therapy are not included.
[TSFDTH01.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFDTH01.SAS] 30JUN2021, 15:31

In Study CLL3011, the overall incidence of death due to any reason was 10.4% in the Ibr+Ven arm and 11.4% in the Clb+Ob arm. Seven subjects (6.6%) in the Ibr+Ven arm died while on study treatment or within the 30-day period after the last dose of study treatment.

As of the data cut-off for extended follow-up, a total of 27 deaths due to any reason were observed with 10.4% in the Ibr+Ven arm and 15.2% in the Clb+Ob arm.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, the overall incidence of death due to any reason was 0.9%. One subject (0.3%) died while on study treatment or within the 30-day period after the last dose of study treatment.

Deaths due to TEAEs

In Study CLL3011, fatal TEAEs were reported in 7 (6.6%) subjects in the Ibr+Ven arm and 2 (1.9%) subjects in the Clb+Ob arm. Among the 7 deaths in the Ibr+Ven arm, 4 occurred during lead-in treatment with ibrutinib. In 2 of these cases (PTs: metastatic carcinoma, pneumonia), the adverse events were likely present at baseline and unrelated to study treatment. Among the 3 deaths from a fatal TEAE that occurred during combination treatment with Ibr+Ven, one (PT: ischemic stroke) had an autopsy that revealed obliterating atherosclerosis as the potential cause of death. The chronic nature of atherosclerosis development argues against the death being related to an acute study drug-related effect. The 4 remaining treatment-emergent deaths from the Ibr+Ven arm were either cardiac (PTs: cardiac arrest [n=1] and cardiac failure, pneumonia, sinus node dysfunction, in 1 subject) or potentially cardiac in nature (PT: sudden death [n=2]). All these 4 subjects had a baseline CIRS score ≥10 or an ECOG performance status of 2 and all of them had underlying baseline cardiac risks. In addition, the majority of subjects in the study had hypertension (66.8%) and/or metabolism disorders (57.8%) that increase the risk for cardiovascular complications with any antineoplastic treatment. Overall, with 3 of the 7 treatment emergent deaths in the Ibr+Ven arm unlikely to be related to study treatment, the early imbalance in death cases may be overestimated. Although the 4 other deaths are

confounded by pre-existing medical conditions, a potential association with ibrutinib cannot be ruled out.

In Study 1142, 1 (0.3%) subject in the FD cohort + first 16 cycles of the MRD cohort had a TEAE of sudden death with a fatal outcome. The event was considered related to study treatment by the investigator. The medical examiner concluded the death was due to natural causes based on the available information.

Table 14. TEAEs leading to death

Table 9: Incidence of Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Any TEAE leading to death	7 (6.6%)	2 (1.9%)	1 (0.3%)	82 (5.3%)
System Organ Class				
Preferred Term				
Cardiac disorders	2 (1.9%)	0	0	7 (0.5%)
Cardiac arrest	1 (0.9%)	0	0	4 (0.3%)
Cardiac failure	1 (0.9%)	0	0	0
Sinus node dysfunction	1 (0.9%)	0	0	0
Acute myocardial infarction	0	0	0	1 (0.1%)
Cardiopulmonary failure	0	0	0	1 (0.1%)
Ventricular flutter	0	0	0	1 (0.1%)
General disorders and administration site conditions	2 (1.9%)	0	1 (0.3%)	14 (0.9%)
Sudden death	2 (1.9%)	0	1 (0.3%)	2 (0.1%)
Death	0	0	0	5 (0.3%)
Disease progression	0	0	0	1 (0.1%)
Multiple organ dysfunction syndrome	0	0	0	4 (0.3%)
Systemic inflammatory response syndrome	0	0	0	2 (0.1%)
Infections and infestations	2 (1.9%)	1 (1.0%)	0	23 (1.5%)
Pneumonia	2 (1.9%)	1 (1.0%)	0	4 (0.3%)
Bacterial sepsis	0	0	0	1 (0.1%)
Cytomegalovirus infection	0	0	0	1 (0.1%)
Fungal infection	0	0	0	1 (0.1%)
Klebsiella infection	0	0	0	1 (0.1%)
Neutropenic sepsis	0	0	0	1 (0.1%)
Pneumocystis jirovecii pneumonia	0	0	0	2 (0.1%)
Progressive multifocal leukoencephalopathy	0	0	0	1 (0.1%)
Sepsis	0	0	0	7 (0.5%)
Septic shock	0	0	0	4 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.9%)	0	0	20 (1.3%)
Neoplasm malignant	1 (0.9%)	0	0	0
Adenocarcinoma gastric	0	0	0	1 (0.1%)
Chronic lymphocytic leukaemia	0	0	0	2 (0.1%)
Colorectal cancer metastatic	0	0	0	1 (0.1%)
Gastrointestinal carcinoma	0	0	0	1 (0.1%)
Leukaemia	0	0	0	1 (0.1%)
Malignant histiocytosis	0	0	0	1 (0.1%)
Malignant pleural effusion	0	0	0	1 (0.1%)
Mantle cell lymphoma	0	0	0	7 (0.5%)
Myelodysplastic syndrome	0	0	0	2 (0.1%)

Table 9: Incidence of Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Peripheral T-cell lymphoma unspecified	0	0	0	1 (0.1%)
Richter's syndrome	0	0	0	1 (0.1%)
Transitional cell carcinoma	0	0	0	1 (0.1%)
Nervous system disorders	1 (0.9%)	0	0	0
Ischaemic stroke	1 (0.9%)	0	0	0
Blood and lymphatic system disorders	0	0	0	1 (0.1%)
Aplastic anaemia	0	0	0	1 (0.1%)
Gastrointestinal disorders	0	0	0	2 (0.1%)
Ileus paralytic	0	0	0	1 (0.1%)
Large intestine perforation	0	0	0	1 (0.1%)
Hepatobiliary disorders	0	1 (1.0%)	0	0
Cholestasis	0	1 (1.0%)	0	0
Injury, poisoning and procedural complications	0	0	0	3 (0.2%)
Post procedural haemorrhage	0	0	0	1 (0.1%)
Splenic rupture	0	0	0	1 (0.1%)
Subdural haematoma	0	0	0	1 (0.1%)
Psychiatric disorders	0	0	0	1 (0.1%)
Completed suicide	0	0	0	1 (0.1%)
Renal and urinary disorders	0	0	0	3 (0.2%)
Acute kidney injury	0	0	0	1 (0.1%)
Renal failure	0	0	0	2 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	0	0	8 (0.5%)
Dyspnoea	0	0	0	1 (0.1%)
Lung infiltration	0	0	0	1 (0.1%)
Pleural effusion	0	0	0	1 (0.1%)
Pulmonary embolism	0	0	0	1 (0.1%)
Pulmonary oedema	0	0	0	1 (0.1%)
Respiratory failure	0	0	0	3 (0.2%)
Vascular disorders	0	0	0	1 (0.1%)
Aortic aneurysm rupture	0	0	0	1 (0.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.

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Case narratives for study CLL3011 *(source: CSR CLL3011)*

Ibr+Ven arm:

During ibrutinib lead-in:

- Subject [redacted] ([redacted]-year-old man; PT: **pneumonia**): The subject's medical history included atrial fibrillation, hypertension, diabetes mellitus, and peripheral edema. The subject had a baseline CIRS score of 12 and an ECOG PS of 1. On Study Day -1, Grade 3 pulmonary edema and Grade 2 pleural effusion were noted, and study treatment was initiated on the next day. On Study Day 34, the subject developed progressive dyspnea and was hospitalized for Grade 3 pneumonia. On Study Day 42, the study treatment was permanently discontinued due to pneumonia. On Study Day 45, Grade 3 lung abscess was reported, and 8 days later, on Study Day 53, the subject died from pneumonia.
- Subject [redacted] ([redacted]-year-old man; PTs: **cardiac failure, pneumonia, and sinus node dysfunction**): The subject's medical history included myocardial ischemia, atrial fibrillation, COPD, and epilepsy. The subject had a baseline CIRS score of 12 and an ECOG PS of 1. Additional medical history included prior myocardial infarction, and transient ischemic attack. On Study Day 15, the subject was hospitalized due to Grade 3 cerebral hemorrhage. On Study Day 51, Grade 3 sinus node dysfunction and infection were reported, treatment included antibiotics and a pacemaker was placed. Ibrutinib was permanently discontinued on Study Day 54. On Study Day 61, sinus node dysfunction and infection were reported as resolved and the subject was discharged. On Study Day 70, the subject was admitted for cardiac decompensation, and Grade 4 cardiac failure, pneumonia, and sinus node dysfunction were reported. On Study Day 74, the subject died from these events.

- Subject [redacted] ([redacted]-year-old woman; PT: **malignant neoplasm**): The subject had a baseline CIRS score of 10 and an ECOG PS of 1. On Study Day 41, the subject was hospitalized for Grade 3 malignant neoplasm and Grade 3 arthralgia. CT imaging showed new pleural nodules and a right pleural effusion. On Study Day 65, pleural biopsy confirmed the presence of squamous cell carcinoma of unknown primary origin. On Study Day 78, the subject died from the malignant neoplasm.
- Subject [redacted] ([redacted]-year-old man; PT: **cardiac arrest**): The subject's cardiovascular history included hypertension. The subject had a baseline CIRS score of 10 and an ECOG PS of 1. On Study Day 85, the subject was electively hospitalized for initiation of venetoclax treatment. Before the first dose of venetoclax was administered, the subject went into cardiac arrest. Ventricular fibrillation was noted during resuscitation. Coronary angiography, CT pulmonary angiogram, and CT imaging of the head were unremarkable. On Study Day 89, the subject died from the cardiac arrest.

During ibrutinib + venetoclax treatment:

- Subject [redacted] ([redacted]-year-old women; PT: **ischemic stroke**): The subject's cardiovascular history included diabetes mellitus, hypertension, and coronary artery disease. The subject had a baseline CIRS score of 8 and an ECOG PS of 1. On Study Day 84, the subject presented with Grade 2 atrial fibrillation which resolved on Study Day 113. On Study Day 220, the subject was reported to have died from a serious adverse event of ischemic stroke. Autopsy revealed an obliterating atherosclerotic lesion in the brain. The investigator confirmed that no embolic event was identified.
- Subject [redacted] ([redacted]-year-old man; PT: **sudden death**): The subject's medical history included hypertension, diabetes mellitus, and chronic renal failure. The subject had a baseline CIRS score of 13 and an ECOG PS of 2. On Study Day 224, the subject's pre-existing chronic renal failure worsened to Grade 3. Treatment with venetoclax was interrupted. On Study Day 226, ibrutinib treatment was interrupted in preparation for an elective kidney biopsy. On Study Day 230 (and before the biopsy could be performed), sudden death was reported.
- Subject [redacted] ([redacted]-year-old man; PT: **sudden death**): The subject's medical history included atrial fibrillation. The subject had a baseline CIRS score of 5 and an ECOG PS of 2. On Study Day 239, the subject was reported to have died from sudden death. The subject lived alone, and relatives reported that the subject complained of fatigue a few days prior to death. No further information was provided, and an autopsy was not performed.

Clb+Ob arm:

- Subject [redacted] ([redacted]-year-old man; PT: **pneumonia**): The subject´s medical history included asthma, angina pectoris, arteriosclerosis, atrial flutter, hypertension and hypercholesterolemia. The subject had a baseline CIRS score of 13 and an ECOG PS of 1. On Study Day −18, the subject was hospitalized for Grade 3 pneumonia which resolved on Study Day −9. On Study Day 94, the subject was re-hospitalized for Grade 3 pneumonia and supraventricular tachycardia. On Study Day 107, the subject was discharged to a rehabilitation center, and re-admitted for persistent pneumonia on Study Day 113. On Study Day 121, Grade 2 cryptogenic organizing pneumonia was reported. On Study Day 157, the subject died from the pneumonia.
- Subject [redacted] ([redacted]-year-old man; PT: **cholestasis**): The subject had a baseline CIRS score of 4 and an ECOG PS status of 1. On Study Day 75, the subject developed elevated ALP. CT imaging on Study Day 84 revealed a new hepatic lesion. Subsequent laboratory testing showed elevated hepatic transaminases and elevated GGT. On Study Day 113, a liver biopsy revealed

transformation of CLL to Hodgkin lymphoma and study treatment was permanently discontinued. On Study Day 117, Grade 3 spinal cord compression was reported. On Study Day 155, the subject died due to the cholestasis.

Case narratives for study 1142

In the FD cohort, 1 subject experienced sudden death within the first month of the study, which was during the 3-cycle ibrutinib lead-in period.

- Subject [redacted] ([redacted]-year-old man; PT: **sudden death**): This subject had a history of tobacco use (approximately 16 cigarettes/day) and an ongoing medical history including hypertension, gastrointestinal reflux disease, insomnia, depression, hyperlipidemia, and congenital heart disease (atrioventricular malformation). This subject died in his sleep on Day 23. The autopsy report indicated that the cause of death was cardiomegaly and coronary artery disease in a man with CLL. In summary, the medical examiner concluded the death was due to natural causes based on the available information. The event was assessed by the investigator as possibly related to ibrutinib. **Adverse events of clinical interest and other safety observations**

Haemorrhage

Treatment-emergent bleeding events were identified by hemorrhage (excluding laboratory terms) standardized MedDRA query (SMQ) search. Major hemorrhage TEAEs were defined as Grade 3 or higher, or serious, or central nervous system hemorrhage of any grade identified by manual safety review.

Table 15. Incidence of treatment-emergent haemorrhage (table abbreviated by the assessor)

TSFAE27: Incidence of Treatment-emergent Hemorrhage Adverse Events by Toxicity Grade and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Any Treatment-emergent Hemorrhage Adverse Events	37 (34.9%)	4 (3.8%)	0	8 (7.6%)	1 (1.0%)	0	196 (60.7%)	3 (0.9%)	0	694 (44.7%)	47 (3.0%)	3 (0.2%)
Preferred Term												
Epistaxis	12 (11.3%)	0	0	3 (2.9%)	0	0	42 (13.0%)	0	0	125 (8.1%)	1 (0.1%)	0
Haematoma	8 (7.5%)	0	0	2 (1.9%)	0	0	6 (1.9%)	0	0	52 (3.4%)	3 (0.2%)	0
Contusion	5 (4.7%)	0	0	0	0	0	55 (17.0%)	0	0	230 (14.8%)	0	0
Ecchymosis	5 (4.7%)	1 (0.9%)	0	1 (1.0%)	0	0	11 (3.4%)	0	0	49 (3.2%)	2 (0.1%)	0
Petechiae	5 (4.7%)	0	0	0	0	0	37 (11.5%)	0	0	89 (5.7%)	0	0
Haematuria	4 (3.8%)	2 (1.9%)	0	2 (1.9%)	0	0	21 (6.5%)	0	0	86 (5.5%)	5 (0.3%)	0

Table 16. Incidence of treatment-emergent major haemorrhage (study CLL3011)

Table 26: Incidence of Treatment-emergent Major Hemorrhage Events by Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54179060CLL3011)

	Ibr+Ven			Clb+Ob		
	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5
Analysis set: Safety	106			105		
Subjects with 1 or more AEs	4 (3.8%)	4 (3.8%)	0	1 (1.0%)	1 (1.0%)	0
Preferred term						
Haematuria	2 (1.9%)	2 (1.9%)	0	0	0	0
Cerebral haemorrhage	1 (0.9%)	1 (0.9%)	0	0	0	0
Ecchymosis	1 (0.9%)	1 (0.9%)	0	0	0	0
Haemoptysis	1 (0.9%)	1 (0.9%)	0	0	0	0
Melaena	0	0	0	1 (1.0%)	1 (1.0%)	0

Key: AE = adverse event
Major hemorrhage includes serious or grade >= 3 hemorrhage and or CNS hemorrhage at any grade among bleeding events identified by haemorrhage SMQ excluding laboratory terms.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event.
Adverse events are presented by decreasing frequency of preferred term by Any Grade column within Ibr+Ven group; those with the same frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 23.0.
[TSFAEMH1.RTF] [JNJ-54179060\54179060CLL3011\DBR_CSR\RE_CSR\PROD\TSFAEMH1.SAS] 26JUL2021, 06:01

Source: CSR for study CLL3011.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, hemorrhagic TEAEs occurred in 60.7% of subjects. The most frequently reported hemorrhagic TEAEs (≥ 5% of subjects) were increased tendency to bruise (21.7%), contusion (17.0%), epistaxis (13.0%), and petechiae (11.5%). Major hemorrhage events were reported for 1.5% of subjects (cerebral hemorrhage, eye hemorrhage, hemorrhagic cerebral infarction, menorrhagia, and retinal hemorrhage; 0.3% each) and none were fatal.

Tumour Lysis Syndrome

Table 17. Incidence of treatment-emergent tumour lysis syndrome

TSFAE47: Incidence of Treatment-emergent Tumour Lysis Syndrome Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
		Ibr+Ven			Clb+Ob			Ibr+Ven		Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Tumour Lysis Syndrome	0	0	0	6 (5.7%)	6 (5.7%)	0	1 (0.3%)	1 (0.3%)	0	15 (1.0%)	14 (0.9%)	0
System Organ Class Preferred Term												
Metabolism and nutrition disorders	0	0	0	6 (5.7%)	6 (5.7%)	0	1 (0.3%)	1 (0.3%)	0	15 (1.0%)	14 (0.9%)	0
Tumour lysis syndrome	0	0	0	6 (5.7%)	6 (5.7%)	0	1 (0.3%)	1 (0.3%)	0	15 (1.0%)	14 (0.9%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
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No TEAEs of TLS were reported for subjects in the Ibr+Ven arm versus 6 (5.7%) subjects with TLS in the Clb+Ob arm in Study CLL3011. Three (2.9%) subjects had serious TLS events. Hospitalization for TLS prophylaxis after ibrutinib lead-in was reported for 55.7% of subjects in the Ibr+Ven arm. Although no TEAEs of TLS were reported for subjects in the Ibr+Ven arm, review of laboratory data identified 4 subjects that met Howard criteria for laboratory TLS. No subject met Howard criteria for clinical TLS.

A TEAE of TLS occurred in 1 subject in the FD cohort + the first 16 cycles of the MRD cohort of Study 1142. This subject experienced non-serious Grade 3 laboratory TLS but did not have any evidence of acute kidney injury or reports of any other events consistent with clinical TLS per Howard criteria. The TLS event was transient in nature; no treatment discontinuation or dose reduction was performed due to this event. No clinical symptoms or corrective measures (eg, fluid hydration, phosphate binders) were reported. In addition, this subject did not receive any TLS prophylaxis.

Cytopenic Events

Table 18. Incidence of treatment-emergent cytopenia

Table 11: Incidence of Treatment-emergent Cytopenia Adverse Events by Toxicity Grade, Grouped Term and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Cytopenia	59 (55.7%)	42 (39.6%)	0	74 (70.5%)	61 (58.1%)	0	180 (55.7%)	124 (38.4%)	0	903 (58.2%)	555 (35.8%)	0
Grouped Term Preferred Term												
Anaemia*	19 (17.9%)	3 (2.8%)	0	19 (18.1%)	2 (1.9%)	0	21 (6.5%)	6 (1.9%)	0	484 (31.2%)	92 (5.9%)	0
Anaemia	19 (17.9%)	3 (2.8%)	0	19 (18.1%)	2 (1.9%)	0	21 (6.5%)	6 (1.9%)	0	479 (30.9%)	89 (5.7%)	0
Haemoglobin decreased	0	0	0	0	0	0	0	0	0	6 (0.4%)	3 (0.2%)	0
Febrile neutropenia	2 (1.9%)	2 (1.9%)	0	3 (2.9%)	3 (2.9%)	0	4 (1.2%)	4 (1.2%)	0	67 (4.3%)	64 (4.1%)	0
Neutropenia*	44 (41.5%)	37 (34.9%)	0	61 (58.1%)	52 (49.5%)	0	153 (47.4%)	119 (36.8%)	0	582 (37.5%)	449 (28.9%)	0
Neutropenia	36 (34.0%)	30 (28.3%)	0	56 (53.3%)	47 (44.8%)	0	136 (42.1%)	110 (34.1%)	0	363 (23.4%)	307 (19.8%)	0
Neutrophil count decreased	11 (10.4%)	9 (8.5%)	0	9 (8.6%)	7 (6.7%)	0	20 (6.2%)	11 (3.4%)	0	228 (14.7%)	147 (9.5%)	0
Thrombocytopenia*	15 (14.2%)	7 (6.6%)	0	29 (27.6%)	22 (21.0%)	0	64 (19.8%)	12 (3.7%)	0	491 (31.6%)	146 (9.4%)	0
Thrombocytopenia	12 (11.3%)	6 (5.7%)	0	28 (26.7%)	21 (20.0%)	0	51 (15.8%)	10 (3.1%)	0	246 (15.9%)	118 (7.6%)	0
Platelet count decreased	3 (2.8%)	1 (0.9%)	0	1 (1.0%)	1 (1.0%)	0	15 (4.6%)	2 (0.6%)	0	253 (16.3%)	31 (2.0%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
* grouped term.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
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Infections including viral reactivation

All infection TEAEs

In Study CLL3011, a higher proportion of subjects in the Ibr+Ven arm (60.4%) than the Clb+Ob arm (48.6%) had TEAEs within the SOC of Infections and infestations. Treatment-emergent infection events reported in ≥10% of subjects in the Ibr+Ven arm were urinary tract infection (16.0%), upper respiratory tract infection (12.3%), and pneumonia (10.4%). Similarly, for the Clb+Ob arm, upper respiratory tract infection (13.3%) was reported in ≥10% of subjects. The proportion of subjects with Grade 3 or 4 TEAEs within the SOC of Infections and infestations were 15.1% in the Ibr+Ven arm and 10.5% in the Clb+Ob arm. The most frequently reported Grade 3 or 4 infection was pneumonia, with similar proportions between the Ibr+Ven arm and Clb+Ob arm (4.7% and 4.8%, respectively). Serious adverse events of any grade in the SOC of Infections and infestations were reported for 12.3% of subjects in the Ibr+Ven arm and 8.6% of subjects in the Clb+Ob arm. The most frequently reported serious adverse event of infection was pneumonia, reported in 5.7% of subjects in both arms. Two (1.9%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm were reported with fatal pneumonia.

In Study 1142, 69.7% of subjects had TEAEs within the SOC of Infections and infestations. Treatment-emergent infection event reported in ≥10% of subjects was upper respiratory tract infection (26.3%). Grade 3 or 4 TEAEs within the SOC of Infections and infestations were reported for 8.4% of subjects. The most frequently reported Grade 3 or 4 infection was pneumonia (1.9%). Serious adverse events of any grade in the SOC of Infections and infestations were reported for 8.0% of subjects. The most frequently reported serious adverse events of infection was pneumonia, reported in 1.9% of subjects.

Two subjects (0.6%) discontinued ibrutinib due to an infection TEAE. No subjects had an infection TEAE with a fatal outcome.

Table 19. Incidence of treatment-emergent SAEs of infections (Table abbreviated by the assessor)

TSFAE07: Incidence of Treatment-emergent Serious Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Infections and infestations	13 (12.3%)	9 (8.5%)	2 (1.9%)	9 (8.6%)	6 (5.7%)	1 (1.0%)	26 (8.0%)	24 (7.4%)	0	254 (21.2%)	208 (17.3%)	23 (1.9%)
Pneumonia	6 (5.7%)	4 (3.8%)	2 (1.9%)	6 (5.7%)	5 (4.8%)	1 (1.0%)	6 (1.9%)	6 (1.9%)	0	94 (7.8%)	82 (6.8%)	4 (0.3%)

Viral reactivation TEAEs

In Study CLL3011 and in the FD cohort + the first 16 cycles of the MRD cohort for Study 1142, there were no treatment-emergent reports of hepatitis B reactivation.

Sepsis

Sepsis events were identified by PTs containing sepsis, bacteremia, fungaemia, viraemia, or septic (excluding septic screen or aseptic).

In Study CLL3011, treatment-emergent septic shock was reported in 1 (0.9%) subject in the Ibr+Ven arm and pneumococcal sepsis was reported in 1 (1.0%) subject in the Clb+Ob arm. Both events were serious and Grade 3 or 4 in severity. No subjects had ibrutinib dose reductions as a result of sepsis events, and the PT of septic shock led to ibrutinib discontinuation in 1 (0.9%) subject.

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, 3 subjects (0.9%) experienced treatment-emergent sepsis (ie, 1 subject with bacteremia, 1 subject with Escherichia bacteremia, 1 subject with Staphylococcal bacteremia). Of these events, 2 events (Escherichia bacteremia and Staphylococcal bacteremia) were Grade 3 or 4 in severity. Two (0.6%) subjects had serious sepsis events and none of the events were fatal. No subjects had ibrutinib dose reductions or ibrutinib discontinuation as a result of sepsis events.

Cardiac arrhythmias

Atrial Fibrillation

In Study CLL3011, the proportion of subjects with atrial fibrillation (based on the PT of atrial fibrillation) was higher in the Ibr+Ven arm (14.2%) compared with the Clb+Ob arm (1.9%). Grade 3 or 4 TEAEs of atrial fibrillation were reported in 7 (6.6%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. Similarly, atrial fibrillation as a serious adverse event was reported in 7 (6.6%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. There were no fatal atrial fibrillation events. Atrial fibrillation led to ibrutinib discontinuation in 2 (1.9%) subjects, ibrutinib dose reduction in 1 subject (0.9%). None of the subjects with a TEAE of atrial fibrillation had an action taken against venetoclax nor a discontinuation of study treatment due to the event.

In Study 1142, treatment-emergent atrial fibrillation was reported for 5.9% of subjects. Five subjects (1.5%) had Grade 3 or 4 atrial fibrillation. Atrial fibrillation as a serious adverse event was reported in 6 (1.9%) subjects. There were no fatal atrial fibrillation events. Atrial fibrillation led to ibrutinib discontinuation for 1 subject (0.3%).

Table 20. Incidence of treatment-emergent ventricular tachyarrhythmia

TSFAE35: Incidence of Treatment-emergent Ventricular Tachyarrhythmia Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
		Ibr+Ven			Clb+Ob			Ibr+Ven		Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Ventricular Tachyarrhythmia	0	0	0	0	0	0	3 (0.9%)	2 (0.6%)	0	16 (1.0%)	2 (0.1%)	1 (0.1%)
System Organ Class Preferred Term												
Cardiac disorders	0	0	0	0	0	0	3 (0.9%)	2 (0.6%)	0	16 (1.0%)	2 (0.1%)	1 (0.1%)
Torsade de pointes	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Ventricular arrhythmia	0	0	0	0	0	0	0	0	0	4 (0.3%)	0	0
Ventricular extrasystoles	0	0	0	0	0	0	1 (0.3%)	0	0	8 (0.5%)	0	0
Ventricular fibrillation	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	1 (0.1%)	1 (0.1%)	0
Ventricular flutter	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Ventricular tachyarrhythmia	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0
Ventricular tachycardia	0	0	0	0	0	0	0	0	0	3 (0.2%)	2 (0.1%)	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
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In Study CLL3011, no TEAEs of ventricular tachyarrhythmias (based on the ventricular tachyarrhythmia SMQ search) were reported.

In Study 1142, ventricular tachyarrhythmias TEAEs occurred in 3 subjects (0.9%), with ventricular extrasystoles, ventricular fibrillation, and ventricular tachyarrhythmia (serious) observed in individual subjects (0.3% each). Events of ventricular tachyarrhythmia did not result in ibrutinib dose reduction for any subjects. For 2 subject (0.6%), events of Grade 3 or 4 ventricular fibrillation or ventricular tachyarrhythmia resulted in ibrutinib discontinuation.

Other Cardiac Arrhythmias (excluding atrial fibrillation and ventricular tachyarrhythmias)

Table 21. Incidence of treatment-emergent cardiac arrhythmias (excluding atrial fibrillation and ventricular tachyarrhythmia)

TSFAE31: Incidence of Treatment-emergent Cardiac Arrhythmias (Excluding Atrial Fibrillation and Ventricular Tachyarrhymia) Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Cardiac Arrhythmias	15 (14.2%)	3 (2.8%)	4 (3.8%)	11 (10.5%)	2 (1.9%)	0	56 (17.3%)	7 (2.2%)	1 (0.3%)	192 (12.4%)	36 (2.3%)	6 (0.4%)
System Organ Class Preferred Term												
Cardiac disorders	11 (10.4%)	1 (0.9%)	2 (1.9%)	10 (9.5%)	1 (1.0%)	0	53 (16.4%)	4 (1.2%)	0	162 (10.4%)	19 (1.2%)	4 (0.3%)
Palpitations	6 (5.7%)	0	0	3 (2.9%)	0	0	36 (11.1%)	0	0	63 (4.1%)	0	0
Sinus node dysfunction	2 (1.9%)	1 (0.9%)	1 (0.9%)	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Arrhythmia	1 (0.9%)	0	0	1 (1.0%)	0	0	0	0	0	1 (0.1%)	0	0
Bundle branch block left	1 (0.9%)	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Cardiac arrest	1 (0.9%)	0	1 (0.9%)	0	0	0	2 (0.6%)	2 (0.6%)	0	6 (0.4%)	2 (0.1%)	4 (0.3%)
Extrasystoles	1 (0.9%)	0	0	0	0	0	3 (0.9%)	0	0	3 (0.2%)	0	0
Arrhythmia supraventricular	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Atrial flutter	0	0	0	1 (1.0%)	0	0	1 (0.3%)	0	0	10 (0.6%)	6 (0.4%)	0
Atrial tachycardia	0	0	0	0	0	0	0	0	0	5 (0.3%)	1 (0.1%)	0
Atrioventricular block	0	0	0	0	0	0	0	0	0	3 (0.2%)	2 (0.1%)	0
Atrioventricular block first degree	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Atrioventricular block second degree	0	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Bradycardia	0	0	0	0	0	0	2 (0.6%)	1 (0.3%)	0	10 (0.6%)	0	0
Bundle branch block right	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Cardiac flutter	0	0	0	0	0	0	1 (0.3%)	0	0	0	0	0
Cardio-respiratory arrest	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Chronotropic incompetence	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Sinus arrest	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0
Sinus arrhythmia	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Sinus bradycardia	0	0	0	2 (1.9%)	0	0	4 (1.2%)	0	0	25 (1.6%)	1 (0.1%)	0
Sinus tachycardia	0	0	0	1 (1.0%)	0	0	4 (1.2%)	0	0	24 (1.5%)	0	0
Supraventricular extrasystoles	0	0	0	0	0	0	1 (0.3%)	0	0	3 (0.2%)	0	0
Supraventricular tachycardia	0	0	0	1 (1.0%)	1 (1.0%)	0	0	0	0	9 (0.6%)	3 (0.2%)	0
Tachycardia	0	0	0	1 (1.0%)	0	0	3 (0.9%)	0	0	14 (0.9%)	1 (0.1%)	0
Tachycardia paroxysmal	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
General disorders and administration site conditions	2 (1.9%)	0	2 (1.9%)	0	0	0	1 (0.3%)	0	1 (0.3%)	2 (0.1%)	0	2 (0.1%)
Sudden death	2 (1.9%)	0	2 (1.9%)	0	0	0	1 (0.3%)	0	1 (0.3%)	2 (0.1%)	0	2 (0.1%)
Investigations	2 (1.9%)	0	0	0	0	0	0	0	0	8 (0.5%)	0	0
Heart rate irregular	2 (1.9%)	0	0	0	0	0	0	0	0	3 (0.2%)	0	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	0	0	0	3 (0.2%)	0	0
Heart rate decreased	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Heart rate increased	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Nervous system disorders	2 (1.9%)	2 (1.9%)	0	1 (1.0%)	1 (1.0%)	0	4 (1.2%)	3 (0.9%)	0	26 (1.7%)	18 (1.2%)	0
Syncope	2 (1.9%)	2 (1.9%)	0	1 (1.0%)	1 (1.0%)	0	4 (1.2%)	3 (0.9%)	0	25 (1.6%)	18 (1.2%)	0
Loss of consciousness	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
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In Study CLL3011, cardiac arrhythmias (identified by the cardiac arrhythmia SMQ excluding the preferred term of atrial fibrillation and ventricular arrhythmias) were reported for 15 subjects (14.2%) in the Ibr+Ven arm and 11 subjects (10.5%) in the Clb+Ob arm. The PT of palpitations was reported in 6 (5.7%) subjects in the Ibr+Ven arm and 3 (2.9%) of subjects in the Clb+Ob arm. All other PTs were reported in 1 or 2 subjects in either treatment arm. The proportion of subjects with Grade 3 or 4 TEAEs of cardiac arrhythmias was similar between the Ibr+Ven arm and Clb+Ob arm (3 [2.8%] and 2 [1.9%] subjects, respectively). Fatal cardiac arrhythmias were reported in 4 (3.8%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. The fatal events were sudden death (2 [1.9%] subjects), cardiac arrest (1 [0.9%] subject), and sinus node dysfunction (1 [0.9%] subject). No subjects had ibrutinib dose reductions as a result of cardiac arrhythmias, and 4 (3.8%) subjects had ibrutinib treatment discontinuation as a result of cardiac arrhythmias (2 [1.9%] subjects with the PT of sudden death and 1 [0.9%] subject each with PTs of fatal sinus node dysfunction and non-fatal cardiac arrest).

In Study 1142, cardiac arrhythmias excluding the preferred term of atrial fibrillation and ventricular arrhythmias, were reported for 56 subjects (17.3%) in the FD cohort + the first 16 cycles of the MRD cohort, with 2.2% having a Grade 3 or 4 event. The PT of palpitations was reported in 36 (11.1%) subjects, and sinus bradycardia, sinus tachycardia, and syncope in 4 (1.2%) subjects each. All other PTs were reported in 1 to 3 subjects. Fatal cardiac arrhythmias were reported in 1 (0.3%) subject (sudden death). One subject had an ibrutinib dose reduction as a result of palpitations. Ibrutinib treatment discontinuation resulted from cardiac arrest in 2 subjects (0.6%) and sinus arrest in 1 subject (0.3%).

Cardiac failure

Table 22. Incidence of treatment-emergent cardiac failure

TSFAE43: Incidence of Treatment-emergent Cardiac Failure Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
		Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool	
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Cardiac Failure	5 (4.7%)	3 (2.8%)	1 (0.9%)	1 (1.0%)	1 (1.0%)	0	1 (0.3%)	1 (0.3%)	0	27 (1.7%)	16 (1.0%)	2 (0.1%)
System Organ Class Preferred Term												
Cardiac disorders	5 (4.7%)	3 (2.8%)	1 (0.9%)	1 (1.0%)	1 (1.0%)	0	1 (0.3%)	1 (0.3%)	0	21 (1.4%)	15 (1.0%)	1 (0.1%)
Cardiac failure	5 (4.7%)	3 (2.8%)	1 (0.9%)	0	0	0	1 (0.3%)	1 (0.3%)	0	12 (0.8%)	9 (0.6%)	0
Cardiac failure chronic	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Cardiac failure congestive	0	0	0	1 (1.0%)	1 (1.0%)	0	0	0	0	6 (0.4%)	5 (0.3%)	0
Cardiogenic shock	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Cardiopulmonary failure	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)
Left ventricular failure	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Investigations	0	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Ejection fraction decreased	0	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	0	0	0	0	6 (0.4%)	2 (0.1%)	1 (0.1%)
Acute pulmonary oedema	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Pulmonary oedema	0	0	0	0	0	0	0	0	0	5 (0.3%)	1 (0.1%)	1 (0.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
[TSFAE43.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE43.SAS] 30JUN2021, 15:22

In Study CLL3011, treatment-emergent cardiac failure events (identified by cardiac failure SMQ narrow search) were reported in 5 (4.7%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. All of these subjects had multiple comorbidities including cardiac disorders and/or hypertension at baseline. Grade 3 or 4 cardiac failure was reported in 3 (2.8%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. One subject in the Ibr+Ven arm was reported with a fatal cardiac failure event (0.9%), this subject had a history of myocardial infarction, myocardial ischemia, and atrial fibrillation at study entry. No subjects had ibrutinib dose reductions as a result of cardiac failure events, and all 5 (4.7%) subjects in the Ibr+Ven arm had ibrutinib treatment discontinuation as a result of cardiac failure events.

In Study 1142, 1 subject (0.3%) reported treatment-emergent cardiac failure event of Grade 3 or 4 severity. This cardiac failure event was serious and did not lead to a fatal outcome, dose ibrutinib reduction, or discontinuation of ibrutinib treatment.

Other malignancies

Primary Analysis

Table 23. Incidence of treatment-emergent other malignancies

Table 12: Incidence of Other Malignancies by Preferred Term During Entire Study Period - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011		PCYC-1142-CA	
	Ibr+Ven	Clb+Ob	Ibr+Ven	Current Label Pool
Analysis Set: Safety Population	106	105	323	1552
Subjects with Any Other Malignancy	8 (7.5%)	10 (9.5%)	18 (5.6%)	141 (9.1%)
Type				
Preferred Term				
Non-melanoma skin cancer	3 (2.8%)	2 (1.9%)	12 (3.7%)	89 (5.7%)
Basal cell carcinoma	2 (1.9%)	1 (1.0%)	10 (3.1%)	56 (3.6%)
Squamous cell carcinoma of skin	1 (0.9%)	1 (1.0%)	0	8 (0.5%)
Atypical fibroxanthoma	0	0	0	1 (0.1%)
Basosquamous carcinoma	0	0	0	1 (0.1%)
Basosquamous carcinoma of skin	0	0	0	1 (0.1%)
Penile squamous cell carcinoma	0	0	0	2 (0.1%)
Skin cancer	0	0	0	4 (0.3%)
Squamous cell carcinoma	0	0	2 (0.6%)	26 (1.7%)
Melanoma skin cancer	0	2 (1.9%)	6 (1.9%)	10 (0.6%)
Malignant melanoma	0	2 (1.9%)	6 (1.9%)	8 (0.5%)
Malignant melanoma in situ	0	0	0	2 (0.1%)
Non-skin cancer	5 (4.7%)	6 (5.7%)	4 (1.2%)	48 (3.1%)
Hepatocellular carcinoma	1 (0.9%)	0	0	0
Lung neoplasm malignant	1 (0.9%)	0	0	0
Neoplasm malignant	1 (0.9%)	0	0	1 (0.1%)
Plasma cell myeloma	1 (0.9%)	0	0	0
T-cell lymphoma	1 (0.9%)	0	0	0
Adenocarcinoma	0	0	0	1 (0.1%)
Adenocarcinoma gastric	0	1 (1.0%)	0	1 (0.1%)
Adenocarcinoma of colon	0	0	0	1 (0.1%)
Adenocarcinoma pancreas	0	0	0	1 (0.1%)
Anal squamous cell carcinoma	0	0	0	1 (0.1%)
B-cell lymphoma	0	0	0	1 (0.1%)
Bladder cancer	0	0	0	1 (0.1%)
Bladder transitional cell carcinoma	0	0	0	2 (0.1%)
Breast cancer	0	0	0	3 (0.2%)
Chronic myelomonocytic leukaemia	0	0	0	1 (0.1%)
Colon cancer	0	0	0	1 (0.1%)
Colorectal cancer	0	0	0	1 (0.1%)
Colorectal cancer metastatic	0	0	0	1 (0.1%)
Diffuse large B-cell lymphoma	0	0	0	1 (0.1%)
Essential thrombocythaemia	0	0	0	1 (0.1%)
Fibrous histiocytoma	0	0	0	1 (0.1%)
Gastric cancer	0	0	0	1 (0.1%)
Gastrointestinal carcinoma	0	0	0	1 (0.1%)
Invasive ductal breast carcinoma	0	0	1 (0.3%)	1 (0.1%)
Invasive papillary breast carcinoma	0	0	0	1 (0.1%)
Lung adenocarcinoma	0	1 (1.0%)	1 (0.3%)	2 (0.1%)
Malignant histiocytosis	0	0	0	1 (0.1%)
Metastases to peritoneum	0	1 (1.0%)	0	0
Metastatic neoplasm	0	0	0	1 (0.1%)
Mucinous breast carcinoma	0	0	0	1 (0.1%)
Myelodysplastic syndrome	0	0	1 (0.3%)	4 (0.3%)
Non-small cell lung cancer	0	0	0	2 (0.1%)
Papillary thyroid cancer	0	1 (1.0%)	0	1 (0.1%)
Peripheral T-cell lymphoma unspecified	0	0	0	1 (0.1%)
Prostate cancer	0	1 (1.0%)	0	7 (0.5%)
Prostate cancer metastatic	0	1 (1.0%)	0	0
Renal cell carcinoma	0	0	0	1 (0.1%)
Renal oncocytoma	0	0	1 (0.3%)	0
Salivary gland cancer	0	0	0	1 (0.1%)
Sarcoma	0	0	0	1 (0.1%)

Table 12: Incidence of Other Malignancies by Preferred Term During Entire Study Period - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

Squamous cell carcinoma	0	0	0	1 (0.1%)
Squamous cell carcinoma of lung	0	0	0	2 (0.1%)
Throat cancer	0	0	0	1 (0.1%)
Transitional cell carcinoma	0	0	0	1 (0.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Events include all other malignancies reported during the treatment and follow-up.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending frequency of PT in the CLL3011 Ibr + Ven group, those with the same frequency are presented alphabetically.
Only the pre-randomization phase (the first 16 cycles) of MRD cohort was used in this SCS/ISS analyses as it is comparable to the Fixed Duration cohort in this study.

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Extended follow-up

In Study CLL3011, the number of subjects who developed other malignancies during the entire study remained similar between the treatment arms with the extended follow-up, but increased from 8 (7.5%) to 10 (9.4%) in the Ibr+Ven arm and from 10 (9.5%) to 12 (11.4%) in the Clb+Ob arm. Non-skin cancers were reported in 7 (6.6%) subjects in the Ibr+Ven arm and 7 (6.7%) subjects in the Clb+Ob arm. Melanoma was reported in 2 (1.9%) subjects in the Clb+Ob arm. Non-melanoma skin cancer was reported in 4 (3.8%) subjects in the Ibr+Ven arm and 3 (2.9%) subjects in the Clb+Ob arm. One subject in the Clb+Ob arm was diagnosed with 2 new and serious secondary malignancies after primary analysis. Because the investigator assessed the events of MDS and MPN as very likely related to chlorambucil, both were considered treatment emergent.

In Study 1142, the number of subjects who developed other malignancies during the entire study remained the same with extended follow-up.

Hypertension

In Study CLL3011, hypertension events (identified by hypertension narrow MedDRA SMQ) were reported for 15 (14.2%) subjects in the Ibr+Ven arm and 5 (4.8%) subjects in the Clb+Ob arm. Overall, Grade 3 or 4 hypertension was reported in 9 (8.5%) subjects in the Ibr+Ven arm and 2 (1.9%) subjects in the Clb+Ob arm. Two (1.9%) subjects in the Ibr+Ven arm had serious hypertension TEAEs. No subjects had ibrutinib discontinued and no dose reductions were reported as a result of treatment-emergent hypertension in either treatment arm.

In Study 1142, hypertension events were reported for 16.4% of subjects in the FD cohort + the first 16 cycles of the MRD cohort. Grade 3 or 4 hypertension was reported in 23 (7.1%) subjects. One (0.3%) subject had a serious hypertension TEAE. No subjects had treatment discontinued and no dose reductions were reported as a result of treatment-emergent hypertension.

Hepatoxicity including hepatic failure

Treatment-emergent adverse events of any grade within the SOC of Hepatobiliary Disorders were reported in 7 (6.6%) subjects in the Ibr+Ven arm and 4 (3.8%) subjects in the Clb+Ob arm. Grade 3 or 4 events were reported for 4 (3.8%) subjects in the Ibr+Ven arm and 1 (1.0%) subject in the Clb+Ob arm. One subject (1.0%) in the Clb+Ob arm had a fatal hepatic TEAE of cholestasis.

In the FD cohort + the first 16 cycles of the MRD cohort of Study 1142, hepatic TEAEs were reported for 4.3% of subjects. Grade 3 or 4 hepatic events were observed in 1.9% of subjects. No subjects had a fatal hepatic TEAEs.

Ischemic stroke

Table 24. Incidence of treatment-emergent ischaemic stroke

TSFAE39: Incidence of Treatment-emergent Ischaemic Stroke Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA					
	Ibr+Ven			Clb+Ob			Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			105			323			1552		
Subjects with Any Treatment-emergent Ischaemic Stroke	3 (2.8%)	0	1 (0.9%)	0	0	0	2 (0.6%)	0	0	22 (1.4%)	8 (0.5%)	0
System Organ Class Preferred Term												
Nervous system disorders	3 (2.8%)	0	1 (0.9%)	0	0	0	2 (0.6%)	0	0	21 (1.4%)	8 (0.5%)	0
Ischaemic stroke	2 (1.9%)	0	1 (0.9%)	0	0	0	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)	0
Cerebral infarction	1 (0.9%)	0	0	0	0	0	0	0	0	0	0	0
Carotid artery stenosis	0	0	0	0	0	0	1 (0.3%)	0	0	2 (0.1%)	0	0
Cerebral ischaemia	0	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Cerebrovascular accident	0	0	0	0	0	0	0	0	0	4 (0.3%)	3 (0.2%)	0
Hypoxic-ischaemic encephalopathy	0	0	0	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0
Lacunar infarction	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Thalamic infarction	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Transient ischaemic attack	0	0	0	0	0	0	1 (0.3%)	0	0	7 (0.5%)	3 (0.2%)	0
Vascular encephalopathy	0	0	0	0	0	0	0	0	0	2 (0.1%)	0	0
Eye disorders	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0
Amaurosis fugax	0	0	0	0	0	0	0	0	0	1 (0.1%)	0	0

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events were coded using MedDRA version 23.1.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the CLL3011 Ibr + Ven group; those with the same total frequency are presented alphabetically.
[TSFAE39.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE39.SAS] 30JUN2021, 15:21

In Study CLL3011, treatment-emergent ischemic stroke (identified by ischemic central nervous system vascular conditions SMQ narrow search) was reported in 3 (2.8%) subjects in the Ibr+Ven arm and no subjects in the Clb+Ob arm. By PT, 2 (1.9%) subjects had ischemic stroke and 1 (0.9%) subject had cerebral infarction in the Ibr+Ven arm. No subjects had ibrutinib dose reductions as a result of ischemic stroke events. Both events with PTs of ischemic stroke were serious; 1 ischemic stroke event was fatal and the other led to discontinuation of ibrutinib.

In Study 1142, ischemic stroke was reported for 2 (0.6%) subjects in the FD cohort + the first 16 cycles of the MRD cohort (PTs: Grade 1 or 2 carotid artery stenosis, ischemic stroke, and transient ischemic attack). One event (ie, ischemic stroke in 1 subject) was serious and resulted in ibrutinib discontinuation.

Diarrhoea

In Study CLL3011, treatment-emergent diarrhea was reported in 50.9% of subjects in the Ibr+Ven arm and 12.4% of subjects in the Clb+Ob arm. Grade 3 diarrhea was reported in 10.4% of subjects in the Ibr+Ven arm and 1.0% of subjects in the Clb+Ob arm. There were no Grade 4 or fatal events. Most subjects who experienced diarrhea only had one event (30.2% of subjects in the Ibr+Ven arm and 9.5% of subjects in the Clb+Ob arm). The median time to resolution or improvement of Grade 3 event was 9.0 days in the Ibr+Ven arm and 8.0 days in the Clb+Ob arm. Treatment-emergent diarrhea led to ibrutinib dose reduction in 7 (6.6%) subjects and to venetoclax dose reduction in 6 (5.7%) subjects. In the Clb+Ob arm, diarrhea led to chlorambucil dose reduction in 1 (1.0%) subject. In the Ibr+Ven arm, diarrhea led to ibrutinib and venetoclax dose interruption in 11 (10.4%) and 7 (6.6%) subjects, respectively. In the Clb+Ob arm, diarrhea led to obinutuzumab dose interruption (ie, infusion interrupted, delayed, or skipped) in 2 (1.9%) subjects. For 3 (2.8%) subjects in the Ibr+Ven arm, diarrhea led to study treatment discontinuation.

In Study 1142, diarrhea was reported for 66.6% of subjects for the FD cohort + the first 16 cycles of the MRD cohort, with 4.0% of subjects experiencing diarrhea of Grade 3 or 4 severity. Diarrhea led to ibrutinib dose reduction in 8 (2.5%) subjects, and no diarrhea events led to ibrutinib discontinuation.

Embryofoetal toxicity

No TEAEs of embryofetal toxicity were reported in Study CLL3011 or for the FD cohort + the first 16 cycles of the MRD cohort in Study 1142.

Laboratory findings

Haematology

Decreases in ANC, hemoglobin, and platelet counts

A summary of treatment-emergent worsening of hematological abnormalities is provided in Table 13; iwCLL 2008 criteria were used for the CLL studies (Hallek 2008). In these guidelines, Grade 3 and 4 decreases in hemoglobin and platelet count are defined as a reduction from baseline of ≥50% and ≥75%, respectively. Note, platelet and hemoglobin levels must have been below normal levels for any grade toxicity. Grade 3 and 4 decreases in ANC are defined as ANC of ≥500 to <1000/µl and <500/µl, respectively. Other non-CLL studies in the Current Label Pool used the NCI-CTCAE grading.

Table 25. Haematology events

Table 13: Hematology: Incidence of Treatment-Emergent Worst Toxicity Grade During Treatment - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA			Current Label Pool		
		Ibr+Ven			Clb+Ob			Ibr+Ven				
	Any Grades	Grade 1/2	Grade 3/4	Any Grades	Grade 1/2	Grade 3/4	Any Grades	Grade 1/2	Grade 3/4	Any Grades	Grade 1/2	Grade 3/4
Analysis Set: Safety Population	106			105			323			1552		
Hemoglobin (Decrease)	38 (35.8%)	38 (35.8%)	0	42 (40.0%)	42 (40.0%)	0	72 (22.3%)	71 (22.0%)	1 (0.3%)	555 (35.8%)	525 (33.8%)	30 (1.9%)
Platelets (Decrease)	52 (49.1%)	38 (35.8%)	14 (13.2%)	78 (74.3%)	45 (42.9%)	33 (31.4%)	194 (60.1%)	158 (48.9%)	36 (11.1%)	849 (54.7%)	628 (40.5%)	221 (14.2%)
ANC (Decrease)	81 (76.4%)	37 (34.9%)	44 (41.5%)	95 (90.5%)	38 (36.2%)	57 (54.3%)	233 (72.1%)	112 (34.7%)	121 (37.5%)	874 (56.3%)	345 (22.2%)	529 (34.1%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: ANC = Absolute neutrophils counts.
Note: Only subjects whose grade worsened from baseline were counted in numerator. Percentages are calculated with the number of subjects in safety population as the denominators.
For CLL studies, IWCLL2008 guideline is used; and for other studies, NCI CTCAE criteria are used.
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Lymphocytosis

Lymphocytosis, defined as an increase in ALC ≥50% from baseline to a level of ≥5 x 10^9/L, was reported in 43.4% of subjects in the Ibr+Ven arm and 1.0% of subjects in the Clb+Ob arm in Study CLL3011. The onset of lymphocytosis occurred within the first month (median of 4.1 weeks in Ibr+Ven arm), and resolved in all but 1 subject. The median time to resolution of lymphocytosis was 8.3 weeks (range: 1.6 to 15.1 weeks).

For the FD cohort + the first 16 cycles of the MRD cohort in Study 1142, lymphocytosis was reported in 47.0% of subjects. The onset of lymphocytosis occurred within the first month (median of 4.1 weeks). Lymphocytosis resolved in all but 2 subjects. The median time to resolution of lymphocytosis was 8.4 weeks (range: 0.1 to 16.3 weeks).

Clinical chemistry

Grade 3 or 4 changes in clinical chemistry laboratory parameters were infrequent for each safety population.

Table 14: Chemistry: Incidence of Treatment-Emergent Worst Toxicity Grade During Treatment - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011						PCYC-1142-CA			Current Label Pool		
	Ibr+Ven			Clb+Ob			Ibr+Ven					
Analysis Set: Safety Population	Any Grades 106	Grade 1/2	Grade 3/4	Any Grades 105	Grade 1/2	Grade 3/4	Any Grades 323	Grade 1/2	Grade 3/4	Any Grades 1552	Grade 1/2	Grade 3/4
Sodium (Decrease)	25 (23.6%)	16 (15.1%)	9 (8.5%)	26 (24.8%)	25 (23.8%)	1 (1.0%)	26 (8.0%)	22 (6.8%)	4 (1.2%)	217 (14.0%)	163 (10.5%)	54 (3.5%)
Sodium (Increase)	13 (12.3%)	13 (12.3%)	0	8 (7.6%)	8 (7.6%)	0	140 (43.3%)	140 (43.3%)	0	220 (14.2%)	215 (13.9%)	5 (0.3%)
Magnesium (Decrease)	N/A	N/A	N/A	N/A	N/A	N/A	98 (30.3%)	98 (30.3%)	0	201 (13.0%)	193 (12.4%)	8 (0.5%)
Magnesium (Increase)	N/A	N/A	N/A	N/A	N/A	N/A	58 (18.0%)	57 (17.6%)	1 (0.3%)	71 (4.6%)	60 (3.9%)	11 (0.7%)
Potassium (Decrease)	25 (23.6%)	22 (20.8%)	3 (2.8%)	9 (8.6%)	9 (8.6%)	0	37 (11.5%)	33 (10.2%)	4 (1.2%)	185 (11.9%)	158 (10.2%)	27 (1.7%)
Potassium (Increase)	31 (29.2%)	29 (27.4%)	2 (1.9%)	22 (21.0%)	21 (20.0%)	1 (1.0%)	84 (26.0%)	78 (24.1%)	6 (1.9%)	190 (12.2%)	168 (10.8%)	22 (1.4%)
Corrected calcium (Increase)	13 (12.3%)	13 (12.3%)	0	3 (2.9%)	3 (2.9%)	0	56 (17.3%)	56 (17.3%)	0	35 (4.9%)	34 (4.8%)	1 (0.1%)
Corrected calcium (Decrease)	27 (25.5%)	27 (25.5%)	0	30 (28.6%)	30 (28.6%)	0	123 (38.1%)	122 (37.8%)	1 (0.3%)	150 (21.1%)	147 (20.7%)	3 (0.4%)
Albumin (Decrease)	36 (34.0%)	36 (34.0%)	0	20 (19.0%)	18 (17.1%)	2 (1.9%)	59 (18.3%)	59 (18.3%)	0	246 (15.9%)	238 (15.3%)	8 (0.5%)
Total Bilirubin (Increase)	36 (34.0%)	34 (32.1%)	2 (1.9%)	25 (23.8%)	24 (22.9%)	1 (1.0%)	91 (28.2%)	82 (25.4%)	9 (2.8%)	393 (25.3%)	370 (23.8%)	23 (1.5%)
Creatinine clearance (Decrease)	40 (37.7%)	35 (33.0%)	5 (4.7%)	17 (16.2%)	16 (15.2%)	1 (1.0%)	42 (13.0%)	42 (13.0%)	0	463 (29.8%)	423 (27.3%)	40 (2.6%)
Creatinine (Increase)	33 (31.1%)	32 (30.2%)	1 (0.9%)	17 (16.2%)	17 (16.2%)	0	66 (20.4%)	66 (20.4%)	0	374 (24.1%)	358 (23.1%)	16 (1.0%)
ALT (Increase)	22 (20.8%)	19 (17.9%)	3 (2.8%)	26 (24.8%)	23 (21.9%)	3 (2.9%)	66 (20.4%)	60 (18.6%)	6 (1.9%)	216 (13.9%)	202 (13.0%)	14 (0.9%)
AST (Increase)	23 (21.7%)	21 (19.8%)	2 (1.9%)	30 (28.6%)	27 (25.7%)	3 (2.9%)	75 (23.2%)	70 (21.7%)	5 (1.5%)	326 (21.0%)	308 (19.8%)	18 (1.2%)
ALP (Increase)	19 (17.9%)	19 (17.9%)	0	21 (20.0%)	19 (18.1%)	2 (1.9%)	70 (21.7%)	69 (21.4%)	1 (0.3%)	223 (14.4%)	217 (14.0%)	6 (0.4%)
Phosphate (Decrease)	16 (15.1%)	11 (10.4%)	5 (4.7%)	6 (5.7%)	4 (3.8%)	2 (1.9%)	59 (18.3%)	48 (14.9%)	11 (3.4%)	217 (14.0%)	194 (12.5%)	23 (1.5%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: ALT = Alanine Aminotransferase. AST = Aspartat Aminotransferase. ALP = Alkaline Phosphatase.
Note: Only subjects whose grade worsened from baseline were counted in numerator. Percentages are calculated with the number of subjects in safety population as the denominators.
Only subjects with both baseline and post-baseline are included.
Magnesium was not collected in CLL3011 clinical data.
Corrected calcium in current label pool only available in studies PCYC-1102-CA, PCYC-1104-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1127-CA and PCYC-1130-CA, the percentage are calculated based on safety population from these studies.
[TSFLAB02.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFLAB02.SAS] 04NOV2021, 10:56

Hepatic abnormalities

In Study CLL3011 (Ibr+Ven and Clb+Ob arms) and Study 1142, the majority of subjects maintained normal serum levels (Grade 0) of ALT, AST, ALP, and bilirubin post-baseline. Most post-baseline increases in ALT, AST, ALP, and bilirubin were mild (Grade 1). In Study 1142, 1 subject (0.3%) met the requisite laboratory criteria for potential Hy's Law based on ALT/AST, alkaline phosphatase, and bilirubin toxicities post-baseline, and none met the requisite laboratory criteria for potential Hy's Law in Study CLL3011.

Serum creatinine abnormalities

In Study CLL3011, baseline CrCl <60 to 30 mL/min were observed in 36.2% of subjects in the Ibr+Ven arm and 39.0 % of subjects in the Clb+Ob arm. Five (4.8%) subjects in the Ibr+Ven and 1 (1.0%) subject in the Clb+Ob arm had a post-baseline worsening of CrCl to <30 mL/min.

In the FD cohort + the first 16 cycles of the MRD cohort in Study 1142, baseline CrCl <60 to 30 mL/min were observed in 3.2% of subjects. No subjects had a post-baseline worsening of CrCl to <30 mL/min.

Uric acid

In Study CLL3011, the proportion of subjects with treatment-emergent worsening in serum uric acid level was higher in the Ibr+Ven arm (34.9%) compared with the Clb+Ob arm (16.2%), however, was consistent with the Current Label Pool (35.4%). In Study 1142, the proportion of subjects with treatment-emergent worsening in serum uric acid level was 25.5%, and lower than the Current Label Pool.

Safety in special populations

Age

<65 versus ≥65 years

Table 26. Summary of TEAEs by age group (≥65 vs. <65)

TSFAE13: Overall Summary of Treatment-emergent Adverse Events by Age Group (>= 65 vs. < 65) - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011				PCYC-1142-CA			
	Ibr+Ven Age (years)		Clb+Ob Age (years)		Ibr+Ven Age (years)		Current Label Pool Age (years)	
	>= 65	< 65	>= 65	< 65	>= 65	< 65	>= 65	< 65
Analysis Set: Safety Population	90	16	94	11	86	237	808	744
Any TEAE	90 (100.0%)	15 (93.8%)	91 (96.8%)	8 (72.7%)	86 (100.0%)	236 (99.6%)	801 (99.1%)	736 (98.9%)
Grade >= 3	71 (78.9%)	9 (56.3%)	66 (70.2%)	7 (63.6%)	61 (70.9%)	148 (62.4%)	602 (74.5%)	560 (75.3%)
Drug related	80 (88.9%)	9 (56.3%)	90 (95.7%)	7 (63.6%)	86 (100.0%)	221 (93.2%)	695 (86.0%)	665 (89.4%)
Grade >= 3	55 (61.1%)	6 (37.5%)	63 (67.0%)	5 (45.5%)	49 (57.0%)	132 (55.7%)	393 (48.6%)	382 (51.3%)
Any TESAE	43/90 (47.8%)	6/16 (37.5%)	26/94 (27.7%)	3/11 (27.3%)	22/86 (25.6%)	48/237 (20.3%)	393/765 (51.4%)	181/435 (41.6%)
Grade >= 3	37/90 (41.1%)	4/16 (25.0%)	20/94 (21.3%)	3/11 (27.3%)	17/86 (19.8%)	42/237 (17.7%)	355/765 (46.4%)	151/435 (34.7%)
Drug related	24/90 (26.7%)	2/16 (12.5%)	19/94 (20.2%)	1/11 (9.1%)	12/86 (14.0%)	27/237 (11.4%)	182/765 (23.8%)	79/435 (18.2%)
TEAE leading to Ibrutinib discontinuation	19 (21.1%)	2 (12.5%)	NA	NA	9 (10.5%)	10 (4.2%)	105 (13.0%)	80 (10.8%)
TEAE leading to Ibrutinib dose reduction	17 (18.9%)	2 (12.5%)	NA	NA	13 (15.1%)	26 (11.0%)	89 (11.0%)	73 (9.8%)
TEAE with outcome death	5 (5.6%)	2 (12.5%)	2 (2.1%)	0	0	1 (0.4%)	57 (7.1%)	25 (3.4%)
Deaths within 30 days after last dose of study treatment [1]	5 (5.6%)	2 (12.5%)	0	0	0	1 (0.4%)	56 (6.9%)	27 (3.6%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[1] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population per subgroup as denominator.
Adverse events were coded using MedDRA version 23.1.
Study 1126e is excluded from SAE summary.

[TSFAE13.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE13.SAS] 30JUN2021, 15:01

In the Ibr+Ven arm for Study CLL3011, TEAEs were generally consistent between subjects aged ≥65 years (n=90) and those aged <65 years (n=16) in the overall frequencies; however, differences (>10%) were observed in TEAEs of diarrhea (54.4% vs 31.3%), neutropenia (35.6% vs 25.0%), rash (18.9% vs 6.3%), hypertension (15.6% vs 0%), peripheral edema (13.3% vs 25.0%), cataract (1.1% vs 12.5%), influenza (0% vs 12.5%), and back pain (11.1% vs 0%). Differences between subjects aged ≥65 years and those aged <65 years were observed in Grade 3 or higher TEAEs (78.9% versus 56.3% respectively), and drug-related TEAEs (88.9% versus 56.3%), noting the limited number of subjects aged <65 years. There were no meaningful (ie, >10%) differences between subjects aged ≥65 years and those aged <65 years in the overall frequencies of TEAEs leading to ibrutinib dose reduction (18.9% versus 12.5%), TEAEs leading to ibrutinib discontinuation (21.1% versus 12.5%). TEAEs with an outcome of death occurred in 5.6% versus 12.5% of subjects <65 years and ≥65 years, respectively.

In Study 1142, TEAEs were generally consistent between subjects aged ≥65 years (n=86) and those aged <65 years (n=237) in the overall frequencies; a difference (>10%) was observed in TEAEs of hypertension (23.3% vs 13.1%). There were no meaningful (>10%) differences between subjects aged ≥65 years and those aged <65 years in the overall frequencies of Grade 3 or higher TEAEs (70.9% versus 62.4% respectively), drug-related TEAEs (100% versus 93.2%), TEAEs leading to ibrutinib dose reduction (15.1% versus 11.0%), TEAEs leading to ibrutinib discontinuation (10.5% versus 4.2%), and TEAEs with an outcome of death (0 subjects versus 0.4%).

<u><70 and ≥70 years</u>

Table 27. Summary of TEAEs by age group (≥70 vs. <70)

TSFAE14: Overall Summary of Treatment-emergent Adverse Events by Age Group (>= 70 vs. < 70) - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011				PCYC-1142-CA			
	Ibr+Ven Age (years)		Clb+Ob Age (years)		Ibr+Ven Age (years)		Current Label Pool Age (years)	
	>= 70	< 70	>= 70	< 70	>= 70	< 70	>= 70	< 70
Analysis Set: Safety Population	67	39	67	38	3	320	524	1028
Any TEAE	67 (100.0%)	38 (97.4%)	64 (95.5%)	35 (92.1%)	3 (100.0%)	319 (99.7%)	520 (99.2%)	1017 (98.9%)
Grade >= 3	59 (88.1%)	21 (53.8%)	47 (70.1%)	26 (68.4%)	3 (100.0%)	206 (64.4%)	395 (75.4%)	767 (74.6%)
Drug related	60 (89.6%)	29 (74.4%)	64 (95.5%)	33 (86.8%)	3 (100.0%)	304 (95.0%)	459 (87.6%)	901 (87.6%)
Grade >= 3	46 (68.7%)	15 (38.5%)	45 (67.2%)	23 (60.5%)	3 (100.0%)	178 (55.6%)	255 (48.7%)	520 (50.6%)
Any TESAE	39/67 (58.2%)	10/39 (25.6%)	21/67 (31.3%)	8/38 (21.1%)	1/3 (33.3%)	69/320 (21.6%)	283/518 (54.6%)	291/682 (42.7%)
Grade >= 3	34/67 (50.7%)	7/39 (17.9%)	16/67 (23.9%)	7/38 (18.4%)	0	59/320 (18.4%)	253/518 (48.8%)	253/682 (37.1%)
Drug related	23/67 (34.3%)	3/39 (7.7%)	16/67 (23.9%)	4/38 (10.5%)	0	39/320 (12.2%)	134/518 (25.9%)	127/682 (18.6%)
TEAE leading to Ibrutinib discontinuation	18 (26.9%)	3 (7.7%)	NA	NA	0	19 (5.9%)	72 (13.7%)	113 (11.0%)
TEAE leading to Ibrutinib dose reduction	12 (17.9%)	7 (17.9%)	NA	NA	1 (33.3%)	38 (11.9%)	59 (11.3%)	103 (10.0%)
TEAE with outcome death	5 (7.5%)	2 (5.1%)	2 (3.0%)	0	0	1 (0.3%)	42 (8.0%)	40 (3.9%)
Deaths within 30 days after last dose of study treatment [1]	5 (7.5%)	2 (5.1%)	0	0	0	1 (0.3%)	42 (8.0%)	41 (4.0%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[1] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population per subgroup as denominator.
Adverse events were coded using MedDRA version 23.1.
Study 1126e is excluded from SAE summary.

[TSFAE14.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE14.SAS] 30JUN2021, 15:01

In the Ibr+Ven arm for Study CLL3011, TEAEs were generally consistent between subjects aged ≥70 years (n=67) and those aged <70 years (n=39) in the overall frequencies, with differences (>10%) for diarrhea (56.7% vs 41.0%), neutropenia (38.8% vs 25.6%), anemia (22.4% vs 10.3%), decreased appetite (17.9% vs 5.1%), conjunctivitis and headache (10.4% vs 0% each), respectively. Differences (>10%) between subjects aged ≥70 years and those aged <70 years were observed in Grade 3 or higher TEAEs (88.1% versus 53.8%), serious TEAEs (58.2% versus 25.6%), drug-related TEAEs (89.6% versus 74.4%), and TEAEs leading to ibrutinib discontinuation (26.9% versus 7.7%), respectively. Grade 3 or 4 neutropenia was observed more frequently in the ≥70 years subgroup (34.3%) versus the <70 years subgroup (17.9%). There were no meaningful differences (>10%) between subjects aged ≥70 years and those aged <70 years in the overall frequencies of TEAEs leading to ibrutinib dose reduction (17.9% versus 17.9%), and TEAEs with an outcome of death (7.5% versus 5.1%), respectively.

Limited information is available for subjects ≥70 years of age in Study 1142 (n=3).

<u><75 versus ≥75 years</u>

Table 28. Summary of TEAEs by age group (≥75 vs. <75)

TSFAE15: Overall Summary of Treatment-emergent Adverse Events by Age Group (>= 75 vs. < 75) - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011				PCYC-1142-CA			
	Ibr+Ven Age (years)		Clb+Ob Age (years)		Ibr+Ven Age (years)		Current Label Pool Age (years)	
	>= 75	< 75	>= 75	< 75	>= 75	< 75	>= 75	< 75
Analysis Set: Safety Population	35	71	37	68	0	323	271	1281
Any TEAE	35 (100.0%)	70 (98.6%)	35 (94.6%)	64 (94.1%)	0	322 (99.7%)	271 (100.0%)	1266 (98.8%)
Grade >= 3	33 (94.3%)	47 (66.2%)	24 (64.9%)	49 (72.1%)	0	209 (64.7%)	215 (79.3%)	947 (73.9%)
Drug related	34 (97.1%)	55 (77.5%)	35 (94.6%)	62 (91.2%)	0	307 (95.0%)	239 (88.2%)	1121 (87.5%)
Grade >= 3	28 (80.0%)	33 (46.5%)	22 (59.5%)	46 (67.6%)	0	181 (56.0%)	139 (51.3%)	636 (49.6%)
Any TESAE	25/35 (71.4%)	24/71 (33.8%)	10/37 (27.0%)	19/68 (27.9%)	0	70/323 (21.7%)	162/271 (59.8%)	412/929 (44.3%)
Grade >= 3	21/35 (60.0%)	20/71 (28.2%)	6/37 (16.2%)	17/68 (25.0%)	0	59/323 (18.3%)	143/271 (52.8%)	363/929 (39.1%)
Drug related	16/35 (45.7%)	10/71 (14.1%)	7/37 (18.9%)	13/68 (19.1%)	0	39/323 (12.1%)	74/271 (27.3%)	187/929 (20.1%)
TEAE leading to Ibrutinib discontinuation	13 (37.1%)	8 (11.3%)	NA	NA	0	19 (5.9%)	38 (14.0%)	147 (11.5%)
TEAE leading to Ibrutinib dose reduction	10 (28.6%)	9 (12.7%)	NA	NA	0	39 (12.1%)	37 (13.7%)	125 (9.8%)
TEAE with outcome death	3 (8.6%)	4 (5.6%)	1 (2.7%)	1 (1.5%)	0	1 (0.3%)	22 (8.1%)	60 (4.7%)
Deaths within 30 days after last dose of study treatment [1]	3 (8.6%)	4 (5.6%)	0	0	0	1 (0.3%)	21 (7.7%)	62 (4.8%)

Current Label Pool includes 1102, 1104, 1112, 1115, 1118E, CLL3001, MCL3001, 1127 (Arm A, C), 1130, and 1126e.
Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[1] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population per subgroup as denominator.
Adverse events were coded using MedDRA version 23.1.
Study 1126e is excluded from SAE summary.

[TSFAE15.RTF] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_GLOW_2021\RE_ISS_CLL_GLOW_2021_VENDOR\PROD\TSFAE15.SAS] 30JUN2021, 15:02

In the Ibr+Ven arm for Study CLL3011, TEAEs were generally consistent between subjects aged ≥75 years (n=35) and those aged <75 years (n=71) in the overall frequencies, with >10% differences for diarrhea (68.6% vs 42.3%), pneumonia (20.0% vs 5.6%), bronchitis (14.3% vs 4.2%), anemia (31.4% vs 11.3%), decreased appetite (20.0% vs 9.9%), fatigue (25.7% vs 9.9%), peripheral edema (22.9% vs 11.3%), vomiting (22.9% vs 9.9%), limb injury (11.4% vs 0%), and weight decrease (20.0% vs 1.4%), respectively. Differences between subjects aged ≥75 years and those aged <75 years were observed in Grade 3 or higher TEAEs (94.3% versus 66.2%), serious TEAEs (71.4% versus 33.8%), drug-related TEAEs (97.1% versus 77.5%), TEAEs leading to ibrutinib discontinuation (37.1% versus 11.3%), and TEAEs leading to ibrutinib dose reduction (28.6% versus 12.7%), respectively. TEAEs with an outcome of death occurred in 8.6% of subjects aged ≥75 years and 5.6% of subjects aged <75 years.

No subjects ≥75 years were enrolled in Study 1142.

Sex

No consistent differences in the TEAE profile for Ibr+Ven between the male and female subgroups were apparent across Study CLL3011, Study 1142, or the Current Label Pool.

Baseline creatinine clearance

The TEAE profile for Ibr+Ven was examined as a function of baseline CrCl (≥60, <60 to 30, and <30 mL/min). The discussion of the ibrutinib safety profile as a function of baseline CrCl focuses on the first 2 subgroups as no subject in Study CLL3011 or Study 1142, and only 7 subjects in the Current Label Pool, had a baseline CrCl of <30 mL/min. No clear and consistent trends in the TEAE profile for ibrutinib as a function of baseline CrCl (≥60, ≥30 to <60 mL/min) were apparent across in Study CLL3011, Study 1142, or the Current Label Pool.

Baseline hepatic function

The TEAE profile for Ibr+Ven was examined as a function of baseline hepatic function (normal, not normal based on NCI Organ Dysfunction Working Group's liver function classification).

Fifteen subjects (14%) in the Ibr+Ven treatment arm of Study CLL3011 had a baseline assessment of not normal (hereafter abnormal) hepatic function. Differences in this treatment arm (>10%) between

subjects with normal versus abnormal baseline hepatic function were observed in the overall frequencies of drug-related TEAEs (86.8% versus 66.7%). Among the common (≥5% overall incidence) Grade 3 or 4 TEAEs reported in the Ibr+Ven arm, a difference (≥5%) for subjects with normal versus abnormal baseline hepatic function, respectively, was observed for thrombocytopenia (4.4% vs 13.3%), diarrhea (12.1% vs 0%), neutrophil count decreased (9.9% vs 0%), atrial fibrillation (7.7% vs 0%), hyponatremia (6.6% vs 0%), and pneumonia (5.5% vs 0%).

Thirty-seven subjects (11%) in the FD cohort + first 16 cycles of the MRD cohort of Study 1142 had a baseline assessment of abnormal hepatic function. Differences in this treatment arm (>10%) between subjects with normal versus abnormal baseline hepatic function were observed in the overall frequencies of TEAEs leading to dose reduction (10.8% versus 21.6%). Among the common (≥5% overall incidence) Grade 3 or 4 TEAEs reported in the Ibr+Ven arm, a difference (≥5%) for subjects with normal versus abnormal baseline hepatic function, respectively, was observed for neutrophil count decreased (2.8% vs 8.1%).

Geographic region

For Study CLL3011, the majority of subjects were enrolled in EU (91.5%). No discernible differences in TEAEs for subjects enrolled in NA (8.5%) were observed, although fewer reported serious TEAEs in NA (2 of 9 subjects; 22.2%) than those in EU (47 of 97 subjects; 48.5%).

For Study 1142 (45.5% of subjects were in NA, 24.1% in EU, and 30.3% in ROW), differences (>10%) were observed across geographic subgroups in the overall incidence of Grade 3 or higher TEAEs (NA: 72.1%, EU: 64.1%, ROW: 54.1%), serious TEAEs (NA: 19.0%, EU: 12.8%, ROW: 32.7%) and TEAEs leading to ibrutinib dose reduction (NA: 16.3%, EU: 5.1%, ROW: 11.2%). Regional differences in common Grade ≥3 TEAEs (≥10% overall incidence) were noted for hypertension (NA: 12.2%, EU: 2.6%, ROW: 2.0%).

Safety related to drug-drug interactions and other interactions

In Study CLL3011, the overall incidence of TEAEs of any grade for subjects treated with Ibr+Ven was similar between subgroups (yes, no) for both moderate/strong and strong CYP3A inhibitors.

Discontinuation due to adverse events

Adverse events leading to treatment discontinuation

Table 29. Overview of TEAEs leading to treatment discontinuation of ibrutinib (table abbreviated by the assessor)

TSFAE10: Incidence of Treatment-emergent Adverse Events Leading to Drug Withdrawal by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population

	CLL3011 Ibr+Ven			PCYC-1142-CA Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			323			1552		
Subjects with Any TEAE Leading to Drug Withdrawal	21 (19.8%)	11 (10.4%)	4 (3.8%)	19 (5.9%)	13 (4.0%)	0	185 (11.9%)	116 (7.5%)	24 (1.5%)

TEAEs leading to treatment discontinuation over the total treatment period, study CLL3011 (table abbreviated)

TSFAE08E: Number of Subjects With Treatment-emergent Adverse Events Leading to Drug Discontinuation by Preferred Term; Safety Analysis Set (Study 54179060CLL3011)								
	Ibr+Ven				Clb+Ob			
	Ibr only [a]	Ven only [a]	Ibr and/or Ven [a]	Ibr and Ven [a]	Clb only [a]	Ob only [a]	Clb and/or Ob [a]	Clb and Ob [a]
Analysis set: Safety	106	106	106	106	105	105	105	105
Subjects with 1 or more AEs	13 (12.3%)	4 (3.8%)	22 (20.8%)	9 (8.5%)	4 (3.8%)	2 (1.9%)	8 (7.6%)	2 (1.9%)
Preferred term								
Cardiac failure	3 (2.8%)	0	5 (4.7%)	2 (1.9%)	0	0	0	0
Diarrhoea	3 (2.8%)	4 (3.8%)	5 (4.7%)	0	0	0	0	0

In the Ibr+Ven arm of Study CLL3011, 21 subjects (19.8%) had a TEAE that resulted in discontinuation of ibrutinib. The following TEAE preferred terms led to ibrutinib discontinuation in >1% of subjects in this treatment arm: cardiac failure (4.7%), diarrhea (2.8%), atrial fibrillation (1.9%), pneumonia (1.9%), sudden death (1.9%), and ischemic stroke (1.9%).

In the FD cohort + first 16 cycles of the MRD cohort of Study 1142, 19 subjects (5.9%) had a TEAE that resulted in discontinuation of ibrutinib. No individual PTs resulted in ibrutinib discontinuation for >1% of subjects.

Adverse events leading to dose reduction

Table 30. Overview of TEAEs leading to ibrutinib dose reduction (table abbreviated by the assessor)

TSFAE11: Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and Preferred Term - CLL3011, PCYC-1142-CA and Current Label Pool; Safety Population									
	CLL3011 Ibr+Ven			PCYC-1142-CA Ibr+Ven			Current Label Pool		
	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5	Any Grades	Grade 3-4	Grade 5
Analysis Set: Safety Population	106			323			1552		
Subjects with Any TEAE Leading to Dose Reduction	19 (17.9%)	10 (9.4%)	0	39 (12.1%)	13 (4.0%)	0	162 (10.4%)	95 (6.1%)	0

TEAEs leading to dose reductions over the total treatment period, study CLL3011 (table abbreviated)

TSFAE09AE: Number of Subjects With Treatment-emergent Adverse Events Leading to Dose Reduction by Preferred Term; Safety Analysis Set (Study 54179060CLL3011)								
	Ibr+Ven				Clb+Ob			
	Ibr only [a]	Ven only [a]	Ibr and/or Ven [a]	Ibr and Ven [a]	Clb only [a]	Ob only [a]	Clb and/or Ob [a]	Clb and Ob [a]
Analysis set: Safety	106	106	106	106	105	105	105	105
Subjects with 1 or more AEs	16 (15.1%)	14 (13.2%)	28 (26.4%)	4 (3.8%)	22 (21.0%)	0	22 (21.0%)	0

In Study CLL3011, TEAEs of any grade leading to an ibrutinib dose reduction were reported for 17.9% of subjects in the Ibr+Ven arm. Diarrhea (6.6%) and neutropenia (2.8%) were the only individual TEAEs that led to a reduction in the dose of ibrutinib in 2% or more of subjects.

In Study 1142, overall incidence of TEAEs leading to ibrutinib dose reduction was 12.1% for the FD cohort + first 16 cycles of the MRD cohort. Diarrhea (2.5%) was the only individual TEAEs that led to a reduction in the dose of ibrutinib in 2% or more of subjects.

Adverse Drug Reactions

The specific methodology for determination and assessment of ADRs was performed based on integration of data from Study CLL3011 with that from other RCT studies forming the basis of the ADR information in the currently approved SmPC.

ADRs for the Overall Label Pool in CLL, WM, and MCL, updated to include new information from Study CLL3011 and Study 1142, are listed in Table 8 by SOC and frequency grouping. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the

available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Important differences versus the adverse reaction table in the currently approved SmPC include:

- Dyspepsia has been added as a new ADR within the Gastrointestinal disorders SOC Dyspepsia (any grade): 10.3% incidence for ibrutinib versus 3.6% for comparator (ie, ≥10% of subjects in the pooled RCT ibrutinib group and reported at a ≥5% higher incidence compared to the pooled RCT comparator group)
- Within the Nervous system disorders SOC, the frequency category for ischemic stroke was changed from "Rare" to "Uncommon"
- Within the Cardiac disorders SOC, the frequency category for ventricular tachyarrhythmia was changed from "Common" to "Uncommon"
- Within the Skin and subcutaneous tissue disorders SOC, the frequency category for Stevens-Johnson syndrome was changed from "Not known" to "Rare"
- Tumor lysis syndrome within the Metabolism disorders SOC is now a grouped term using a narrow TLS SMQ.

Post marketing experience

The Periodic Benefit Risk Evaluation Report (PBRER) for ibrutinib has been submitted in the EU and includes data by the MAH from worldwide sources for the reporting period from 13 November 2019 through 12 November 2020. The next PBRER will cover the annual period of 13 November 2020 through 12 November 2021 and will be submitted in January 2022. Based on the cumulative total of 39,723,797.3 grams of ibrutinib distributed (cumulative from international birth date of 13 November 2013 through 31 October 2020), the estimated cumulative exposure to ibrutinib in marketed use is 252,101 person-years.

Since the database lock of the last PBRER, the SmPC was updated to include cardiac failure in the Special warnings and precautions for use section (Section 4.4) within the paragraph on Cardiac arrhythmias with recommendation to monitor cardiac arrhythmias and cardiac failure at baseline in addition to the existing language for the periodic monitoring of cardiac arrhythmias.

2.5.1. Discussion on clinical safety

The safety data in support of this application to extend the existing indication in first line CLL with combination therapy with ibrutinib and venetoclax is based on 2 studies. The main study, study CLL3011, was a phase 3, randomized, open-label study of Ibr+Ven (N=106) versus Clb+Ob (N=105) in subjects with treatment-naïve CLL/SLL. Supportive safety data were derived from study 1142, a phase 2 study assessing Ibr+Ven in subjects with treatment-naïve CLL/SLL in a fixed duration treatment cohort (FD cohort; N=159) and the pre-randomization phase of the MRD-guided treatment discontinuation cohort (MRD cohort; N=164), the latter with an additional cycle of Ibr+Ven (Cycle 16).

The treatment regimen in the Ibr+Ven arm in both studies consisted of 3 cycles of ibrutinib monotherapy, followed by 12 cycles of ibrutinib in combination with venetoclax; except for the treatment duration, posology for ibrutinib and venetoclax was according to the SmPC for both products. Treatment in the Clb+Ob arm consisted of 6 cycles.

Patient exposure

At the time of the primary analysis data cut-off (Study CLL3011: 26 February 2021; Study 1142: 12 November 2020), none of the patients in either study was still on treatment. In study CLL3011, median treatment duration was 2.7 times longer in the Ibr+Ven arm (13.8 months) vs. the Clb+Ob arm (5.1 months), reflecting the fixed duration of treatment in both arms. Median treatment duration in the Ibr+Ven cohort in study 1142 was 14.1 months. Median relative dose intensity for ibrutinib treatment in the Ibr+Ven cohorts was 97.7% and 98.8% in study CLL3011 and 1142, respectively. Median relative dose intensity for venetoclax was 97.6% in study CLL3011 and 99.4% and 99.3% in the FD and MRD cohort, respectively, in study 1142. Also, median dose intensity based on the cumulative total dose received/planned was high (98.4%).

The combined treatment of ibrutinib and venetoclax led to higher steady state venetoclax exposure based on plasma trough levels in comparison with historical control data. Assessment of the impact of the higher exposure levels of venetoclax on its safety profile as a single component is seriously hampered by a) the design of both studies (2 different combination therapies in both treatment arms for study CLL3011; single arm design for both the FD cohort and the pre-randomisation phase of the MRD cohort in study 1142) and b) the impact of combination therapy with ibrutinib, with partially overlapping toxicities. Overall, the safety profile of ibrutinib in combination with venetoclax is generally in line with the established safety profile of venetoclax in the CLL indication.

Demographics

Patient characteristics were balanced in both arms of study CLL3011. In the Ibr+Ven arm in study CLL3011, median age was 71 years (range 47-93 years) with 84.9% of patients ≥65 years of age; 54.7% of patients had an ECOG performance status of 1 and 12.3% with ECOG 2. In study 1142, median age was 59 years (range 28-71 years) with 26.6% of patients ≥65 years of age; 66.6% had ECOG 0; no patients with ECOG 2 were included in the study. Generally, the patient population in the Ibr+Ven arms enrolled in studies CLL3011 and 1142 differed in terms of age and ECOG performance status with patients in study CLL3011 being older and with a worse ECOG performance status compared with those in study 1142.

Patient disposition

At the time of the primary analysis data cut-off (Study CLL3011: 26 February 2021; Study 1142: 12 November 2020), none of the patients in either study was still on treatment. In study CLL3011, more patients discontinued treatment in the Ibr+Ven arm (22.6%) compared with the Clb+Ob arm (4.8%). The main differences in reasons for discontinuation of treatment concerned AEs (Ibr+Ven vs. Clb+Ob: 10.4% vs. 1.9%) and deaths (Ibr+Ven vs. Clb+Ob: 3.8% vs. 0). Compared with the Ibr+Ven arm in study CLL3011, treatment discontinuation in study 1142 was lower (8.0%); treatment discontinuation due to AEs was 5.3% and discontinuation due to death 0.3%, likely reflecting a younger and more fit patient population.

TEAEs

In study CLL3011, the frequency of patients with any TEAE (Ibr+Ven vs. Clb+Ob: 99.1% vs. 94.3%) and any grade ≥3 TEAE (Ibr+Ven vs. Clb+Ob: 75.5% vs. 69.5%) was similar between treatment arms. Higher frequencies (Ibr+Ven vs. Clb+Ob) were noted for SAEs (46.2% vs. 27.6%; grade ≥3: 38.7% vs. 21.9%) and fatal TEAEs leading to death within 30 days of last dose (6.6% vs. 0). In study 1142, lower frequencies were noted for grade ≥3 TEAE (64.7%), SAEs (21.7%; grade ≥3: 18.3%) and fatal TEAEs (0.3%) compared with the Ibr+Ven arm of study CLL3011. Data on treatment discontinuations are discussed below. Interpretation of the summary of AEs in study CLL3011 is hampered by the difference in treatment duration between both arms. Comparison of the safety profile in study CLL3011 between study arms over the first 6 treatment cycles, corresponding to the fixed treatment duration in the control arm, showed primarily a higher frequency of SAEs with Ibr+Ven

(34.0%; grade ≥3 SAEs 26.4%) compared with Clb+Ob (25.7%; grade ≥3 SAEs 21.0%). SAEs persisted at a similar frequency during both 3-month intervals for Ibr+Ven, while decreasing in frequency after the first 3-month treatment period for Clb+Ob. The addition of venetoclax to the Ibr+Ven treatment regimen indicated an increase in severe TEAEs compared with lead-in ibrutinib treatment (cycles 1-3 vs. cycles 4-6: 35.8% vs. 48.0%). The AE pattern over time during the first 6 months of treatment in study CLL3011 differed between both study arms, with incidence rates for any TEAE, SAEs and grade ≥3 SAEs persisting at a similar frequency with Ibr+Ven, while decreasing with Clb+Ob.

The most common TEAEs (≥20% of patients) in the Ibr+Ven arms were diarrhoea, neutropenia and nausea (reported in both studies); in study 1142, also arthralgia, headache, upper respiratory tract infection, fatigue, muscle spasms, increased tendency to bruise, and vomiting were reported in ≥20% of patients. The reported common TEAEs in the Ibr+Ven arms in both studies were generally consistent with the known safety profile for ibrutinib and/or venetoclax.

In study CLL3011, grade 3 or 4 TEAEs were reported at similar frequency (Ibr+Ven vs. Clb+Ob: 68.9% vs. 67.6%). The most common grade 3 or 4 TEAEs (≥5% of patients) in the Ibr+Ven arm for study CLL3011 were neutropenia, diarrhoea, neutrophil count decreased, hypertension, atrial fibrillation, pneumonia, hyponatremia and thrombocytopenia. In study 1142, grade 3 or 4 TEAEs (64.4%) were reported at a similar frequency as in the Ibr+Ven arm of study CLL3011. The most common grade 3 or 4 TEAEs were neutropenia (34.1%), and hypertension (6.8%).

Compared with the Clb+Ob arm, a higher frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm was noted for diarrhoea (10.4% vs. 1.0%), hyponatraemia (5.7% vs. 0%), hypertension (7.5% vs. 1.9%) and atrial fibrillation (6.6% vs. 0%). A lower frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for neutropenia (28.3% vs. 44.8%), thrombocytopenia (5.7% vs. 20.0%) and tumour lysis syndrome (0% vs. 5.7%).

Dyspepsia is identified as a new ADR based on a higher frequency with Ibr+Ven (9.4%) compared with Clb+Ob (2.9%) in study CLL3011 as well as a higher frequency with ibrutinib in pooled safety data.

SAEs

In study CLL3011, the frequency of SAEs was higher in the Ibr+Ven arm (46.2%) compared with the Clb+Ob arm (27.6%). The difference in incidence of SAEs was less pronounced over the first 6 months of treatment (34.0% vs. 26.7%).

The most common SAEs (≥2% of subjects) in the Ibr+Ven arm were atrial fibrillation, pneumonia, anaemia, cardiac failure and diarrhoea. The most common SAEs in the Clb+Ob arm were pneumonia, febrile neutropenia, infusion-related reaction and TLS. During the first 6 cycles of study CLL3011, the most common SAEs reported in both study arms (pneumonia, anaemia and diarrhoea) did not show a difference in incidence rate between study arms or a difference in trend over time. For atrial fibrillation SAEs reported with Ibr+Ven, incidence rates remained stable over time during the first 6 cycles.

SAEs in the Ibr+Ven arm in study 1142 were generally reported at a lower frequency compared with study CLL3011.

Deaths due to TEAEs

In study CLL3011, fatal TEAEs (death within 30 days of last dose) were reported for 7 patients (6.6%) in the Ibr+Ven arm vs. no patients in the Clb+Ob arm. Of the 7 deaths in the Ibr+Ven arm, 4 deaths occurred during ibrutinib lead-in therapy and 3 during ibrutinib and venetoclax combination therapy.

PTs were as follows: pneumonia, malignant neoplasm and cardiac arrest (1 patient each) and 1 patient with cardiac failure, pneumonia and sinus node dysfunction during ibrutinib lead-in; 1 case of

ischaemic stroke and 2 cases of sudden death during ibrutinib + venetoclax treatment. In both cases of sudden death reported during Ibr+Ven treatment, the data is not sufficient to assess if venetoclax might indirectly contribute to the fatal cardiac events.

In 4 of the 7 cases, the fatal events were cardiac in nature and assessed as possibly related to ibrutinib. Baseline factors in these 4 cases were as follows: age 63-80 years, CIRS score of 5-13, ECOG PS of 1 or 2 and cardiac risk factors (hypertension, hypercholesterolaemia, atrial fibrillation, myocardial ischaemia, myocardial infarction and diabetes mellitus).

In study 1142, sudden death was reported in 1 patient (0.3%) during ibrutinib lead-in. The cause of sudden death was due to cardiomegaly and coronary artery disease as per the autopsy report. Causality was assessed as possibly related to ibrutinib. This patient had baseline risk factors (hypertension, hyperlipidaemia and congenital heart disease (atrioventricular malformation)); ECOG performance status was 0.

In the cases of cardiac death, baseline factors were consistent with the baseline cardiac risk factors reasonably predicting severe, including fatal, cardiac events based on the results of predictive analyses based on logistic regression models. Based on these analyses, older age, male sex and ECOG PS of 2, in combination with baseline cardiac risk factors, were found to be reasonably predictive for fatal cardiac events. The risk minimisation measures on cardiac arrhythmias and cardiac failure in the SmPC do not fully capture the patient population at risk for cardiac death; sections 4.4 and 4.8 are updated.

AEs of clinical interest and other safety observations

Tumour lysis syndrome

In study CLL3011, tumour lysis syndrome TEAEs were reported in the Clb+Ob arm only (5.7%; all grade 3 or 4). In study 1142, 1 patient (0.3%) reported grade 3 or 4 TLS. In the Ibr+Ven arm in study CLL3011, 55.7% of patients were hospitalised for TLS prophylaxis after ibrutinib lead-in. Based on laboratory data, 4 patients met the Howard criteria for subclinical TLS.

TLS is an identified risk for both ibrutinib and venetoclax. Apart from the prophylactic measures to minimise the risk of TLS with venetoclax as described in the SmPC, a 3-cycle lead-in treatment with ibrutinib was introduced to reduce the risk of TLS based on high tumour burden before starting venetoclax treatment. The reporting of 1 case of TLS across the Ibr+Ven arms in both studies is considered as indirectly supporting the effectiveness of ibrutinib lead-in treatment to minimise the risk of TLS with combination therapy.

Cardiac arrhythmias

In study CLL3011, atrial fibrillation was reported more commonly in the Ibr+Ven arm (14.2%; grade 3-4: 6.6%) compared with the Clb+Ob arm (1.9%; grade 3-4: 0%). SAEs were reported in 6.6% of patients in the Ibr+Ven arm. Atrial fibrillation with Ibr+Ven was more commonly reported in study CLL3011 compared with study 1142 (5.9%; grade 3-4: 1.5%).

Ventricular tachyarrhythmia events were reported in 0.9% (grade 3-4: 0.6%) of patients in the Ibr+Ven cohort of study 1142.

In study CLL3011, cardiac arrhythmias, excluding atrial fibrillation and ventricular tachyarrhythmias, were reported at similar frequency in the Ibr+Ven arm (14.2%; grade 3-4: 2.8%) compared with the Clb+Ob arm (10.5%; grade 3-4: 1.9%). At PT level, palpitations was the most commonly reported cardiac arrhythmia in either study arm. Incidences of cardiac arrhythmias in study 1142 were generally consistent with those in the Ibr+Ven arm of study CLL3011. Fatal cardiac arrhythmias in the Ibr+Ven arms were reported in 4 patients (3.8%) in study CLL3011 and in 1 patient (0.3%) in study 1142. No fatal cardiac arrhythmias were reported in the Clb+Ob arm.

Cardiac failure events in study CLL3011 were reported in 5 patients (4.7%) in the Ibr+Ven arm vs. 1 patient (1.0%) in the Clb+Ob arm. Fatal cardiac failure was reported in 1 patient in the Ibr+Ven arm of study CLL3011.

It should be noted that a type II variation into the assessment of sudden death and cardiac death with ibrutinib is currently ongoing. The cases of cardiac arrhythmias and cardiac failure reported in the Ibr+Ven arms of studies CLL3011 and 1142 are consistent with the known safety profile of ibrutinib in terms of cardiotoxicity.

Ischaemic stroke

Ischaemic stroke was reported in the Ibr+Ven arms only (2.8% and 0.6% in studies CLL3011 and 1142, respectively). One event of fatal ischaemic stroke was reported in the Ibr+Ven arm of study CLL3011. The remaining events were grade 1 or 2.

Ischaemic stroke is an identified risk for ibrutinib; the reported events were consistent with the known safety profile of ibrutinib.

Other malignancies

The frequency of other malignancies was similar across both Ibr+Ven arms and the Clb+Ob arm. No trends or clustering was noted for the individual PTs.

With regard to the other AEs of special interest (haemorrhage, including major haemorrhage; hepatotoxicity, including hepatic failure; hypertension; infections, including viral reactivation) no new concerns were identified. The TEAEs reported for these safety topics were generally consistent with the established safety profiles for ibrutinib and/or venetoclax.

Discontinuation due to adverse events

In the Ibr+Ven arms of studies CLL3011 and 1142, 21 patients (19.8%) and 19 patients (5.9%) discontinued ibrutinib treatment.

Over the total treatment period, treatment discontinuations for either study drug were reported at a higher rate in the Ibr+Ven arm (20.8%) compared with the Clb+Ob arm (7.6%). TEAEs leading to treatment discontinuation were reported in 12.3% of patients for ibrutinib only, in 3.8% for venetoclax only and in 8.5% for both Ibr+Ven. Over the first 6 cycles, treatment discontinuations for either study drug was slightly higher for Ibr+Ven (12.3%) compared with Clb+Ob (7.6%). Treatment discontinuation rate across cycles 1-3 vs. cycles 4-6 was similar for the Ibr+Ven arm (6.6% vs. 6.1%) and decreased slightly in the Clb+Ob arm (5.7% vs. 2.0%). In study 1142, treatment discontinuations for either study drug were reported in 6.5% of patients over the total treatment period, with 3.7% discontinuing ibrutinib only, 0.6% venetoclax only and 2.2% both Ibr+Ven.

Dose reductions

In the Ibr+Ven arms of studies CLL3011 and 1142, dose reductions for ibrutinib were reported in 19 patients (17.9%) and 39 patients (12.1%), respectively. Over the total treatment period, treatment discontinuations for either study drug were reported at a higher rate in the Ibr+Ven arm (20.8%) compared with the Clb+Ob arm (7.6%). Over the first 6 cycles, treatment discontinuations for either study drug was slightly higher for Ibr+Ven (12.3%) compared with Clb+Ob (7.6%). Treatment discontinuation rate across cycles 1-3 vs. cycles 4-6 was similar for the Ibr+Ven arm (6.6% vs. 6.1%) and decreased slightly in the Clb+Ob arm (5.7% vs. 2.0%).

The first-line treatment of CLL patients with ibrutinib in combination with venetoclax in study CLL3011 indicates a more pronounced toxicity profile in terms of higher incidence rates of SAEs and fatal TEAEs in comparison with chlorambucil and obinutuzumab treatment. The TEAEs reported with

ibrutinib/venetoclax combination treatment were generally consistent with the known safety profile for either ibrutinib or venetoclax.

Comparison of the general safety profile for the ibrutinib/venetoclax arms across studies CLL3011 and 1142, indicated a similar incidence rate for grade 3 or 4 TEAEs and lower incidence rates for SAEs and fatal TEAEs in study 1142, possibly reflecting a younger and more fit patient population.

2.5.2. Conclusions on clinical safety

The safety profile of ibrutinib in combination with venetoclax in the first line treatment of CLL is largely consistent with the known safety profiles of ibrutinib and venetoclax. An update of sections 4.4 and 4.8 related to cardiac arrhythmias and cardiac failure is implemented in order to fully capture the patient population at risk for cardiac death.

Based on the safety data for study CLL3011 as well as pooled safety data, dyspepsia is identified as a new ADR.

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 18.4 is acceptable.

The CHMP endorsed the Risk Management Plan version 18.4 with the following content:

Safety concerns

Table 31: Summary of Safety Concerns

Important identified risks	Hemorrhage
	Hepatotoxicity (including hepatic failure)
	Atrial fibrillation
	Ventricular tachyarrhythmias
	Hypertension
	Ischemic stroke
	Cardiac failure
Important potential risks	Progressive multifocal leukoencephalopathy (PML)
	Infections (including viral reactivation)

	Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)
	Other malignancies (excluding non-melanoma skin cancer)
Missing information	Use in patients with severe cardiac disease

Pharmacovigilance plan

Table 32: 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				
Analysis of aggregate randomized controlled clinical trial data Planned	To further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs	Hemorrhage	Final report	3rd Quarter 2022
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	1st Quarter 2022

Risk minimisation measures

Table 33: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • Analysis of aggregate randomized controlled clinical trial data Final report: 3rd Quarter 2022

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatotoxicity (including hepatic failure)	**Routine risk minimization measures:** SmPC Section 4.4 SmPC Section 4.8 SmPC Section 4.9 PL Section 2 PL Section 4 Recommendations regarding assessment of liver function and viral hepatitis status prior to ibrutinib initiation and periodic monitoring for changes in liver function parameters during treatment are provided in SmPC Section 4.4 A recommendation for patients diagnosed with hepatic events regarding consultation of a liver disease expert for management is provided in SmPC Section 4.4 Warning for patients who have liver problems is provided in PL Section 2 Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Atrial fibrillation	**Routine risk minimization measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 A recommendation regarding further evaluation (e.g., ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 Recommendations regarding monitoring and 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Ventricular tachyarrhythmias	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • Recommendations regarding monitoring and 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Ischemic stroke	**Routine risk minimization measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4 Signs and symptoms of stroke are provided in PL Section 2 Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Cardiac failure	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (e.g., ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and symptoms of cardiac failure are provided in SmPC Section 4.4 • Warning for patients with a history of severe heart failure or with signs and symptoms of heart failure are provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire for PML **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	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 • Recommendations regarding preventive measures in patients who are at increased risk for opportunistic infections and for monitoring and management of infections are provided in SmPC Section 4.4 • A recommendation regarding viral load and serological testing for infectious hepatitis is 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:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 5.1 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (e.g., ECG, echocardiogram) for patients in whom there are cardiovascular concerns is 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None
Other malignancies (excluding non-melanoma skin cancer)	**Routine risk minimization measures:** Legal status: restricted medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Use in patients with severe cardiac disease	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (e.g., ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Recommendations regarding monitoring and 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

2.7. Update of the Product information

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

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.

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

Disease or condition

IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

3.1.1. Available therapies and unmet medical need

This application provides data for a new oral fixed duration (FD) combination of ibrutinib, a BCR inhibitor, and venetoclax, a BCL-2 inhibitor. An oral time-limited therapy associated with an acceptable safety profile and effective in a broad spectrum of patients including those with high-risk disease fulfils an unmet medical need, but only if supported by data proving at least no detriment on time to next treatment and overall survival; eventually essentially all patients will require new treatment.

3.1.2. Main clinical studies

Based on promising preclinical and early clinical data a cohort with FD ibrutinib + venetoclax (ibr+ven) was added through an amendment to the ongoing 1142 single-arm study - the randomized 3011 study. In the randomized 3011 study, this means that a SOC treatment (clb+obi; see below) of ~6 months duration is compared to an experimental regimen of ~14 months duration.

Study 3011

This was an open study randomizing previously untreated subjects older than 64 years or with comorbidities, excluding those with del17p/TP53 mutated disease, 1:1 between the experimental regimen and the approved chlorambucil + obinutuzumab (clb+olb) regimen. Stratification factors were IGHV and del11q status. The primary endpoint was PFS assessed by IRC, stratified test, with the following secondary endpoints tested hierarchically in the given order: MRD negativity rate in bone marrow by NGS, defined as the proportion of subjects who reached MRD negative disease status (<1

CLL cell per 10,000 leukocytes) on or prior to initiation of subsequent anti-leukemic therapy; CR; ORR; OS; rate of sustained platelet improvement; rate of sustained hemoglobin improvement; time to improvement in FACIT fatigue score. Ibrutinib was administrated for a total of 15 cycles (15x28=420 days, corresponding to approximately 14 months) and venetoclax was introduced after 3 cycles of ibrutinib monotherapy as an attempt to reduce frequency/severity of tumour lysis syndrome (TLS), and continued for 12 cycles.

The ITT analysis set consisted of 211 subjects, 106 in the experimental arm and 105 in the control arm. The primary analysis was event-driven, planned after 71 observed events, and based on a cut-off on 26 February 2021 with a median follow-up of ~28 months. An analysis with extended follow-up was also provided, cut-off 19 August 2021 with a median follow-up of ~34 months. With the response to the RSI, updates on OS, PFS, and DOR based on a 17 January 2022 cut-off were provided, covering a median time on study of 38.9 months.

Study 1142, FD cohort

This was a single-arm trial enrolling previously untreated subjects 18-70 years old with or without del17p/TP53 mutation, i.e., a more fit population compared to that enrolled in the 3011 study. The sample size/power calculation was based on assumptions in the non-del17p population and accordingly at least 125 subjects without this genetic aberration were to be recruited. The primary endpoint was CRR (CR/CRi) per investigator in the non-del17p population, testing ≤37% *vs* >37%.

The analysis set used for the primary analysis consisted of 159 subjects whereof 27 with del17p/TP53 mutation. The primary analysis was planned when the last enrolled subject had the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of posttreatment follow-up) and based on a data extract on 12 November 2020, with a median follow-up of ~28 months. An analysis with extended follow-up was also provided, cut-off 4 August 2021 with a median follow-up of ~39 months. With the response to the RSI, an analysis based on a 07 March 2022 cut-off was provided, covering a median time on study of 44.3 months.

3.2. Favourable effects

Study 3011

The experimental regimen was statistically superior over control in terms of PFS, HR=0.216 (95% CI: 0.131, 0.357); p<0.0001, at the primary analysis by IRC, with an event rate of 64% for the control arm. This is supported by presented alternative analyses, and a generally consistent treatment effect across predefined subgroups. By an additional follow-up of 6 months, the outcome remains stable. With the response to the RSI, an analysis with a median of 39 months on study was provided, showing a HR of 0.188 (0.116, 0.307).

With sample rates of 87% in the experimental arm and 80% in the control arm, the primary analysis of best MRD response in bone marrow (BM) assessed by NGS showed a response rate of 55.7% in the experimental arm and 21.0% in the control arm, rate ratio 2.65 (95% CI: 1.75, 3.99); p<0.0001.

At 3 months post-treatment, the MRD negativity rates in the experimental arm *vs* the control arm were 52% *vs* 17% in BM (sample rates 80% *vs* 77%) and 55% *vs* 39% in peripheral blood (PB) (sample rates 83% *vs* 84%), respectively. At 12 months post treatment, corresponding to 26 months after randomisation, and with a sampling rate of 77%, the MRD negativity rate in PB was 49% in the experimental arm, therefore significantly more subjects in the experimental arm reached MRD negativity in BM than subjects in the control arm.

With extended follow up, the 30-month landmark estimate for IRC-assessed DOR was 86.7% in the experimental arm and 35.5% in the control arm. With ~34 months median follow-up for the 3011 study (6 additional months compared to the inferential analysis): stable PFS (event rate 65% in the control arm, 20% in the experimental arm) with a 24-month landmark of 85% for the experimental arm *vs* 46% in the control arm, MRD negativity rate of 49% in PB in the experimental arm at 26 months after randomisation (reasonably stable compared to 3 months post-treatment, 55%), the 18-month landmark estimate for duration of IRC-assessed CRR was 98% in the experimental arm and 85% in the control arm, the 30-month landmark estimate for IRC-assessed DOR was 87% in the experimental arm and 36% in the control arm, and the HR point estimate for time to next treatment was 0.147.
At the 17 January 2022 cut-off and an event rate of 70% in the control arm and 21% in the experimental arm, the HR for PFS was 0.188 (95% CI: 0.116, 0.307). The median DOR was still not reached in the experimental arm and was 21.6 months in the control arm. The 30-month DOR rates were 86.5% in the experimental arm and 39.1% in the control arm.

Regarding OS, at the primary analysis, 11 (10.4%) death events were observed in the experimental arm and 12 (11.4%) in the control arm; HR=1.048 (95% CI: 0.454, 2.419). Based on the data cut-off of 17 January 2022 with a median time on study of 39 months and a maturity of 21% in the control arm and 11% in the experimental arm, the HR for OS was estimated at 0.582 (95% CI: 0.286, 1.187). Thus, with 5 months further follow-up after the August 2021 cut-off, no longer-term detrimental effect on OS is noted.

Regarding time to next treatment, at the primary analysis, 4 subjects in the experimental arm and 27 in the control arm had received subsequent anticancer therapy; median not reached in any arm, HR 0.143 (95% CI: 0.050, 0.410). With extended follow-up, 6 subjects in the experimental arm and 35 in the control arm had received subsequent anticancer therapy; median not reached in any arm, HR 0.147 (95% CI: 0.062, 0.350). In the experimental arm, 2/6 subjects received a BTK inhibitor. In the control arm, 28 and 4 subjects received a BTK inhibitor and venetoclax, respectively.

Regarding TLS risk reduction, after 3 months lead-in treatment with ibrutinib monotherapy, baseline TLS risk "high" based on high tumour burden was reduced to medium or low risk in 22/26 (85%) subjects, and of the 69 subjects in the experimental arm that had an indication for hospitalization, hospitalization was no longer indicated for 24 (35%) of these subjects.

Study 1142, FD cohort

At the primary analysis, the CRR per investigator for all subjects was 55.3% (95% CI: 47.6, 63.1) and 55.9% (95% CI: 47.5, 64.2) for subjects without del 17p. The CR rate for subjects without del 17p was significantly higher than the study-assumed minimum rate of 37% (1-sided p-value < 0.0001) as well as the 40% rate achieved in this population with FCR. CRR in del 17p/TP53 mutated disease (n=27) was similar to the complement, 56%. With extended follow-up, CRR was 58% per investigator and 64% per IRC in the non-del17 population. At the primary analysis and with extended follow-up, the durable complete response rate (1 year, corresponding to 12 cycles) in the non-del17 population was 48.5% and 53.7%, respectively. In del 17p/TP53 mutated disease the durable complete response rate was 48.1% [95% CI: 29.3, 67.0]; no changes were observed with extended follow-up.

At the primary analysis, the ORR per investigator assessment as well as IRC was 96.2% for all subjects and 95.6% for subjects without del 17p. For subjects with del 17p/TP53 mutated disease, the ORR was 96.3%. No change in ORR per investigator assessment was observed after extended follow-up.

At the primary analysis, the median DOR per investigator assessment were not reached for all subjects or for subjects without del 17p; the 24-month landmark estimates were 94.7% for all subjects and 96.1% for subjects without del 17p based on an overall median follow-up of 27.9 months.

With extended follow-up, similar outcomes in DOR were observed for all subjects and subjects without del 17p (median not reached for both populations; 30-month landmark estimates of 88.6% and 89.8%, respectively). At the primary analysis, the 24-month landmark estimate for DOR was 84% for the del17p/TP53 population; at a median follow-up of 44 months, the 30-month landmark estimate was 80%. For contextualisation, the corresponding figures for the non-del17p/TP53 mutated population were 96% and 90%, respectively.

With ~39 months median follow-up for the 1142 study (9 additional months compared to the inferential analysis): CRR of 58% per investigator and 64% per IRC in the non-del17p population, a durable CRR (1 year, corresponding to 12 cycles) of 54% in the non-del17p population, 30-month landmark estimate for DOR of 89% in the all-treated population, and a MRD negativity rate in PB 12 months post-treatment of 43% in an analysis associated with uncertainties. CRR in del 17p/TP53 mutated disease (n=27) was roughly similar to the complement, 56%, per investigator assessment and durable complete response was 48.1% [95% CI: 29.3, 67.0].

At the primary analysis, with MRD assessed by flow cytometry in the all-treated population, the overall negativity rate was 60% in BM and 77% in PB, and the corresponding figures 52% and 57% for MRD negativity rate 3 months post-treatment. The outcomes were similar at extended follow-up. At the time of the planned analysis 12 months post-treatment (PB only), 39 subjects (roughly 25%) were non-evaluable and therefore the outcome is deemed non-robust. With extended follow-up, only 9 subjects remained non-evaluable, and here the MRD negativity was 43% in the all-treated population. This outcome is, however, also subject to uncertainties as samples may have been collected at later time points. With that, the outcome may be conservative. The overall MRD negativity rate in PB in the del17p/TP53 population was 82% at the primary analysis, 59% at 3 months post-treatment, and 37% at 12 months post-treatment. The corresponding figures for BM were 41%, 41% and not applicable. For contextualisation, the corresponding figures for the non-del17p/TP53 population were: PB: 76%, 57%, and 35%; BM: 62%, 54% and not applicable.

Regarding OS, the K-M point estimates at 24 months were 98.1% for all subjects and 97.7% for non-del 17p subjects. For subjects with del 17p/TP53 mutated disease, the K-M point estimate at 24 months was 96.2%.

Time to next treatment was not analysed. At the primary analysis, 4 subjects (2.5%) had reintroduced ibrutinib post-PD; 5 subjects had received other therapy (mainly systemic therapy). With extended follow-up, an additional 5 subjects had reintroduced ibrutinib post-PD relative to the primary analysis; 6 subjects had received other therapy (mainly systemic therapy).

3.3. Uncertainties and limitations about favourable effects

With current follow-up times, median ~39 months in the 3011 study and ~44 months in the FD cohort of the 1142 study, the most important uncertainties relate to persistence of treatment effect with the experimental regimen, not least in subjects with adverse prognostic factors such as del17p/TP53 mutated disease. Here, also data on PFS2 would be of principal interest, especially as treatment regimens with different duration were compared in the randomised study. Further and robust follow-up is needed.

Data on OS is currently immature which is expected in a 1st line setting in CLL and further follow-up is needed. Data on del17p/TP53 mutated disease is scarce with the entire dataset consisting of only 27 subjects in the 1142 SAT.

Further follow-up on survival and persistence of response will be submitted as post authorisation commitments.

For study CLL3011, the MAH proposes yearly updates on survival and efficacy until study completion, 2024 or after 50% of the subjects have died, whichever comes first. The first such data cut will be scheduled in February 2023 with the report to be provided by August 2023.

For Study 1142, the study completion date is currently anticipated in 2023 with approximately 5 and 7 years of follow-up for the FD and MRD cohorts, respectively. Updates based on a February 2023 cutoff will be provided. A final CSR will also be submitted based on the later study completion date.

3.4. Unfavourable effects

Study CLL3011

Patient characteristics were balanced in both arms of study CLL3011. In the Ibr+Ven arm in study CLL3011, median age was 71 years (range 47-93 years) with 84.9% of patients ≥65 years of age; 54.7% of patients had an ECOG performance status of 1 and 12.3% with ECOG 2. The frequency of patients with any TEAE (Ibr+Ven vs. Clb+Ob: 99.1% vs. 94.3%) and any grade ≥3 TEAE (Ibr+Ven vs. Clb+Ob: 75.5% vs. 69.5%) was similar between treatment arms. Higher frequencies (Ibr+Ven vs. Clb+Ob) were noted for SAEs (46.2% vs. 27.6%; grade ≥3: 38.7% vs. 21.9%) and fatal TEAEs leading to death within 30 days of last dose (6.6% vs. 0).

A higher frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for diarrhoea (10.4% vs. 1.0%), hyponatraemia (5.7% vs. 0%), hypertension (7.5% vs. 1.9%) and atrial fibrillation (6.6% vs. 0%). A lower frequency in grade 3 or 4 TEAEs (>5% difference) in the Ibr+Ven arm vs. the Clb+Ob arm was noted for neutropenia (28.3% vs. 44.8%), thrombocytopenia (5.7% vs. 20.0%) and tumour lysis syndrome (0% vs. 5.7%).

The frequency of SAEs was higher in the Ibr+Ven arm (46.2%) compared with the Clb+Ob arm (27.6%). The most common SAEs (≥2% of subjects) in the Ibr+Ven arm were atrial fibrillation, pneumonia, anaemia, cardiac failure, and diarrhoea. The most common SAEs in the Clb+Ob arm were pneumonia, febrile neutropenia, infusion-related reaction, and TLS.

Fatal TEAEs (death within 30 days of last dose) were reported for 7 patients (6.6%) in the Ibr+Ven arm vs. no patients in the Clb+Ob arm. Of the 7 deaths in the Ibr+Ven arm, 4 deaths occurred during ibrutinib lead-in therapy and 3 during ibrutinib and venetoclax combination therapy. For the deaths reported during ibrutinib lead-in, the following PTs were reported: pneumonia, malignant neoplasm, and cardiac arrest (1 patient each) and 1 patient with cardiac failure, pneumonia, and sinus node dysfunction. During ibrutinib + venetoclax treatment, 3 deaths were reported with the following PTs: 1 case of ischaemic stroke and 2 cases of sudden death. In 4 of 7 patients, death was cardiac in nature and the fatal events were assessed as possibly related to ibrutinib. Baseline factors in these 4 cases were as follows: age 63-80 years, CIRS score of 5-13, ECOG PS of 1 or 2 and cardiac risk factors (hypertension, hypercholesterolaemia, atrial fibrillation, myocardial ischaemia, myocardial infarction, and diabetes mellitus).

Tumour lysis syndrome TEAEs were reported in the Clb+Ob arm only (5.7%; all grade 3 or 4). In the Ibr+Ven arm in study CLL3011, 55.7% of patients were hospitalised for TLS prophylaxis after ibrutinib lead-in. Based on laboratory data, 4 patients met the Howard criteria for subclinical TLS.

Dyspepsia is identified as a new ADR based on a higher frequency with Ibr+Ven (9.4%) compared with Clb+Ob (2.9%) in study CLL3011 as well as a higher frequency with ibrutinib in pooled safety data.

Treatment discontinuations for either study drug were reported at a higher rate in the Ibr+Ven arm (20.8%) compared with the Clb+Ob arm (7.6%). TEAEs leading to treatment discontinuation were

reported in 12.3% of patients for ibrutinib only, in 3.8% for venetoclax only and in 8.5% for both Ibr+Ven.

Study 1142

Median age was 59 years (range 28-71 years) with 26.6% of patients ≥65 years of age; 66.6% had ECOG 0; no patients with ECOG 2 were included in the study. Lower frequencies were noted for grade ≥3 TEAE (64.7%), SAEs (21.7%; grade ≥3: 18.3%) and fatal TEAEs (0.3%) compared with the Ibr+Ven arm of study CLL3011. The fatal event was reported as sudden death in 1 patient (0.3%) during ibrutinib lead-in. The sudden death in this patient was due to cardiac related events; the patient had an ECOG PS of 0 and baseline cardiac risk factors. Causality was assessed as possibly related to ibrutinib. Grade 3 or 4 TLS was reported in 1 patient (0.3%).

Treatment discontinuations for either study drug were reported in 6.5% of patients over the total treatment period, with 3.7% discontinuing ibrutinib only, 0.6% venetoclax only and 2.2% both Ibr+Ven

3.5. Uncertainties and limitations about unfavourable effects

The sample size in the CLL3011 study is relatively small. There is a trend to an increase in treatment associated deaths; however, uncertainty of the magnitude of any difference is large.

The precise impact of each agent in the combination on the safety profile cannot be ascertained in the absence of single agent treatment arms. Given the few cases of fatal cardiac death during ibrutinib/venetoclax combination treatment, there is uncertainty regarding a potential indirect role of venetoclax. The effect of increased exposure of venetoclax on the safety profile of venetoclax when given in combination with ibrutinib cannot be assessed.

3.6. Effects Table

Table 2. Effects Table for study CLL3011 (data cut-off: 26 Feb 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by IRC		HR (95% CI)	0.216 (0.131, 0.357), p<0.0001 Median exp not reached, 21 months in ctrl		Event rate 21% in exp, 64% in ctrl	
	24-months landmark estimate	%	84.4	44.1		
MRD negativity rate in BM by NGS	Overall	%	55.7 RR 2.65 (1.75, 3.99), p<0.0001	21.0	Sampling rate 87% in exp, 80% in ctrl	
	3 months post treatment	%	51.9	17.1	Sampling rate 80% in exp, 77% in ctrl	
CR/CRi rate		%	38.7 RR 3.43 (1.91, 6.15) p<0.0001	11.4		
ORR		%	86.8	84.8	Not statistically	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			RR 1.02 (0.92, 1.14) p<0.6991		significant	
OS	Inferential analysis	HR (95% CI)	1.048 (0.454, 2.419)		Event rate 10.4% in exp, 11.4% in ctrl	
	Extended FU		0.760 (0.352, 1.642)		Median FU 34 months (4 more events in ctrl)	

Table 3. Effects Table for study 1142 FD cohort (data cut-off: 12 Nov 2020)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CR/CRi rate, investigator	Non-del17p (n=136)	%	55.9 (95% CI: 47.5, 64.2)			
	del17p (n=27)	%	55.6			
Durable CRR (1 year)	Non-del17p	%	48.5 (95% CI: 40.1, 56.9)			
	All subjects	%	49.1 (95% CI: 41.3, 56.8)			
MRD negativity in BM, overall	All subjects	%	59.7		Flow cytometry	
MRD negativity in PB, overall	All subjects	%	76.7			
MRD negativity in BM, 3 months post-treatment	All subjects	%	52.2			
MRD negativity in PB, 3 months post-treatment	All subjects	%	56.6			
ORR	Non-del17p	%	95.6			
	del17p	%	96.3			
DOR: 24-months landmark estimate	Non-del17p	%	96.1		Median not reached	
	All subjects	%	94.7			
OS: 24-months landmark estimate	Non-del17p	%	97.7		Median not reached	
	del17p	%	96.2			

Table 4. Effects Table for studies CLL3011 (data cut-off: 26 Feb 2021) and 1142 FD cohort (data cut-off: 12 Nov 2020)

Effect	Short description	Unit	Treatment Ibr+Ven		Control Clb+Ob		Uncertainties / Strength of evidence	References
Unfavourable Effects								
			Any grade	Grade 3-4	Any grade	Grade 3-4		
AE Summary	AEs	%	99.1	NA	94.3	NA	Median treatment duration: Ibr+Ven 13.8 mon; Clb+Ob 5.1 mon	CLL3011
	Grade 3-5 AEs	%	75.5	NA	69.5	NA		
	SAEs	%	46.2	NA	27.6	NA		
	Death due to AE	%	6.6	NA	1.9	NA		
	Discontinuation of either drug due to AE	%	20.8	NA	7.6	NA		
	Discontinuation of Ibr only due to AE	%	12.3	NA	NA	NA		
	AEs	%	99.7					1142
	Grade 3-5	%	64.7					
	SAEs	%	21.7					
	Death due to AE	%	0.3					
	Discontinuation of either drug due to AE	%	6.5	NA	NA	NA		
	Discontinuation of Ibr only due to AE	%	3.7	NA	NA	NA		
AEOSI	Haemorrhage	%	34.9	3.8	7.6	1.0		CLL3011
	Tumour lysis syndrome	%	0	0	5.7	5.7		
	Hepatotoxicity	%	6.6	3.8	3.8	1.0		
	Atrial fibrillation	%	14.2	6.6	1.9	0		
	Ventricular tachyarrhythmias	%	0	0	0	0		
	Other cardiac arrhythmias	%	14.2	2.8	10.5	1.9		
	Cardiac failure	%	4.7	2.8	1.0	1.0		
	Hypertension	%	14.2	8.5	4.8	1.9		
	Ischaemic stroke	%	2.8	0	0	0		
	Infections	%	60.4	15.1	48.6	10.5		
	Other malignancies	%	7.5	NA	9.5	NA		
AEOSI	Haemorrhage	%	60.7	0.9				1142
	Tumour lysis syndrome	%	0.3	0.3				
	Hepatotoxicity	%	4.3	1.9				

	Atrial fibrillation	%	5.9	1.5				
	Ventricular tachyarrhythmias	%	0.9	0.6				
	Other cardiac arrhythmias	%	17.3	2.2				
	Cardiac failure	%	0.3	0.3				
	Hypertension	%	16.4	7.1				
	Ischaemic stroke	%	0.6	0				
	Infections	%	69.7	8.4				
	Other malignancies	%	5.6	NA				

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the randomised 3011 study, enrolling previously untreated subjects older than 64 years or with comorbidities, excluding those with del17p/TP53 mutated disease, the experimental regimen was significantly and robustly superior to clb+obi in terms of PFS, with a HR point estimate of 0.216. This outcome is supported by significantly higher best MRD response in BM and CRR in the experimental arm. With a median time on study of ~39 months, no detrimental effect on OS was noted. A high CRR in study 1142 of 56% was noted, independently of del17p, supported by an ORR of 96% and overall MRD negativity rates of 60% in BM and 77% in PB. Persistence of effect is supported by the long term outcomes (see section 3.4). Data investigating the ibr+ven regimen in fit patients is derived in the 1142 SAT and compatible with a highly efficient treatment regimen in terms of activity and a high fraction of durable complete responses.

From a safety perspective, the imbalance in fatal events in study CLL3011 is mainly driven by cardiac related deaths in 4 patients. The 4 cardiac deaths reported in the Ibr+Ven arm of study CLL3011 as well as the death in study 1142 were assessed as possibly related to ibrutinib and occurred in patients with baseline risk factors. The baseline factors identified in these patients were consistent with the baseline cardiac risk factors reasonably predicting severe, including fatal, cardiac events based on the results of predictive analyses based on logistic regression models. Based on these analyses, older age, male sex and ECOG PS of 2, in combination with baseline cardiac risk factors, were found to be reasonably predictive for fatal cardiac events.

It is acknowledged that with further follow-up of the 3011 study (median 39 months), a HR of 0.582 (95% CI: 0.286, 1.187) was estimated; thus, no longer-term detrimental effect on OS is noted.

The oral, ven+ibr treatment intended for a limited treatment duration, further provides convenience and the possibility of a drug holiday, and will be important as one of several reasonable treatment options for 1L CLL patients who are sufficiently fit for its use.

3.7.2. Balance of benefits and risks

3.7.3. Additional considerations on the benefit-risk balance

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the MAH applied for an additional one year marketing protection period in the framework of this extension of indication. The request was based on the MAH's position that Imbruvica represents a significant clinical benefit in

Ibrutinib plus Venetoclax Fixed Duration Combination Treatment of Adult Patients with Previously Untreated Chronic Lymphocytic Leukemia in comparison with existing therapies.

The CHMP accepted the argument in support of the use of all oral, ven+ibr for a limited treatment duration, providing the possibility of a drug holiday, is one of several reasonable treatment options for 1L CLL patients. Further, the MAH has shown that landmark estimate 24-month PFS and OS, CR and MRD rates, as well as rates of hematological toxicity are at least comparable or better than available alternatives. It was pointed out that each of the available options have specific pro's in form of convenience, and cons in terms of qualitative side effects profiles, that make different regimens best fit for different patients. There is no one size fits all in 1L CLL treatment. It is recognised that the side effect profile of ven+ibr is less favourable than some less effective treatment regimens; however, it is well characterised and manageable. In patients who are sufficiently fit for its use, and who wish for the possibility of a treatment holiday, ven+ibr would be an appropriate treatment option. It can be concluded that overall the B/R of time-limited ven+ibr is not worse than for available treatment alternatives.

In conclusion, significant clinical benefit over available options, has been demonstrated either through being an all-oral option or by allowing for a treatment holiday based on a fixed duration of treatment.

3.8. Conclusions

The overall B/R of imbruvica in combination with venetoclax in the first line 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 approved one	Type II	I and IIIB

Extension of the existing CLL indication to include combination treatment with venetoclax for previously untreated patients based on efficacy and safety data from phase 3 study GLOW and phase 2 study CAPTIVATE; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. The package leaflet is updated accordingly. The RMP was amended as version 19.3 in line with the extension of indication.

The variation leads to amendments to the Summary of Product Characteristics 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 and IIIB and to the Risk

Management Plan are recommended.

Similarity with authorised orphan medicinal products

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

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

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-0070'