21 July 2016
EMA/623036/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0017/G

Marketing authorisation holder (MAH): Janssen-Cilag International NV

Note

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

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List of abbreviations

B-cells	B lymphocytes
BCR	B-cell antigen receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CSR	clinical study report
CV	coefficient of variation
Cys	cysteine residue
del(11q)	deletion of the long arm of chromosome 11
del(17p)	deletion of the short arm of chromosome 17
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EU	European Union
FCR	fludarbarine + cyclophosphamide + rituximab
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
Ig	immunoglobulin
INR	international normalized ratio
IRC	independent review committee
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	mantle cell lymphoma international prognostic index
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not estimable (not evaluated)
NF-κB	nuclear factor kappa beta
NHL	non-Hodgkin lymphoma
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
P-gp	p-glycoprotein
PLCγ (or PLCγ2)	phospholipase-Cγ2
PR	partial response
QTcB	QT interval corrected for heart rate using Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
SAE	serious adverse event(s)
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SCT	stem cell transplantation
SLL	small lymphocytic lymphoma
TEAE	treatment-emergent adverse event
WM	Waldenstrom's Macroblobulinaemia

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 13 November 2015 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
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Update of sections 4.8 and 5.1 of the SmPC in order update the safety and efficacy information following conclusion of studies MCL 3001 and CLL 3001. Update of Annex II to remove the obligation to submit final CSR of study MCL 3001. The Package Leaflet and RMP are updated accordingly. In addition, the Marketing authorisation holder (MAH) introduced minor editorial changes throughout the PI.

Submission of final CSRs for studies MCL 2001 and 1117 in fulfilment of post-authorisation measures; in addition to the above trials, data from 2 other trials are included in support of the use of ibrutinib in combination with other agents in patients with relapsed/refractory CLL.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the Risk Management Plan (RMP).

On 26 April 2012, Imbruvica was designated as an orphan medicinal product EU/3/12/984. Imbruvica was designated as an orphan medicinal product in the following indication: for the treatment of chronic lymphocytic leukaemia.

Following the assessment of the data presented in this variation, the CHMP adopted a new indication and a revision of the existing indications, which falls within the above mentioned orphan designations.

Information on paediatric requirements

Chronic lymphocytic leukaemia is covered by a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the Marketing Authorisation Holder submitted during the procedure a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	13 November 2015
Start of procedure:	28 November 2015
CHMP Rapporteur Assessment Report	2 February 2016
PRAC Rapporteur Assessment Report	3 February 2016
PRAC members comments	4 February 2016
Updated PRAC Rapporteur Assessment Report	18 February 2016
PRAC Outcome	11 February 2016
CHMP members comments	N/A
Request for supplementary information (RSI)	25 February 2016
CHMP Rapporteur Assessment Report	30 May 2016
2nd Request for supplementary information (RSI)	23 June 2016
CHMP Rapporteur Assessment Report	6 July 2016
Opinion	21 July 2016
The CHMP adopted a report on similarity of Imbruvica with Arzerra and Gazyvaro on 21 July 2016 (Appendix 1)	21 July 2016

2. Scientific discussion

2.1. Introduction

Ibrutinib is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK). It is authorized in the EU for the treatment of adult patients with:

- relapsed or refractory MCL based on the Phase 2, open-label, monotherapy study with ibrutinib 560 mg/day (Study 1104) ;

- CLL who have received at least 1 prior therapy, and as a single agent for the treatment of adult patients with previously untreated CLL, - based on the Phase 3, open-label, randomized monotherapy study in which subjects received either ibrutinib 420 mg/day or ofatumumab (Study 1112) and on the Phase 3 open-label randomized monotherapy study in which previously untreated subjects received either ibrutinib or chlorambucil.
- WM who have received at least 1 prior therapy or in first-line treatment for patients unsuitable for chemoimmunotherapy - based on the Phase 2, open-label, monotherapy study with ibrutinib 420 mg/day (Study 1118E).

The Applicant has been requested to provide the final clinical study reports (CSR) for Studies; PCI-32765MCL3001 (MCL3001), PCI-32765MCL2001 (MCL2001), PCYC-1117-CA (1117) and PCI-32765CLL3001 (CLL3001); These additional studies were performed in adult patients with relapsed or refractory MCL and CLL, in order to fulfil post authorisation measures and Annex II obligations.

Studies in this application include the first randomized Phase 3 study of ibrutinib monotherapy in subjects with relapsed or refractory MCL (Study MCL3001) and the first randomized Phase 3 study of ibrutinib in combination with chemoimmunotherapy in subjects with relapsed or refractory CLL (Study CLL3001). Phase 2 studies in subjects with relapsed or refractory MCL (Study MCL2001) and relapsed or refractory CLL with del17p (Study 1117) are also included in this submission. In addition, data from 2 studies supportive of the use of ibrutinib combination therapy are also presented (Studies 1108 and 1109).

Based on the results of these studies changes have been proposed to the SmPC and Package Leaflet. In Annex II, the PCI-32765MCL3001 study has been deleted from the list of post-authorisation obligations. In addition the Applicant has taken the opportunity to make minor editorial amendments to the SmPC. The revised RMP version 5.1 has been included in the submission.

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 applicant.

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

- Tabular overview of clinical studies

Table 1: Description of Studies in This Submission

Study	Design	Treatment	N	Data Presented	Status
Studies Fulfilling Post-Authorization Measures					
Study MCL3001	Phase 3, randomized, controlled, open-label, multicenter study to evaluate the efficacy and safety of ibrutinib vs. temsirolimus in previously treated subjects (≥1 RTX-containing chemotherapy)	Ibrutinib capsule: 560 mg daily continuously. Temsirolimus: 175 mg IV on Days 1, 8, 15 of Cycle 1, followed by 75 mg IV on Days 1, 8, 15 of each subsequent 21-day cycle until PD or unacceptable toxicity	Randomized: 280 Ibrutinib: 139 Temsirolimus: 141 Treated: 278 Ibrutinib: 139 Temsirolimus: 139	Efficacy, Safety	Primary CSR completed CCO: 22Apr2015 CSR: 11Sep2015
Study CLL3001	Phase 3, randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of ibrutinib in combination with BR vs. BR alone in previously treated subjects with CLL/SLL.	Placebo capsules, daily continuously or ibrutinib capsules: 420 mg daily continuously; Background therapy: bendamustine HCl 70 mg/m^2 30 min IV infusion on Cycle 1, Days 2 and 3, and Cycles 2 to 6, Days 1 and 2 for up to 6 cycles; rituximab: 375 mg/m^2 IV in Cycle 1, Day 1, and 500 mg/m^2 IV in Cycles 2 through 6, Day 1, until PD or unacceptable toxicity.	Randomized: 578 Ibrutinib+BR: 289 Placebo+BR: 289 Treated: 574 Ibrutinib+BR: 287 Placebo+BR: 287	Efficacy, Safety	Primary CSR completed CCO: 12Jan2015 CSR: 27Jul2015
Study MCL2001	Phase 2, multicenter, single-arm study to evaluate efficacy and safety in subjects with ≥1 RTX-containing prior treatments and PD after ≥2 cycles of bortezomib in previously treated subjects with MCL	Ibrutinib capsule (oral): 560 mg daily continuously; 21-day treatment cycle; until PD (or relapse if the subject achieved a CR) or unacceptable toxicity	Enrolled and treated: Ibrutinib: 120	Efficacy, Safety	Completed CCO: 29Apr2014 CSR: 09Oct2014
Study 1117	Phase 2, open-label, single-arm, multicenter study to evaluate safety and efficacy in previously treated CLL/SLL with del 17p	Ibrutinib capsule (oral): 420 mg daily; until PD or unacceptable toxicity	Enrolled: Ibrutinib: 145 Treated: Ibrutinib: 144	Efficacy, Safety	Completed CCO: 20Jun2014 CSR: 07Apr2015
Studies Contributing Supportive Safety and Efficacy Data					
Study 1108	Phase 1b, multicenter, open-label, parallel-group safety study of ibrutinib in combination with chemotherapy in subjects with CLL/SLL	Ibrutinib capsule: 420 mg daily (28-day cycle) until PD or unacceptable toxicity; BR: administered IV for maximum 6 cycles until Grade 4 hematologic toxicity or clinically significant Grade ≥3 toxicity, PD, or CR; FCR[b]: administered IV for maximum 6 cycles or unacceptable toxicity, PD, or CR	Enrolled and treated: 33 Ibrutinib+BR: 30[a] Ibrutinib+FCR: 3	Efficacy, Safety	Completed CCO: 12Nov2012 CSR: 20Oct2013
Study 1109	Phase 1b/2 open-label, sequential-group, nonrandomized study to evaluate the safety and efficacy of 3 schedules of ibrutinib in combination with ofatumumab in previously treated CLL/SLL and PLL	Ibrutinib capsule: 420 mg daily: 1) 1 cycle before ofatumumab begins; 2) concomitantly with ofatumumab; and 3) added at the start of Cycle 3. Ibrutinib continued until PD or unacceptable toxicity. Ofatumumab IV dosing schedule: Day 1: 300 mg; Weeks 2 to 8: 2,000 mg once weekly; thereafter, 2,000 mg once/month for 4 months	Enrolled and treated: Ibrutinib+Ofa: 71	Efficacy, Safety	Completed CCO: 28May2013 CSR: 02Jul2014
Previously Submitted Studies Contributing Comparative Efficacy or Safety Data[b]					
Study 1104	Phase 2, open-label, nonrandomized, multicenter study to evaluate efficacy and safety in previously treated subjects with MCL	Ibrutinib capsule (oral): 560 mg daily (28-day cycle); as long as there is clinical benefit and no unacceptable toxicity	Enrolled: Ibrutinib: 115 Treated: Ibrutinib: 111	Efficacy, Safety	Completed CCO: 26Dec2012 CSR: 22May2013
Study 1112	Phase 3, randomized, multicenter, open-label study to evaluate the efficacy and safety of ibrutinib vs. ofatumumab in previously treated CLL/SLL	Ibrutinib capsule: 420 mg daily until PD or unacceptable toxicity Ofatumumab: 12 doses total, Week 1: 300 mg IV once; Weeks 2 to 8: 2,000 mg IV weekly; Weeks 12 to 24: 2,000 mg IV (every 4 weeks)	Randomized: 391 Ibrutinib: 195 Ofatumumab: 196 Treated: 386 Ibrutinib: 195 Ofatumumab: 191	Efficacy, Safety	Primary CSR completed CCO: 06Nov2013 CSR: 25Mar2014
Study 1102	Phase 1b/2, open-label, nonrandomized, multicenter study to determine the safety of 2 fixed-doses of ibrutinib in treatment-naïve (≥65 yrs) or previously treated (≥18 yrs).	Ibrutinib capsule: 420 mg or 840 mg once daily until PD, withdrawal of consent, unacceptable toxicity, death, lost to follow-up, or study termination.	Enrolled: 133 Treated: 132[c]	Safety	Completed CCO: 18Sep2012 CSR: 4Sep2013
Study 1118E	Phase 2, open-label, single-arm study to evaluate the efficacy and safety of ibrutinib monotherapy in subjects with previously treated WM.	Ibrutinib capsules (oral) 420 mg daily until PD	Enrolled and treated: 63	Safety	Completed CCO: 28Feb2014 CSR: 29Sep2014
Study Contributing Adverse Drug Reaction Data					
Study 1115	Phase 3, randomized, multicenter, open-label, comparator-controlled study in subjects with treatment-naive CLL/SLL who are 65 years or older	Ibrutinib capsules: 420 mg/day Chlorambucil: 0.5 mg/kg (could be increased in 0.1 mg/kg increments up to 0.8 mg/kg if well-tolerated)	Randomized: 269 Ibrutinib: 136 Chlorambucil: 133 Treated: 267 Ibrutinib: 135 Chlorambucil: 132	Adverse Drug Reactions	Completed CCO: 28May2015 CSR: 4Aug2015

BR=bendamustine and rituximab; BTK=Bruton's tyrosine kinase; CCO=clinical cutoff; CLL=chronic lymphocytic leukemia; CR=complete response; CSR=clinical study report; del 17p=deletion in the short arm of chromosome 17; FCR=fludarabine, cyclophosphamide, and rituximab; IV=intravenous; MCL=mantle cell lymphoma; Ofa=ofatumumab; PD=progressive disease; PFS=progression-free survival; PLL=prolymphocytic leukemia; RTX=rituximab; SLL=small lymphocytic lymphoma

[a] Efficacy and safety analyses for Study 1108 present the ibrutinib+BR subjects only.

[b] Studies 1102, 1104, 1112, and 1118E are part of the current dossier and form the basis for the current approved product.

[c] Safety analyses and the current monotherapy label pool include 51 subjects in Study 1102 with relapsed or refractory CLL treated with 420 mg/day ibrutinib.

2.3.2. Pharmacokinetics

The previously available population pharmacokinetic model (included in original MAA) was updated with data from the studies included in this submission. The updated population pharmacokinetic analysis was submitted through a separate procedure (variation II/20).

Systemic exposure data, collected using a sparse sampling scheme in all studies included in this submission, showed substantial overlap of observed and predicted exposure values based on the previous population pharmacokinetic model, indicating that the pharmacokinetic behaviour was consistent with the previous assessments.

In study CLL3001 (a phase 3 combination study with bendamustine and rituximab), sparse pharmacokinetic samples were collected at selected sites to assess whether there was an effect of ibrutinib on the pharmacokinetic profiles of bendamustine or rituximab. The pharmacokinetic report from this study was submitted separately (variation II/20). In this study, the systemic exposure of rituximab was higher in subjects receiving ibrutinib compared to those receiving placebo. Pre-dose serum concentrations were on average 2- to 3-fold higher in the first three cycles and 1.17- to 1.71-fold higher in the subsequent cycles.

Pharmacokinetics using human biomaterials

After assessment of the primary MAA, there were some remaining uncertainties regarding the potential of ibrutinib to induce CYP1A2. As part of a relevant post authorisation measure, the MAH submitted a new *in vitro* induction study indicating no potential for induction of CYP1A2. The data from study CLL3001 showed no effect of ibrutinib on bendamustine, a CYP1A2 substrate, at 1, 2, 3 and 4-8 hr post-dose. Although it is unclear whether bendamustine is sensitive to CYP1A2 induction *in vivo* (no interaction data of bendamustine with a known inducer appears to be published), the data from CLL3001 does not contradict the conclusion from the *in vitro* study.

2.3.3. Discussion on clinical pharmacology

An assessment of the pharmacokinetic data from the studies included in this submission was performed as a separate variation II/20.

It is agreed that the effect of ibrutinib treatment on rituximab concentrations is likely not a drug-drug interaction but might possibly be a secondary effect due to increased response and thereby lower target-mediated clearance of rituximab in the ibrutinib arm. Therefore, no change to section 4.5 of the SmPC on the effect of ibrutinib on rituximab is required.

2.3.4. Conclusions on clinical pharmacology

In conclusion, the updated population pharmacokinetic analysis and the analysis of the interaction with bendamustine/rituximab do not affect previous conclusions on ibrutinib pharmacokinetics, dose adjustments or interaction potential. Therefore, the SmPC remains unchanged with regards to the clinical pharmacology aspects.

2.4. Clinical efficacy

2.4.1. Clinical Studies in Support of the CLL Indication

Study	Design	Treatment	N (Randomized/ Enrolled)	Key Efficacy Endpoints (Primary/Key Secondary)	IRC	Status
Additional Studies						
Combination Therapy						
CLL3001	Phase 3, randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of ibrutinib in combination with BR vs. BR alone in previously treated subjects with CLL/SLL.	Placebo capsules, daily continuously or ibrutinib capsules: 420 mg daily continuously; Background therapy: bendamustine HCl 70 mg/m^2 30 min IV infusion on Cycle 1, Days 2 and 3, and Cycles 2 to 6, Days 1 and 2 for up to 6 cycles; rituximab: 375 mg/m^2 IV in Cycle 1, Day 1, and 500 mg/m^2 IV in Cycles 2 through 6, Day 1, until PD or unacceptable toxicity.	578	PFS[a]/ OS, ORR[a]	Yes	Primary CSR completed; study ongoing CCO 12Jun2015 CSR 27Jul2015 Mod5.3.5.1/CLL3001
Supportive Combination Therapy Studies						
Study 1108	Phase 1b, open-label, parallel-group, multicenter, safety study of ibrutinib, in combination with chemotherapy in subjects with CLL/SLL	Ibrutinib capsule (oral): 420 mg daily (28-day cycle) until PD or unacceptable toxicity; BR: administered IV for maximum 6 cycles until Grade 4 hematologic toxicity or clinically significant Grade ≥3 toxicity, PD, or CR; FCR[b]: administered IV for maximum 6 cycles or unacceptable toxicity, PD, or CR.	33 (30 i+BR; 3 i+FCR)	ORR[c], PFS[c], DoR	No	Completed CCO 12Nov2012 CSR 20Oct2013 Mod5.3.5.2/1108
Study 1109	Phase 1b/2, nonrandomized, open-label, sequential group study to evaluate the safety and efficacy of 3 schedules of ibrutinib in combination with ofatumumab in previously treated CLL/SLL and PLL	Ibrutinib capsule (oral): 420 mg daily: 1) 1 cycle before ofatumumab begins; 2) concomitantly with ofatumumab; and 3) added at the start of Cycle 3. Ibrutinib continued until PD or unacceptable toxicity. Ofatumumab IV dosing schedule: Day 1: 300 mg; Weeks 2 to 8: 2,000 mg once weekly; thereafter, 2,000 mg once/month for 4 months	71	ORR[a]/ PFS[a], TTR, DoR	No	Completed CCO 28May2013 CSR 02Jul2014 Mod5.3.5.2/1109
Monotherapy in Subjects with CLL Del17p						
Study 1117	Phase 2, single-arm, open-label, multicenter study to evaluate safety and efficacy in previously treated CLL/SLL with del17p	Ibrutinib capsule (oral): 420 mg daily; until PD, unacceptable toxicity	145	ORR[a]/ DoR,[a] PFS, OS	Yes	Completed CCO 20Jun2014 CSR 07Apr2015 Mod5.3.5.2/1117
Previously Submitted Monotherapy Study (for comparison)						
Study 1112	Phase 3, randomized, open-label, multicenter study to evaluate the efficacy and safety of ibrutinib vs. ofatumumab in previously treated CLL/SLL	Ibrutinib capsule (oral): 420 mg daily until PD or unacceptable toxicity ofatumumab: 12 doses total, Week 1: 300 mg IV once; Weeks 2 to 8: 2,000 mg IV weekly; Weeks 12 to 24: 2,000 mg IV (every 4 weeks)	391	PFS[a]/ OS, ORR[a]	Yes	Completed CCO 06Nov2013 CSR 25Mar2014 Mod5.3.5.1/1112

BR=bendamustine and rituximab; BTK=Bruton's tyrosine kinase; CCO=clinical cutoff; CLL=chronic lymphocytic leukaemia; CR=complete response; CSR=clinical study report; del17p=deletion in the short arm of chromosome 17; DoR=duration of response; FCR=fludarabine, cyclophosphamide, and rituximab; IRC=Independent Review Committee; i=ibrutinib; IV=intravenous; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PLL=prolymphocytic leukaemia; SLL=small lymphocytic lymphoma; TTR=time to response

[a] IRC assessed.

[b] During the course of the study, the FCR combination group was suspended as a result of the infrequency of FCR use in the relapsed setting among the study sites. Due to the small number of subjects treated with ibrutinib+FCR (n=3, no formal analysis performed), for this SCE, the focus is the 30 subjects who received ibrutinib+BR.

[c] Investigator-assessed.

Pivotal study PCI-32765CLL3001: *Randomized (1:1), Double-blind, Multicenter (21 countries, 133 centres), Placebo-controlled Study of Ibrutinib, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukaemia/Small Lymphocytic Lymphoma.*

Methods

Study participants

Main eligibility criteria:

- Relapsed/refractory CLL/SLL,
- Active disease according to IWCLL,
- EGOG 0, 1
- Measurable nodal disease (CT)
- ANC ≥ 1
- Platelet ≥50
- Adequate hepatic (ALT/AST ≤ 2.5 XULN, total bil. ≤1.5 x ULN
- Renal function (creatinine ≤2 ULN, GFR ≥ 40 ml/min)

Excluding:

- del.17p
- prior bendamustine if need for retreatment within 24 months,
- prior ibrutinib (or other BTK inhibitor).
- Planned stem cell transplantation,
- CNS involvement
- Richter's transformation
- Anti-vitamin K
- Strong CYP3A4/5 inhibitors

Treatments
Six cycles of BR + ibrutinib (420 mg) or placebo, followed by ibrutinib or placebo until PD or unacceptable toxicity. Cross-over was introduced by amendment INT-3, after IRC confirmed PD.

Outcomes/endpoints
Primary endpoint: PFS

Secondary endpoints:

- overall response rate (ORR) (complete response [CR] + CR with incomplete marrow recovery (CRi) + partial response (PR) + nodular partial response [nPR]),
- overall survival (OS),
- rate of minimal residual disease (MRD)-negative remissions,
- improvement in hematologic parameters (hemoglobin, neutrophil, platelet count),
- improvement of disease-related symptoms (fatigue, night sweats, weight loss, fever, and abdominal discomfort due to splenomegaly), patient-reported outcomes (PRO),
- pharmacokinetics (PK) of ibrutinib and to explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information, biomarkers related to B-cell receptor (BCR) and compensatory signaling pathways and to explore their association with resistance to ibrutinib treatment.

The order of these endpoints were as follows: ORR, OS, MRD negative rate, time to improvement in FACT fatigue score, rate of sustained hemoglobin improvement, rate of sustained platelet improvement.

Randomisation

Participants were randomised 1:1 to receive BR + ibrutinib vs BR + placebo

Participants were stratified by 1 prior vs. >1 prior line of therapy, purine analogue refractory yes vs. no.

Blinding (masking)

The study was double blind

Statistical methods
Interim analysis planned after 171 events (in 289+289 patients).

Results

Participant flow

Disposition of Study Treatment Phase; ITT Analysis Set (Study PCI-32765CLL3001)

	Ibrutinib+BR	Placebo+BR	Total
Analysis set: ITT	289	289	578
Study treatment phase disposition, n (%)			
Did not receive study drug	2 (0.7%)	2 (0.7%)	4 (0.7%)
Adverse event	1 (0.3%)	1 (0.3%)	2 (0.3%)
Investigator or sponsor decision	1 (0.3%)	0	1 (0.2%)
Withdrawal by subject	0	1 (0.3%)	1 (0.2%)
Ongoing	203 (70.2%)	100 (34.6%)	303 (52.4%)
Discontinued	84 (29.1%)	187 (64.7%)	271 (46.9%)
Primary reason for discontinuation of study treatment phase[a]			
Adverse event	41 (14.2%)	34 (11.8%)	75 (13.0%)
Death	9 (3.1%)	8 (2.8%)	17 (2.9%)
Lost to follow-up	1 (0.3%)	1 (0.3%)	2 (0.3%)
Pregnancy	0	0	0
Progressive disease or relapse	14 (4.8%)	130 (45.0%)	144 (24.9%)
Investigator or sponsor decision	4 (1.4%)	4 (1.4%)	8 (1.4%)
Withdrawal of consent	17 (5.9%)	12 (4.2%)	29 (5.0%)

[a] Includes subjects who did not receive study medication.
Note: Percentages are calculated with the number of ITT subjects in each treatment group as the denominators.
Note: The study treatment phase extends from randomization until study treatment (bendamustine, rituximab, and ibrutinib/placebo) discontinuation.
Note: The term 'study drug' refers to ibrutinib/placebo.

Recruitment
Stratified by 1 prior vs. >1 prior line of therapy, purine analogue refractory yes vs. no.

Conduct of the study
By amendment INT-3, cross-over after IRC confirmed PD

Summary of Protocol Amendments for CLL3001	
Amendment INT-1 (5 Dec 2012; 15 subjects enrolled; substantial)	• Clarified management of study drug with concomitant cytochrome (CYP) CYP3A4/5 inhibitors/inducers and warfarin or other anticoagulants during the study to reflect updated standard language across the ibrutinib development program • Removed the eligibility restriction for subjects requiring treatment with strong CYP2D6 inhibitors in the exclusion criteria • Clarified management of study drug during the perioperative periods; • Incorporated feedback from investigators, health authorities, and the study Steering Committee with regard to the platelet cutoff eligibility criteria, and bone marrow and MRD sampling for subjects reaching CR.
Amendment INT-2 (13 Sep 2013; 358 subjects enrolled; substantial)	• Updated the protocol with safety information in the Investigator's Brochure • Implemented a recommendation from the DMC to use anti-microbial prophylaxis. • Added that data related to the occurrence of other malignancies or transformation to a more aggressive histology (Richter's transformation) during the Follow-up phase should be collected.
Amendment INT-3 (30 Jan 2014; 578 subjects enrolled; substantial)	• Provided access to next-line treatment with ibrutinib for subjects initially assigned to placebo who had IRC-confirmed disease progression (ie, each subject had met the primary endpoint), at investigator's discretion, and with medical monitor approval.

Baseline data
Demography: Median/ mean age 64/64 years of age, >70 years of age about 30%. Male about 2/3. Caucasian 90%, Europe 70%.

Baseline Disease Characteristics; ITT Analysis Set (Study PCI-32765CLL3001)

Bulky disease, n (%)			
N	289	289	578
Yes(>= 5 cm)	168 (58.1%)	156 (54.0%)	324 (56.1%)
No(< 5 cm)	121 (41.9%)	133 (46.0%)	254 (43.9%)
Chromosome 11q deletion positive, n (%)			
N	289	289	578
Yes	87 (30.1%)	65 (22.5%)	152 (26.3%)
No	202 (69.9%)	224 (77.5%)	426 (73.7%)
Chromosome 17p deletion positive[a], n (%)			
N	289	289	578
Yes	2 (0.7%)	0	2 (0.3%)
No	287 (99.3%)	289 (100.0%)	576 (99.7%)
IgVH status, n (%)			
N	259	260	519
Hypermutated	49 (18.9%)	52 (20.0%)	101 (19.5%)
Unmutated	210 (81.1%)	208 (80.0%)	418 (80.5%)
ZAP-70 (% expression level)			
N	271	276	547
Elevated	204 (75.3%)	190 (68.8%)	394 (72.0%)
Not elevated	67 (24.7%)	86 (31.2%)	153 (28.0%)
CD38 (% expression level)			
N	271	276	547
Positive (>= 30)	166 (61.3%)	146 (52.9%)	312 (57.0%)
Negative (<30)	105 (38.7%)	130 (47.1%)	235 (43.0%)
Serum β2 - microglobulin (mg/L)			
N	281	278	559
Mean (SD)	4.81 (2.397)	5.03 (3.790)	4.92 (3.166)
Median	4.23	4.11	4.20
Range	(0.1; 14.1)	(1.0; 51.3)	(0.1; 51.3)
<=3.5 mg/L	92 (32.7%)	99 (35.6%)	191 (34.2%)
>3.5 mg/L	189 (67.3%)	179 (64.4%)	368 (65.8%)
Complex karyotype			
N	289	289	578
Yes	18 (6.2%)	19 (6.6%)	37 (6.4%)
No	271 (93.8%)	270 (93.4%)	541 (93.6%)
Elevated LDH at baseline, n (%)			
N	288	289	577
Yes (>=350 u/L)	82 (28.5%)	86 (29.8%)	168 (29.1%)
No (<350 u/L)	206 (71.5%)	203 (70.2%)	409 (70.9%)
Cytopenia at baseline[b], n (%)			
N	289	289	578
Yes	122 (42.2%)	155 (53.6%)	277 (47.9%)
Platelet count ≤ 100,000/uL	75 (26.0%)	86 (29.8%)	161 (27.9%)
Hgb ≤ 11g/dL	80 (27.7%)	95 (32.9%)	175 (30.3%)
ANC ≤ 1500/uL	27 (9.3%)	33 (11.4%)	60 (10.4%)
No	167 (57.8%)	134 (46.4%)	301 (52.1%)
Stratification factors, n (%)			
Refractory to purine analog therapy			
N	289	289	578
Yes	75 (26.0%)	74 (25.6%)	149 (25.8%)
No	214 (74.0%)	215 (74.4%)	429 (74.2%)

Numbers analysed

Study period: September 2012 – January 2015 (data cut-off)

Outcomes and estimation

The DMC conducted a formal interim analysis with 239 PFS events by IRC that represented 70% of the planned total number of events (interim was originally planned for 50% of events). As a result,

the stopping guideline was updated for efficacy (1-sided p-value of 0.007). The Sponsor Steering Committee was notified that the pre-specified statistical boundary for early stopping was crossed (p-value <0.0001 for the primary endpoint PFS). The DMC recommended unblinding the study.

Progression-Free Survival (IRC); ITT Analysis Set (Study PCI-32765CLL3001)

	Ibrutinib+BR	Placebo+BR	Ibrutinib+BR vs. Placebo+BR
Analysis set: ITT	289	289	
Subjects randomized, n (%)	289 (100.0%)	289 (100.0%)	
PFS events	56 (19.4%)	183 (63.3%)	
Disease progression	42 (14.5%)	166 (57.4%)	
Death	14 (4.8%)	17 (5.9%)	
Censored	233 (80.6%)	106 (36.7%)	
Progression Free Survival			
25th percentile (95% CI)	19.81 (16.66, NE)	8.57 (8.38, 10.15)	
Median (95% CI)	NE (24.90, NE)	13.34 (11.30, 13.90)	
75th percentile (95% CI)	NE (24.90, NE)	17.51 (16.82, NE)	
Range	(0.0+, 27.1+)	(0.0+, 27.8+)	
6-month PFS rate (95% CI)	0.927 (0.890, 0.953)	0.895 (0.853, 0.926)	
12-month PFS rate (95% CI)	0.859 (0.812, 0.896)	0.513 (0.451, 0.571)	
18-month PFS rate (95% CI)	0.786 (0.725, 0.834)	0.242 (0.182, 0.306)	
24-month PFS rate (95% CI)	0.741 (0.667, 0.801)	0.192 (0.128, 0.265)	
Hazard ratio (95% CI)[a]			0.203 (0.150, 0.276)
p-value[b]			< 0.0001

Key: BR=bendamustine and rituximab; CI = confidence interval; IRC=Independent Review Committee; ITT=intent to treat; NE= not evaluable; PFS=progression-free survival

[a] Hazard ratio is from a stratified proportional hazards model. A hazard ratio < 1 favors ibrutinib.

[b] P-value is from a log-rank test stratified by two randomization stratification factors: refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1).

Note: Progression-free survival is defined as the interval between the date of randomization and the date of disease progression or death, whichever is first reported. Subjects without well-documented disease progression or death at the time of analysis are censored at the date of last adequate disease assessment on study. Subjects with no baseline or any on study tumor assessments are censored at randomization.

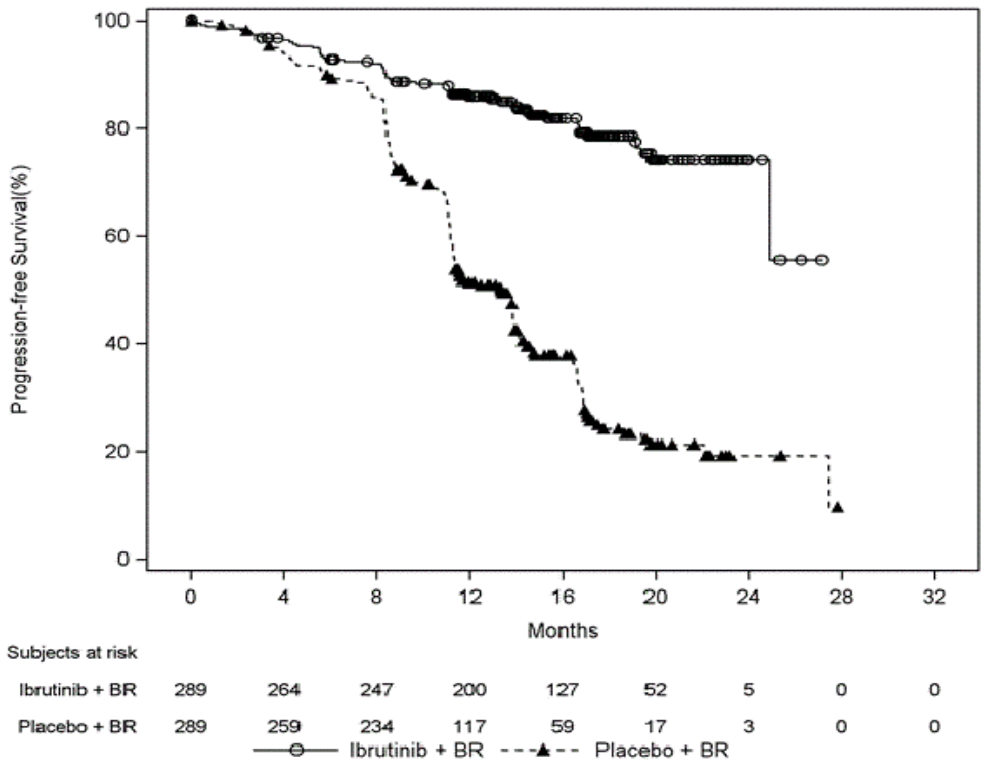


Figure 1

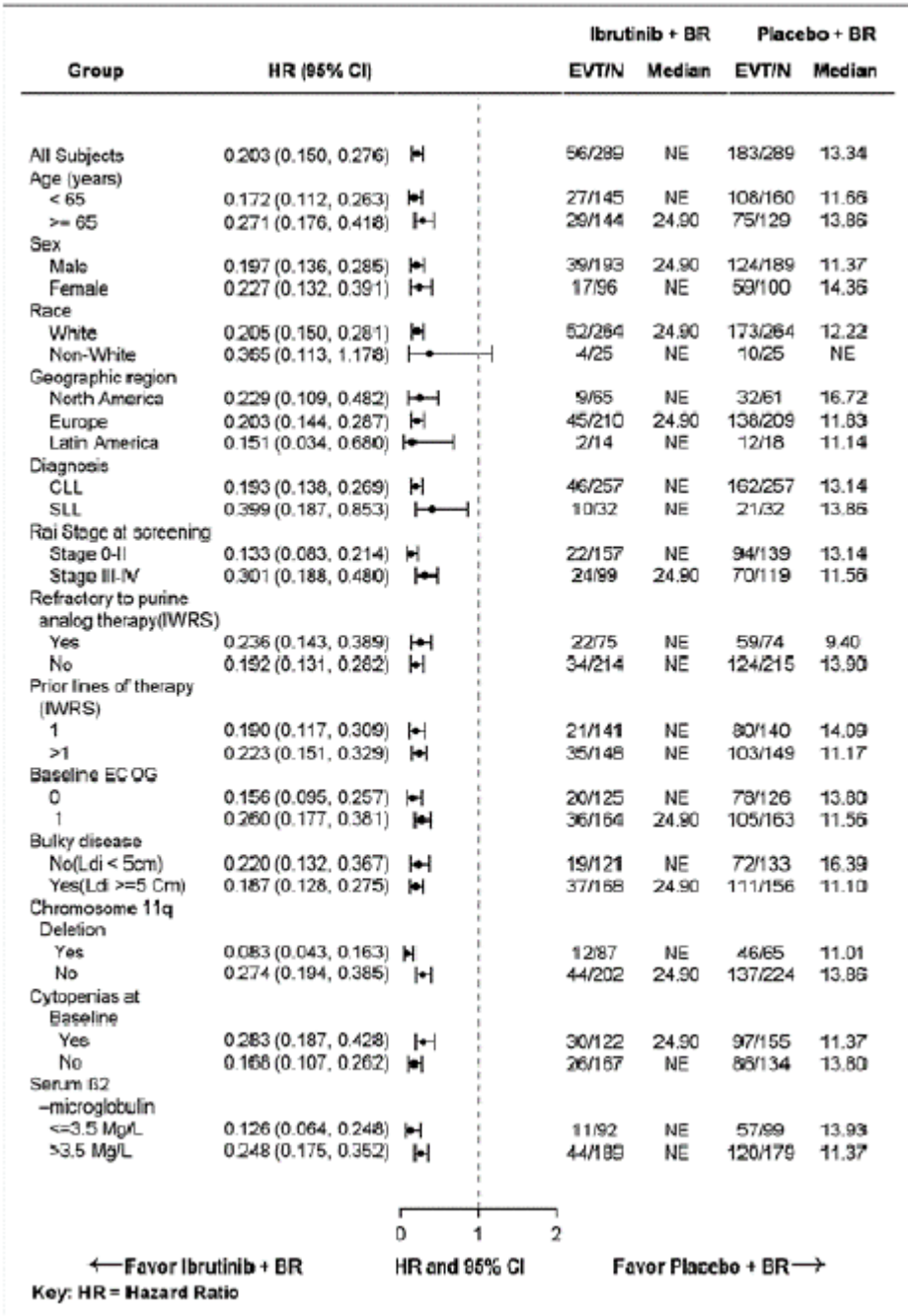
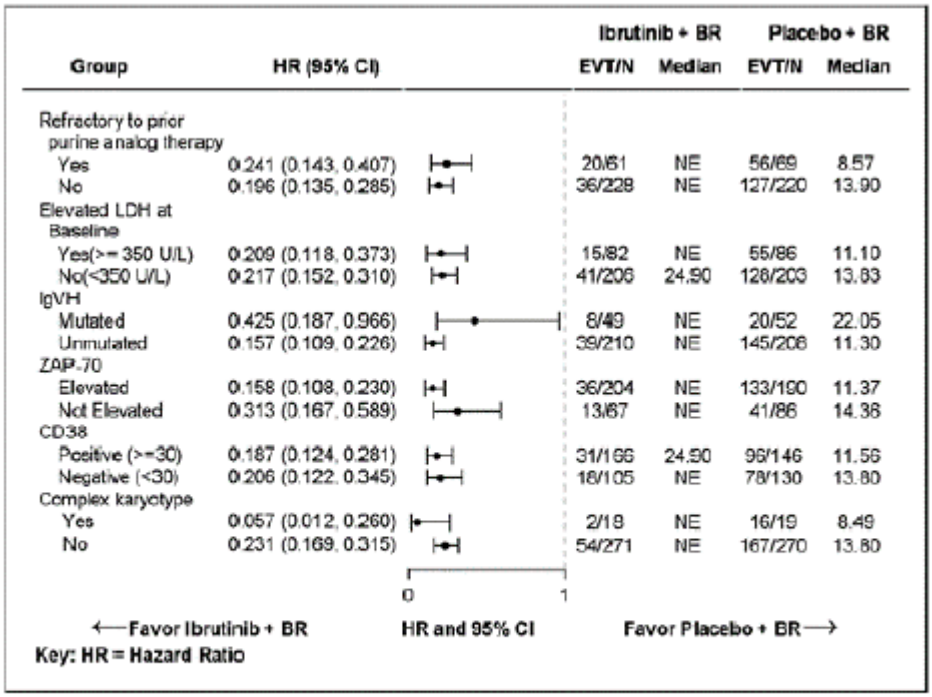

Group
HR (95% CI)
Ibrutinib + BR
EVT/N
Median
Placebo + BR
EVT/N
Median
All Subjects 0.203 (0.150, 0.276) 56/289 NE 183/289 13.34
Age (years)
< 65 0.172 (0.112, 0.263) 27/145 NE 108/160 11.66
>= 65 0.271 (0.176, 0.418) 29/144 24.90 75/129 13.86
Sex
Male 0.197 (0.136, 0.285) 39/193 24.90 124/189 11.37
Female 0.227 (0.132, 0.391) 17/96 NE 59/100 14.36
Race
White 0.205 (0.150, 0.281) 52/264 24.90 173/264 12.22
Non-White 0.365 (0.113, 1.178) 4/25 NE 10/25 NE
Geographic region
North America 0.229 (0.109, 0.482) 9/65 NE 32/61 16.72
Europe 0.203 (0.144, 0.287) 45/210 24.90 136/209 11.83
Latin America 0.151 (0.034, 0.680) 2/14 NE 12/18 11.14
Diagnosis
CLL 0.193 (0.138, 0.269) 46/257 NE 162/257 13.14
SLL 0.399 (0.187, 0.853) 10/32 NE 21/32 13.86
Rai Stage at screening
Stage 0-II 0.133 (0.083, 0.214) 22/157 NE 94/139 13.14
Stage III-IV 0.301 (0.188, 0.480) 24/99 24.90 70/119 11.56
Refractory to purine analog therapy(IWRS)
Yes 0.236 (0.143, 0.389) 22/75 NE 59/74 9.40
No 0.192 (0.131, 0.282) 34/214 NE 124/215 13.90
Prior lines of therapy (IWRS)
1 0.190 (0.117, 0.309) 21/141 NE 80/140 14.09
>1 0.223 (0.151, 0.329) 35/148 NE 103/149 11.17
Baseline ECOG
0 0.156 (0.095, 0.257) 20/125 NE 78/126 13.80
1 0.260 (0.177, 0.381) 36/164 24.90 105/163 11.56
Bulky disease
No(Ldi < 5cm) 0.220 (0.132, 0.367) 19/121 NE 72/133 16.39
Yes(Ldi >=5 Cm) 0.187 (0.128, 0.275) 37/168 24.90 111/156 11.10
Chromosome 11q Deletion
Yes 0.083 (0.043, 0.163) 12/87 NE 46/65 11.01
No 0.274 (0.194, 0.385) 44/202 24.90 137/224 13.86
Cytopenias at Baseline
Yes 0.283 (0.187, 0.428) 30/122 24.90 97/155 11.37
No 0.168 (0.107, 0.262) 26/167 NE 86/134 13.80
Serum B2 -microglobulin
<=3.5 Mg/L 0.126 (0.064, 0.248) 11/92 NE 57/99 13.93
>3.5 Mg/L 0.248 (0.175, 0.352) 44/189 NE 120/179 11.37
0
1
2
←Favor Ibrutinib + BR
HR and 95% CI
Favor Placebo + BR→
Key: HR = Hazard Ratio

Table 1 HR for PFS across subgroups



Key: CLL=chronic lymphocytic leukemia; del(17p)=chromosome 17p deletion; ECOG=Eastern Cooperative Oncology Group; IgVH=immunoglobulin variable heavy gene; IWRS=interactive web response system; LDH=lactic acid dehydrogenase; NE=not evaluable; SLL=small lymphocytic lymphoma

The All Subjects hazard ratio is from a stratified proportional hazards model. Hazard ratios for subgroups are unstratified.

Table 2 IRC assessment of Progressive disease

TEFPFS09: Modality of Progressive Disease per IRC Assessment; ITT Analysis Set (Study PCI-32765CLL3001)

	Ibrutinib+BR	Placebo+BR
Analysis set: ITT	289	289
Subjects with progressive disease (PD) by IRC assessment	42 (100.0%)	166 (100.0%)
PD by radiology component(s)	40 (95.2%)	154 (92.8%)
Target lesion(s)[a]	21 (50.0%)	123 (74.1%)
Non-target lesion(s)[a]	14 (33.3%)	64 (38.6%)
New lesion(s)	7 (16.7%)	11 (6.6%)
Spleen	17 (40.5%)	50 (30.1%)
Liver	0	0
PD by oncology component(s)	3 (7.1%)	20 (12.0%)
CBC (hemoglobin or platelets)	1 (2.4%)	4 (2.4%)
Absolute lymphocyte count (ALC)	0	5 (3.0%)
Transformation	0	1 (0.6%)
Physical examination (PE)	2 (4.8%)	12 (7.2%)
Lymph nodes	2 (4.8%)	9 (5.4%)
Non-target lesion(s) not assessable by radiology	0	3 (1.8%)
New lesion(s) not assessable by radiology[b]	0	0
Spleen	1 (2.4%)	3 (1.8%)
Liver	0	1 (0.6%)

[a] Target lesions and non-target lesions refer to lymph nodes evaluated by radiology.
[b] Including both nodal and extra nodal lesions.
Note: Modality of progressive disease is based on the first documentation of progressive disease. Subjects can be summarized in multiple PD categories.

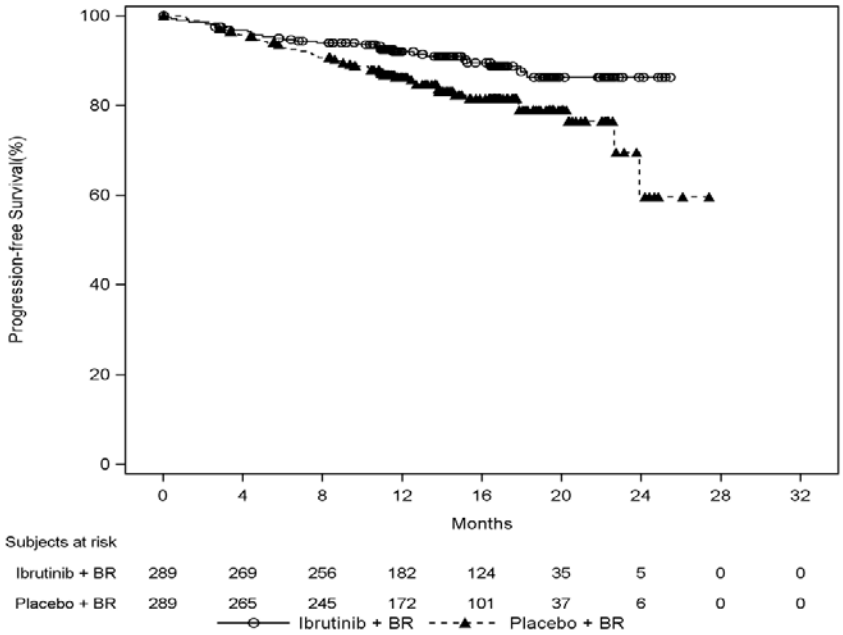


Figure 2 Kaplan-Meier Curves for Progression Free Survival (INV) after Initiation of Subsequent Antineoplastic Therapy (PFS2); ITT Analysis Set

	Ibrutinib+BR	Placebo+BR	Ibrutinib+BR vs. Placebo+BR
Analysis set: ITT	289	289	
Events, n (%)	29 (10.0%)	50 (17.3%)	
PD after subsequent antineoplastic therapy	0	5 (1.7%)	
Death before subsequent antineoplastic therapy	25 (8.7%)	26 (9.0%)	
Death after subsequent antineoplastic therapy	2 (0.7%)	8 (2.8%)	
Second subsequent antineoplastic therapy	2 (0.7%)	11 (3.8%)	
Censored	260 (90.0%)	239 (82.7%)	
Progression Free Survival			
25th percentile (95% CI)	NE (NE, NE)	22.64 (17.84, NE)	
Median (95% CI)	NE (NE, NE)	NE (23.92, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(0.0+, 25.5+)	(0.0+, 27.4+)	
Hazard ratio (95% CI)[a]			0.527 (0.332, 0.835)
p-value[b]			0.0055

Key: CI = confidence interval.
[a] Hazard ratio is from a stratified proportional hazards model. A hazard ratio < 1 favors ibrutinib.
[b] P-value is from a log-rank test stratified by two randomization stratification factors: refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1).
Note: PFS2 is defined as the time interval between randomization and PD by investigator after next line subsequent antineoplastic therapy, death or the start of the next subsequent antineoplastic therapy if no PD is recorded. Subjects who did not experience an event are censored at their last disease assessment.

Response rate

	Ibrutinib+BR	Placebo+BR	Ibrutinib+BR vs. Placebo+BR
Analysis set: ITT	289	289	
Overall Response Rate (CR, Cri, nPR, PR)	239 (82.7%)	196 (67.8%)	
Relative risk (95% CI)[a]			1.22 (1.11, 1.34)
p-value[b]			< 0.0001
Overall Response Rate including PRL (CR, CRi, nPR, PR, PRL)	241 (83.4%)	196 (67.8%)	
Relative risk (95% CI)[a]			1.23 (1.12, 1.35)
p-value[b]			< 0.0001
Best Overall Response, n (%)	289 (100.0%)	289 (100.0%)	
Complete Response (CR)	24 (8.3%)	6 (2.1%)	
Complete Response with Incomplete Marrow Recovery (CRi)	6 (2.1%)	2 (0.7%)	
Nodular Partial Response (nPR)	0	0	
Partial Response (PR)	209 (72.3%)	188 (65.1%)	
Partial Response with Lymphocytosis (PRL)	2 (0.7%)	0	
Stable Disease (SD)	25 (8.7%)	69 (23.9%)	
Progressive Disease (PD)	1 (0.3%)	6 (2.1%)	
No Evidence of Disease (NED)	0	1 (0.3%)	
Not Evaluable (NE)	2 (0.7%)	1 (0.3%)	
Non-PD	11 (3.8%)	9 (3.1%)	
Unknown	8 (2.8%)	6 (2.1%)	
Missing	1 (0.3%)	1 (0.3%)	

Key: CI = confidence interval; ITT=intent to treat
[a] Relative risk > 1 favors ibrutinib.
[b] P-value is from a CMH chi-square test stratified by two randomization stratification factors: refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1).
Note: Percentages are based on number of subjects in the ITT analysis set in each treatment group.

Overall survival

	Ibrutinib+BR	Placebo+BR	Ibrutinib+BR vs. Placebo+BR
Analysis set: ITT	289	289	
Subjects randomized, n (%)	289 (100.0%)	289 (100.0%)	
Death	27 (9.3%)	40 (13.8%)	
Censored	262 (90.7%)	249 (86.2%)	
Overall Survival			
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	
Range	(0.2, 27.1+)	(0.1+, 27.8+)	
6-month survival rate (95% CI)	0.954 (0.922, 0.973)	0.947 (0.913, 0.968)	
12-month survival rate (95% CI)	0.929 (0.892, 0.953)	0.889 (0.845, 0.920)	
18-month survival rate (95% CI)	0.895 (0.847, 0.928)	0.842 (0.788, 0.883)	
24-month survival rate (95% CI)	0.887 (0.835, 0.923)	0.842 (0.788, 0.883)	
Hazard ratio (95% CI)[a]			0.628 (0.385, 1.024)
p-value[b]			0.0598

Key: BR=bendamustine and rituximab; CI = confidence interval. ; ITT=intent to treat; NE=not evaluable
[a] Hazard ratio is from a stratified proportional hazards model. A hazard ratio < 1 favors ibrutinib.
[b] P-value is from a log-rank test stratified by two randomization stratification factors: by refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1).

Minimal residual disease

All subjects with a CR or CRi, except for 1 subject, had an MRD sample obtained. Flow cytometry with a sensitivity <1 cell 10 000 leucocytes were used, i.e. the accepted cut-off for MRD.

	Ibrutinib+BR	Placebo+BR	P-value[a]
Analysis set: ITT	289	289	
MRD-negative disease status (response)			
Yes	37 (12.8%)	14 (4.8%)	0.0011
Bone marrow	20 (6.9%)	7 (2.4%)	
Peripheral blood	28 (9.7%)	10 (3.5%)	
No	252 (87.2%)	275 (95.2%)	
Subjects with MRD samples obtained	120 (41.5%)	57 (19.7%)	

Key: BR=bendamustine and rituximab; ITT=intent to treat; MRD=minimal residual disease
[a] P-value is Fisher's exact test.
Percentages are based on the number of ITT subjects in each treatment group as denominators.
Note: Rate of MRD response is defined as the proportion of subjects who reached MRD-negative disease status (< 1 CLL cell per 10,000 leukocytes). All randomized subjects are included in this analysis. Subjects with missing MRD data are considered non-responders.
Note: MRD samples are collected for subjects who had investigator-assessed complete response.

A summary of the Efficacy results for Study CLL3001 are shown in Table X.

Table 3 Efficacy Results in Study CLL3001

Endpoint	IMBRUVICA + BR N = 289	Placebo + BR N = 289
Progression Free Survival		
Median (95% CI), months	Not reached	13.3 (11.3, 13.9)
	HR = 0.203 [95% CI: 0.150, 0.276]	
Overall Response Rate[a] %	82.7	67.8
Overall Survival (OS)[b]	HR = 0.628 [95% CI: 0.385, 1.024]	

[a] IRC evaluated, ORR (CR, Cri, nPR, PR)
[b] Median OS not reached for both arms

Ancillary analyses
Disease-related Symptoms
There were no overall clinically relevant shifts in disease-related symptoms (fatigue, night sweats, weight loss, fever, and abdominal discomfort due to splenomegaly, anorexia)

Immunoglobulin Effects
No clinically meaningful differences in IgA, IgG and IgM) were observed between the treatment groups.

Patient-reported Outcomes
During the Treatment Phase, the overall compliance rates for each of the patient-reported outcomes measured (FACIT-Fatigue, EORTC QLQ-C30, EORTC QLQ-CLL 16, and EQ-5D-5L) were acceptable with <10% missing at most time points administered.

Mean summary scores for the FACIT-fatigue, EORTC-QLQ-C30, EORTC QLQ-CLL 16 Individual Items, and EQ-5D-5L utility values and visual analogue scale scores were similar for each treatment group at baseline.

No notable mean changes from baseline over time were observed in the scores within or between the treatment groups. Times to improvement and deterioration in patient-reported outcome scores were similar for each treatment group.

Supportive studies

Study 1108: Phase 1b Study in Combination with BR
A Phase 1b, multicenter, open-label, parallel-group safety study of ibrutinib in combination with chemoimmunotherapy in subjects with chronic lymphocytic leukemia/small lymphocytic lymphoma

Ibrutinib 420 mg was administered orally once daily in combination with intravenous bendamustine 70 mg/m2 and intravenous rituximab 375 to 500 mg/m2 (n=30). The safety and tolerability profiles were similar to historical data for BR regimens. The high overall response rate of 93.3% compares favorably to historrical data.

Study 1109

An open-label, Phase 1b/2, safety and efficacy study of ibrutinib and ofatumumab in subjects with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma and prolymphocytic leukemia.

Data Sets Analyzed				
	Group 1 ibrutinib → ofatumumab (N=27)	Group 2 ibrutinib / ofatumumab (N=20)	Group 3 ofatumumab → ibrutinib (N=24)	Total (N=71)
Population, n (%)				
DLT	6	6	NA [1]	12
All-Treated	27	20	24	71
Response-Evaluable	27 (100.0)	18 (90.0)	23 (95.8)	68 (95.8)

DLT=dose-limiting toxicity.
[1] A DLT observation period was not utilized for Group 3.

MAH's conclusions: The study results indicate that ibrutinib, when administered at an oral dose of 420 mg/day in combination with a standard regimen of ofatumumab, was well tolerated and highly active (ORR 81.7% across the three dosing sequences) in this study for subjects with heavily pre-treated relapsed or refractory CLL, SLL, PLL, or RT. With the exception of a higher rate of peripheral sensory neuropathy, the observed safety profile of the combined treatment regimen is consistent with the individual profiles of ibrutinib and ofatumumab. Most subjects (76.1%) continued ibrutinib treatment in a long-term extension study.

Study 1117

A Single-arm, Multicenter Phase 2 Study of Ibrutinib 420 mg daily in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with 17p Deletion.

A total of 144 subjects received at least 1 dose of ibrutinib and represents the analysis set for both efficacy and safety in this study (ie, all treated population).

Primary Endpoint – The ORR per IRC assessment was 63.9% with 95% CI (55.8%, 71.3%).

Duration of Response: At the time of data cut, 83.7% of responders were alive and did not have disease progression; the estimated median DOR per IRC was 13.2 months (95% CI: 13.2, NE).

2.4.2. Clinical Studies in Support of the MCL Indication

MCL-3001: "A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, versus Temsirolimus in Subjects with Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy".

Methods

Study participants

Key inclusion criteria

- 18 years of age or older.
- Diagnosis of MCL reviewed and approved by central pathology laboratory prior to randomization: diagnosis report from local laboratory must include morphology and expression of either cyclin D1 in association with one B-cell marker (eg, CD19, CD20, or PAX5) and CD5 or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain

reaction (PCR); if report from local laboratory is not available, diagnosis must be confirmed by central pathology laboratory based on the criteria above

- Received at least 1 prior rituximab-containing chemotherapy regimen. Separate lines of therapy are defined as single or combination therapies that are either separated by disease progression or by a > 6 month treatment-free interval.
- Documented relapse or disease progression following the last anti-MCL treatment.
- Eastern Cooperative Oncology Group performance status Score 0 or 1.
- Hematology values within the following limits: ANC ≥1000/mm3 independent of growth factor support; Platelets ≥75,000/mm3 or ≥50,000/mm3 if bone marrow involvement independent of transfusion support; Hemoglobin level ≥8 g/dL independent of transfusion support

Notable exclusion criteria

- Had a history of stroke or intracranial hemorrhage within 6 months prior to first dose of study drug.
- Required anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with a strong CYP3A4/5 inhibitor.

Treatments

Subjects randomized to Treatment A received 560 mg oral ibrutinib once daily continuously during the 21-day cycle.

Subjects randomized to Treatment B received temsirolimus IV infusion 175 mg on Days 1, 8, and 15 of the first cycle followed by 75 mg on Days 1, 8, and 15 of each subsequent 21-day cycle.

Treatment on both arms continued until disease progression (or relapse if the subject achieved a CR), or unacceptable toxicity, whichever occurred first.

Objectives

Outcomes/endpoints

Endpoints

Primary endpoint: PFS assessed by IRC and performed on the ITT population. The IRC was blinded to study treatment assignment, and both the IRC and the site performed disease evaluations according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

Disease evaluations included CT, MRI, PET, and clinical evaluation performed every 9 weeks for up to 15 months from the start of study drug, and every 24 weeks thereafter. Whole body FDG-PET scan (skull base to the proximal femur) will be done at Screening. For subjects who are PET-positive at baseline, PET will be done at the time of maximal tumor reduction (eg, CR or PR with 2 consecutive CT scans showing no further tumor reduction). In addition, PET will be performed at suspected disease progression, if a new lesion was detected on CT.

Key secondary endpoints: ORR, OS, 1-year survival rate, duration of response, time to response, time to next treatment, and time to worsening in the Lym subscale of the FACT-Lym.

Important exploratory endpoint: PFS2 (defined as the time interval between the date of randomization to the date of an event, defined as progressive disease as assessed by the investigator after the next line of subsequent therapy, death from any cause, or start of the second line of subsequent therapy if no disease progression is noted).

Statistical methods

Key statistical elements

Open design, central 1:1 randomisation stratified by the number of prior lines of therapy (1 or 2 versus ≥ 3) and simplified MCL international prognostic index (MIPI; low risk [0-3]; versus intermediate risk [4-5]; versus high risk [6-11]).

The study was planned to enroll approximately 280 subjects (about 140 subjects to each arm) to observe 178 PFS events at the primary analysis. Assuming 57% improvement in median PFS of the ibrutinib arm over the temsirolimus arm (a hazard ratio of 0.64 for the ibrutinib relative to temsirolimus arm, under the exponential distribution assumption, or for example, an improvement in median PFS from 7 months to 11 months), with 178 events the study has at least 85% power to achieve a statistical significance level of 2.5% (1-sided).

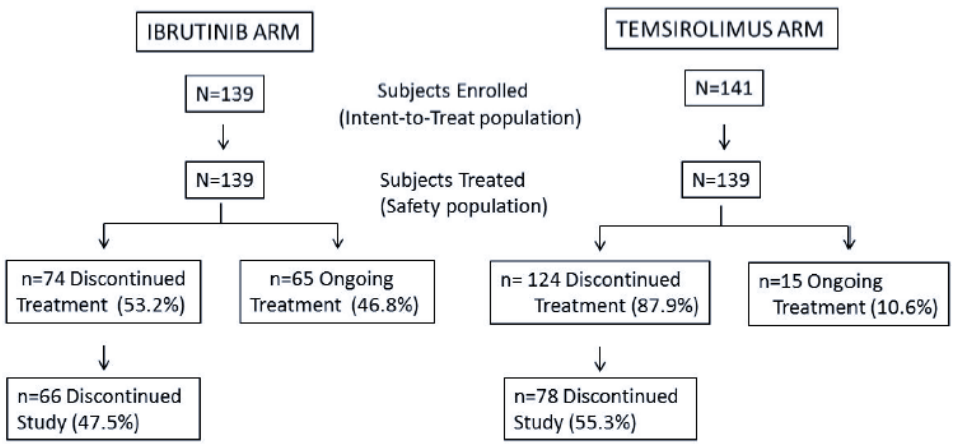
Statistical hypothesis testing for secondary endpoints was performed in a hierarchical manner with an alpha level of 0.05 in the order of ORR, OS, time to next treatment, and time to worsening in the Lym subscale of the FACT-Lym assessment.

The end of study is defined as when 80% of the randomized subjects died, or 3 years after the last subject was randomized, or the sponsor terminates the study, whichever comes first.

Results

Participant flow

Figure 1: Disposition of Subjects Enrolled into Study PCYI32765MCL3001



Recruitment

Study Period: 3 December 2012 to 22 April 2015 (clinical cutoff).

Study Centers: Europe: 79 sites; South Korea: 5 sites; Brazil: 4 sites; Canada: 3 sites, Taiwan: 3 sites, Columbia: 2 sites, Mexico: 2 sites.

Conduct of the study

After protocol Amendment 2 (July 2014), subjects who received treatment with temsirolimus and had IRC-confirmed disease progression were eligible to crossover and receive treatment with ibrutinib 560 mg orally, daily, on a 21-day cycle until disease progression, unacceptable toxicity, or study end.

Table 6: Major Protocol Deviations; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Subjects with major protocol deviation	7 (5.0%)	14 (9.9%)	21 (7.5%)
Protocol deviation coded term			
Developed withdrawal criteria but not withdrawn	0	4 (2.8%)	4 (1.4%)
Entered but did not satisfy criteria	5 (3.6%)	7 (5.0%)	12 (4.3%)
Received a disallowed concomitant treatment	2 (1.4%)	1 (0.7%)	3 (1.1%)
Safety assessment deviation	0	2 (1.4%)	2 (0.7%)

Baseline data

Table 2: Demographics and Baseline Characteristics; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Age (years)			
N	139	141	280
Mean (SD)	66.7 (8.7)	67.1 (9.8)	66.9 (9.3)
Median	67.0	68.0	68.0
Range	(39; 84)	(34; 88)	(34; 88)
< 65	53 (38.1%)	54 (38.3%)	107 (38.2%)
>= 65	86 (61.9%)	87 (61.7%)	173 (61.8%)
Sex			
N	139	141	280
Male	100 (71.9%)	108 (76.6%)	208 (74.3%)
Female	39 (28.1%)	33 (23.4%)	72 (25.7%)
Race			
N	139	141	280
White	115 (82.7%)	129 (91.5%)	244 (87.1%)
Asian	16 (11.5%)	5 (3.5%)	21 (7.5%)
Other	3 (2.2%)	4 (2.8%)	7 (2.5%)
Unknown/ not reported	5 (3.6%)	3 (2.1%)	8 (2.9%)
Ethnicity			
N	139	141	280
Hispanic or Latino	7 (5.0%)	11 (7.8%)	18 (6.4%)
Not Hispanic or Latino	127 (91.4%)	127 (90.1%)	254 (90.7%)
Unknown/ not reported	5 (3.6%)	3 (2.1%)	8 (2.9%)
ECOG performance status			
N	139	141	280
0	67 (48.2%)	67 (47.5%)	134 (47.9%)
1	71 (51.1%)	72 (51.1%)	143 (51.1%)
2	1 (0.7%)	2 (1.4%)	3 (1.1%)

Table 3: Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Time from initial diagnosis to randomization (months)			
N	139	141	280
Mean (SD)	49.98 (42.71)	51.17 (33.60)	50.58 (38.33)
Median	38.90	46.23	42.56
Range	(4.2; 298.7)	(2.7; 159.8)	(2.7; 298.7)
< 36 months	68 (48.9%)	58 (41.1%)	126 (45.0%)
>= 36 months	71 (51.1%)	83 (58.9%)	154 (55.0%)
Time from end of last prior therapy to randomization (months)			
N	139	141	280
Mean (SD)	15.43 (18.62)	16.34 (20.21)	15.88 (19.41)
Median	8.25	7.03	7.23
Range	(0.4; 91.1)	(0.7; 111.2)	(0.4; 111.2)
Stage of MCL at study entry			
N	139	141	280
I	3 (2.2%)	2 (1.4%)	5 (1.8%)
II	7 (5.0%)	5 (3.5%)	12 (4.3%)
III	17 (12.2%)	14 (9.9%)	31 (11.1%)
IV	112 (80.6%)	120 (85.1%)	232 (82.9%)
Types of histology			
N	139	141	280
Blastoid	16 (11.5%)	17 (12.1%)	33 (11.8%)
Diffuse	56 (40.3%)	61 (43.3%)	117 (41.8%)
Nodular	38 (27.3%)	40 (28.4%)	78 (27.9%)
Other	9 (6.5%)	5 (3.5%)	14 (5.0%)
Unknown	20 (14.4%)	18 (12.8%)	38 (13.6%)
Simplified MCL international prognostic index			
N	139	141	280
Low risk (1-3)	44 (31.7%)	42 (29.8%)	86 (30.7%)
Intermediate risk (4-5)	65 (46.8%)	69 (48.9%)	134 (47.9%)
High risk (6-11)	30 (21.6%)	30 (21.3%)	60 (21.4%)
Prior lines of therapy			
N	139	141	280
Mean (SD)	2.1 (1.4)	2.2 (1.3)	2.2 (1.3)
Median	2.0	2.0	2.0
Range	(1; 9)	(1; 9)	(1; 9)
1-2	95 (68.3%)	93 (66.0%)	188 (67.1%)
3-5	41 (29.5%)	45 (31.9%)	86 (30.7%)
>5	3 (2.2%)	3 (2.1%)	6 (2.1%)
Types of treatment indication			
N	139	141	280
Relapsed disease[a]	103 (74.1%)	94 (66.7%)	197 (70.4%)
Refractory disease[b]	36 (25.9%)	47 (33.3%)	83 (29.6%)

Table 4: Extent of Disease at Baseline Assessed by Investigator; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Number of lesions			
N	139	141	280
Mean (SD)	7.1 (4.7)	7.0 (4.2)	7.1 (4.5)
Median	6.0	7.0	6.0
Range	(1; 24)	(1; 23)	(1; 24)
Tumor burden (cm^2)			
N	138	141	279
Mean (SD)	60.79 (70.00)	66.31 (72.44)	63.58 (71.17)
Median	32.72	40.74	36.48
Range	(1.7; 440.9)	(1.4; 347.7)	(1.4; 440.9)
Tumor bulk (largest diameter)			
< 5 cm	64 (46.4%)	66 (46.8%)	130 (46.6%)
>= 5 cm	74 (53.6%)	75 (53.2%)	149 (53.4%)
>= 10 cm	22 (15.9%)	26 (18.4%)	48 (17.2%)
Extranodal disease			
No	56 (40.3%)	56 (39.7%)	112 (40.0%)
Yes	83 (59.7%)	85 (60.3%)	168 (60.0%)
Bone marrow involvement [a]			
No	73 (52.5%)	56 (39.7%)	129 (46.1%)
Yes	66 (47.5%)	85 (60.3%)	151 (53.9%)
Baseline lymphoma symptoms [b]			
No	61 (43.9%)	72 (51.1%)	133 (47.5%)
Yes	78 (56.1%)	69 (48.9%)	147 (52.5%)
B symptoms	33 (23.7%)	39 (27.7%)	72 (25.7%)
Recurrent fevers	6 (4.3%)	10 (7.1%)	16 (5.7%)
Night sweats	28 (20.1%)	32 (22.7%)	60 (21.4%)
Weight loss	10 (7.2%)	9 (6.4%)	19 (6.8%)
Other MCL-related symptoms	65 (46.8%)	57 (40.4%)	122 (43.6%)
Itching	4 (2.9%)	9 (6.4%)	13 (4.6%)
Fatigue (severe and persistent)	28 (20.1%)	21 (14.9%)	49 (17.5%)
Physical discomfort due to enlarged lymph nodes	39 (28.1%)	35 (24.8%)	74 (26.4%)
Other	20 (14.4%)	14 (9.9%)	34 (12.1%)

Key: MCL= mantle cell lymphoma.
[a] Subjects with positive bone marrow aspirate or biopsy results at baseline.
[b] Subjects belong to multiple categories are counted multiple times.

Table 5: Prior Therapy for Mantle Cell Lymphoma; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Prior cancer-related surgery	39 (28.1%)	33 (23.4%)	72 (25.7%)
Prior radiotherapy	26 (18.7%)	26 (18.4%)	52 (18.6%)
Prior systemic therapy	139 (100.0%)	141 (100.0%)	280 (100.0%)
Bortezomib	30 (21.6%)	20 (14.2%)	50 (17.9%)
Rituximab	138 (99.3%)	141 (100.0%)	279 (99.6%)
Alkylator	138 (99.3%)	140 (99.3%)	278 (99.3%)
Anthracycline	129 (92.8%)	123 (87.2%)	252 (90.0%)
Vinca alkyloid	128 (92.1%)	127 (90.1%)	255 (91.1%)
Stem cell transplant	33 (23.7%)	33 (23.4%)	66 (23.6%)
Lenalidomide	8 (5.8%)	7 (5.0%)	15 (5.4%)
Cytarabine	67 (48.2%)	75 (53.2%)	142 (50.7%)
Purine analog	23 (16.5%)	26 (18.4%)	49 (17.5%)

Numbers analysed

Table 1: Subject Disposition and Treatment Withdrawal Information; Intent-to-treat analysis set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus	Total
Analysis set: intent-to-treat	139	141	280
Did not receive study drug	0	2 (1.4%)	2 (0.7%)
Still on treatment	65 (46.8%)	15 (10.6%)	80 (28.6%)
Discontinued treatment	74 (53.2%)	124 (87.9%)	198 (70.7%)
Reason for discontinuation			
Progressive disease or relapse	55 (39.6%)	58 (41.1%)	113 (40.4%)
Adverse event	9 (6.5%)	36 (25.5%)	45 (16.1%)
Death	6 (4.3%)	8 (5.7%)	14 (5.0%)
Lost to follow-up	0	0	0
Pregnancy	0	0	0
Investigator or sponsor decision	0	6 (4.3%)	6 (2.1%)
Subject refuses further treatment	4 (2.9%)	16 (11.3%)	20 (7.1%)

Note: Percentages calculated with the number of subjects in intent-to-treat analysis set as denominator

Outcomes and estimation

Primary endpoint; PFS by IRC

Table 8: Progression-free Survival by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

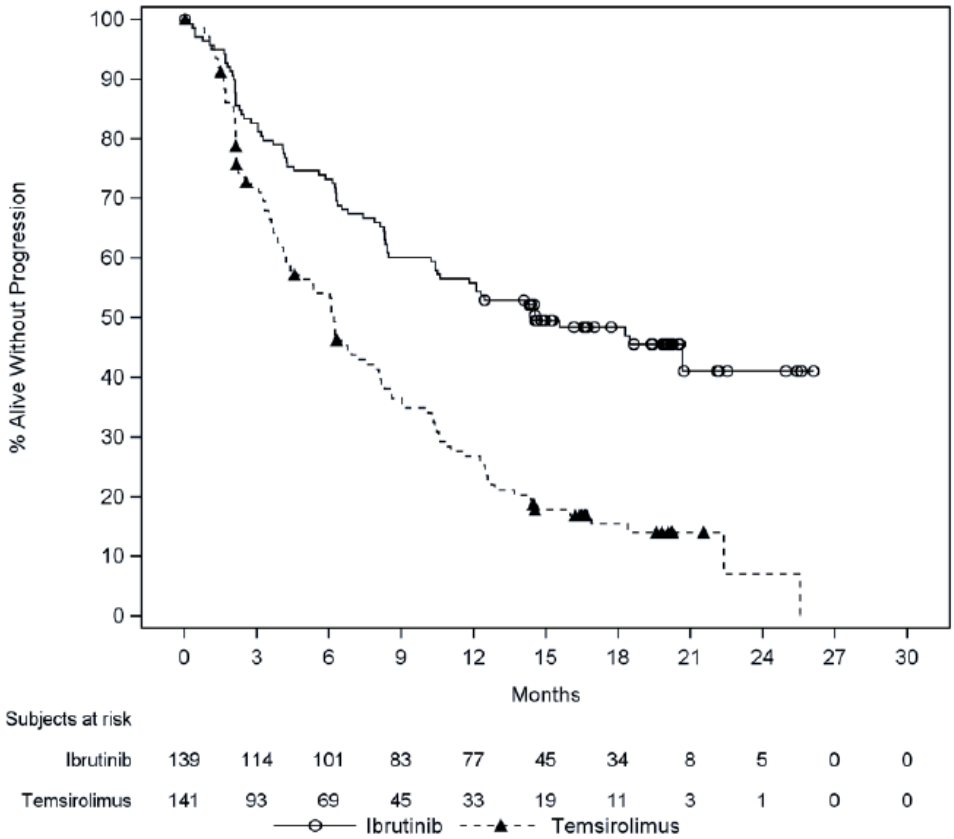
	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Progressed or died (event)	73 (52.5%)	111 (78.7%)
Censored	66 (47.5%)	30 (21.3%)
Progression-free survival (months)[a]		
25% quantile (95% CI)	4.5 (3.1, 6.8)	2.2 (2.1, 3.5)
Median (95% CI)	14.6 (10.4, NE)	6.2 (4.2, 7.9)
75% quantile (95% CI)	NE (NE, NE)	12.5 (10.3, 14.6)
6-months PFS rate (95% CI)	0.73 (0.65, 0.80)	0.54 (0.45, 0.62)
12-months PFS rate (95% CI)	0.56 (0.47, 0.64)	0.27 (0.19, 0.35)
18-months PFS rate (95% CI)	0.48 (0.40, 0.57)	0.15 (0.10, 0.23)
24-months PFS rate (95% CI)	0.41 (0.29, 0.52)	0.07 (0.01, 0.22)
P-value[b]	< 0.0001	
Hazard ratio (95% CI)[c]	0.43 (0.32, 0.58)	

Key: NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on stratified Log rank test with MIPI and prior lines of therapy from IWRS as stratification factors.
[c] Based on stratified Cox´s model with MIPI and prior lines of therapy from IWRS as stratification factors.
A hazard ratio <1 indicates an advantage for Ibrutinib.

TEFPFS05: Reason of Censoring for Progression-free Survival IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

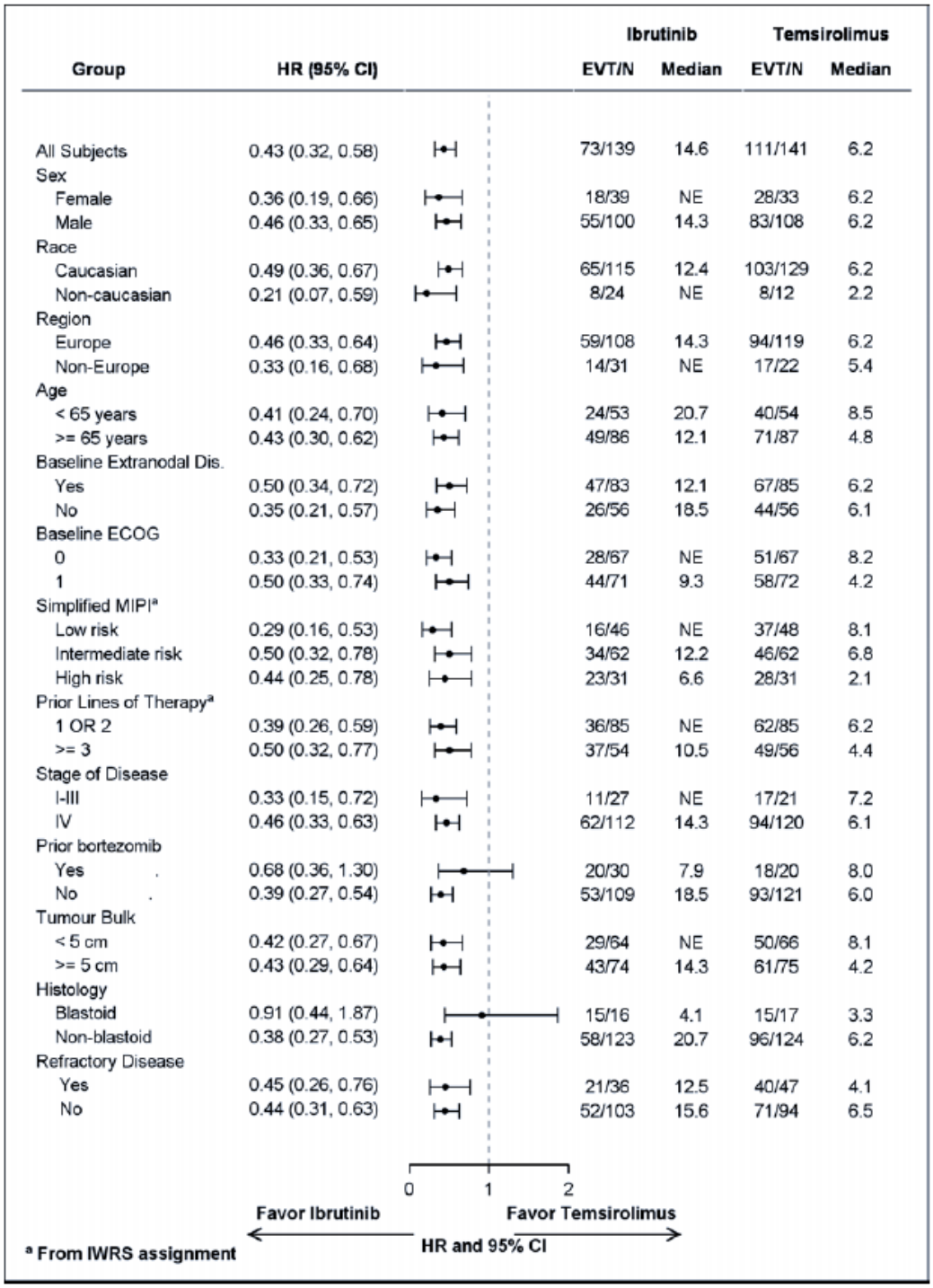
	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Censored	66 (47.5%)	30 (21.3%)
Reason of censoring		
Study cutoff	63 (45.3%)	20 (14.2%)
Withdrew consent	3 (2.2%)	9 (6.4%)
Lost to follow-up	0	1 (0.7%)

Figure 2: Kaplan-Meier Plot of Progression-free Survival by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



- Subgroup analyses of PFS

Figure 3: Subgroup Analysis for Progression-free Survival by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



Group	HR (95% CI)	Ibrutinib EVT/N	Ibrutinib Median	Temsirolimus EVT/N	Temsirolimus Median
All Subjects	0.43 (0.32, 0.58)	73/139	14.6	111/141	6.2
Sex					
Female	0.36 (0.19, 0.66)	18/39	NE	28/33	6.2
Male	0.46 (0.33, 0.65)	55/100	14.3	83/108	6.2
Race					
Caucasian	0.49 (0.36, 0.67)	65/115	12.4	103/129	6.2
Non-caucasian	0.21 (0.07, 0.59)	8/24	NE	8/12	2.2
Region					
Europe	0.46 (0.33, 0.64)	59/108	14.3	94/119	6.2
Non-Europe	0.33 (0.16, 0.68)	14/31	NE	17/22	5.4
Age					
< 65 years	0.41 (0.24, 0.70)	24/53	20.7	40/54	8.5
>= 65 years	0.43 (0.30, 0.62)	49/86	12.1	71/87	4.8
Baseline Extranodal Dis.					
Yes	0.50 (0.34, 0.72)	47/83	12.1	67/85	6.2
No	0.35 (0.21, 0.57)	26/56	18.5	44/56	6.1
Baseline ECOG					
0	0.33 (0.21, 0.53)	28/67	NE	51/67	8.2
1	0.50 (0.33, 0.74)	44/71	9.3	58/72	4.2
Simplified MIPI[a]					
Low risk	0.29 (0.16, 0.53)	16/46	NE	37/48	8.1
Intermediate risk	0.50 (0.32, 0.78)	34/62	12.2	46/62	6.8
High risk	0.44 (0.25, 0.78)	23/31	6.6	28/31	2.1
Prior Lines of Therapy[a]					
1 OR 2	0.39 (0.26, 0.59)	36/85	NE	62/85	6.2
>= 3	0.50 (0.32, 0.77)	37/54	10.5	49/56	4.4
Stage of Disease					
I-III	0.33 (0.15, 0.72)	11/27	NE	17/21	7.2
IV	0.46 (0.33, 0.63)	62/112	14.3	94/120	6.1
Prior bortezomib					
Yes	0.68 (0.36, 1.30)	20/30	7.9	18/20	8.0
No	0.39 (0.27, 0.54)	53/109	18.5	93/121	6.0
Tumour Bulk					
< 5 cm	0.42 (0.27, 0.67)	29/64	NE	50/66	8.1
>= 5 cm	0.43 (0.29, 0.64)	43/74	14.3	61/75	4.2
Histology					
Blastoid	0.91 (0.44, 1.87)	15/16	4.1	15/17	3.3
Non-blastoid	0.38 (0.27, 0.53)	58/123	20.7	96/124	6.2
Refractory Disease					
Yes	0.45 (0.26, 0.76)	21/36	12.5	40/47	4.1
No	0.44 (0.31, 0.63)	52/103	15.6	71/94	6.5

<u>OS</u>

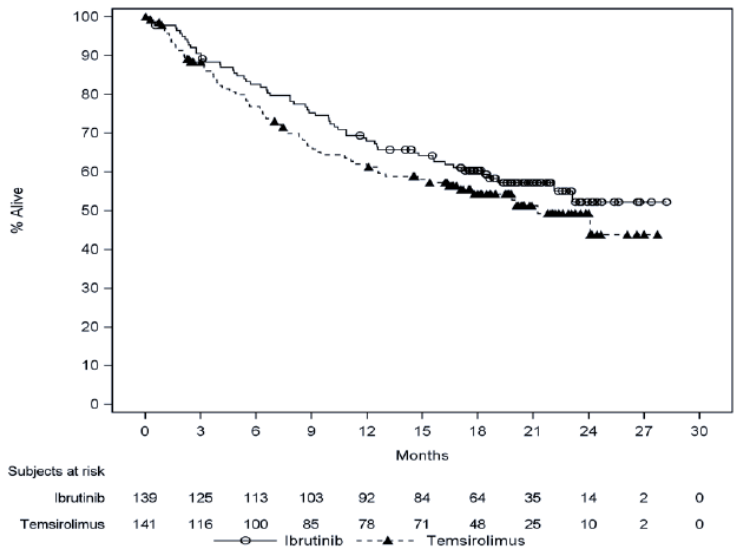
At a median follow-up of 20.4 months for the ibrutinib arm and 19.6 months for the temsirolimus arm (of note, 23 patients crossed over to ibrutinib after progression on temsirolimus):

Table 14: Overall Survival; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Died (event)	59 (42.4%)	63 (44.7%)
Censored	80 (57.6%)	78 (55.3%)
Overall Survival (months)[a]		
25% quantile (95% CI)	9.2 (6.2, 12.4)	6.4 (4.0, 8.6)
Median (95% CI)	NE (18.6, NE)	21.3 (13.0, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
6-months OS rate (95% CI)	0.83 (0.75, 0.88)	0.77 (0.69, 0.83)
12-months OS rate (95% CI)	0.68 (0.59, 0.75)	0.61 (0.52, 0.69)
18-months OS rate (95% CI)	0.60 (0.52, 0.68)	0.54 (0.45, 0.63)
24-months OS rate (95% CI)	0.52 (0.41, 0.62)	0.49 (0.39, 0.58)
P-value[b]	0.1324	
Hazard ratio (95% CI)[c]	0.76 (0.53, 1.09)	

Key: NE=not estimable
[a] Based on Kaplan-Meier product limit estimates.
[b] Based on stratified Log rank test with MIPI and prior lines of therapy from IWRS as stratification factors.
[c]Based on stratified Cox's model with MIPI and prior lines of therapy from IWRS as stratification factors.
A hazard ratio < 1 indicates an advantage for Ibrutinib.

Figure 6: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



ORR by IRC

Table 11: Overall Response Rate by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Best response		
Complete response (CR)	26 (18.7%)	2 (1.4%)
Partial response (PR)	74 (53.2%)	55 (39.0%)
Stable disease (SD)	15 (10.8%)	43 (30.5%)
Progressive disease (PD)	15 (10.8%)	23 (16.3%)
Not evaluable (NE)	7 (5.0%)	17 (12.1%)
No evidence of disease (NED)	2 (1.4%)	1 (0.7%)
Overall response rate (CR or PR)	100 (71.9%)	57 (40.4%)
P-value[a]	<0.0001	
Odds ratio (95% CI)[b]	3.98 (2.38, 6.65)	

[a] P-value from the Cochran Mantel-Haenszel Chi-Squared test with MIPI and prior lines of therapy from IWRS as stratification factors.
[b] Mantel-Haenszel estimate of the common odds ratio with MIPI and prior lines of therapy from IWRS as stratification factors. An odds ratio > 1 indicates an advantage for Ibrutinib.

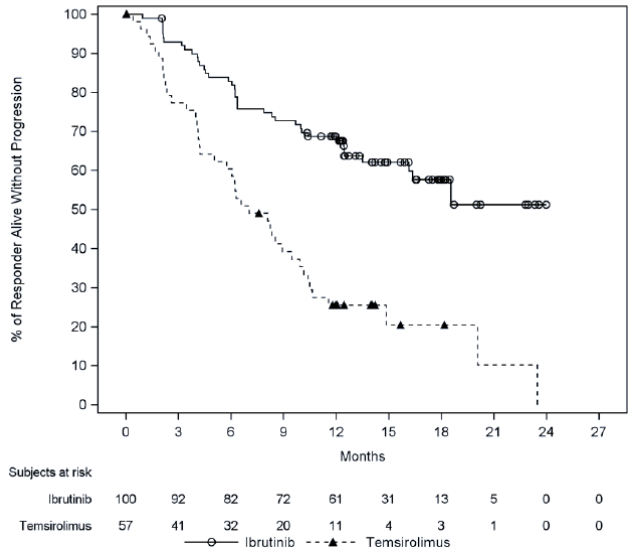
ORR by investigators' assessment was 77% for the ibrutinib arm and 46.1% for the temsirolimus arm, p<0.0001.

Duration of response

Table 12: Duration of Response by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Responder (CR or PR)	100	57
Progressed or died (event)	39 (39.0%)	42 (73.7%)
Censored	61 (61.0%)	15 (26.3%)
Duration of response (months)[a]		
25% quantile (95% CI)	7.9 (4.7, 12.4)	4.0 (2.1, 5.1)
Median (95% CI)	NE (16.2, NE)	7.0 (4.2, 9.9)
75% quantile (95% CI)	NE (NE, NE)	14.9 (9.5, 23.5)
6-months DOR rate (95% CI)	0.83 (0.74, 0.89)	0.60 (0.46, 0.72)
12-months DOR rate (95% CI)	0.69 (0.59, 0.77)	0.26 (0.15, 0.38)
18-months DOR rate (95% CI)	0.58 (0.46, 0.68)	0.20 (0.09, 0.35)
24-months DOR rate (95% CI)	0.51 (0.35, 0.65)	0.00 (NE, NE)

Figure 5: Kaplan-Meier Plot of Duration of Response by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



Time to response

Table 13: Time to Response by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Responder (CR or PR)	100	57
Time to initial response (months) [a]		
Median	2.15	2.14
Range	(0.5; 10.4)	(0.9; 12.0)
Time to best response (months) [a]		
Median	2.17	2.14
Range	(0.5; 20.9)	(0.9; 12.0)
Responder (CR)	26	2
Time to CR (months) [b]		
Median	6.28	6.60
Range	(2.1; 20.9)	(6.2; 7.0)

- Exploratory covariate-adjusted analysis of PFS using Cox regression models

Table 10: Covariate Adjusted Analysis for Progression-free Survival by IRC Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Hazard Ratio	95% CI for Hazard Ratio	p-value
Treatment (Ibrutinb vs. Temsirolimus)	0.41	(0.30, 0.57)	<.0001
Sex (male vs. female)	0.82	(0.57, 1.18)	0.2812
Age group (>=65 vs. <65 years)	1.08	(0.74, 1.58)	0.6713
Race (caucasian vs. non-caucasian)	1.05	(0.57, 1.93)	0.8808
Baseline ECOG (1 vs. 0)	1.56	(1.13, 2.16)	0.0069
Region (Europe vs non-Europe)	0.84	(0.53, 1.34)	0.4688
Baseline extranodal disease (yes vs. no)	0.91	(0.62, 1.33)	0.6225
MIPI Score (intermediate vs. low)[a]	1.36	(0.90, 2.03)	0.1400
MIPI Score (high vs. low)[a]	2.51	(1.55, 4.07)	0.0002
Prior lines of therapy (>=3 vs. <3)[a]	1.58	(1.14, 2.19)	0.0066
Stage of disease (IV vs. I-III)	1.08	(0.61, 1.91)	0.7902
Prior bortezomib (yes vs. no)	1.03	(0.70, 1.53)	0.8641
Tumor bulk (>=5 vs. <5 cm)	0.96	(0.66, 1.40)	0.8309
Tumor Burden	1.00	(1.00, 1.00)	0.8147
Histology (blastoid vs. non-blastoid)	2.49	(1.60, 3.86)	<.0001
Refractory Disease (yes vs. no)	1.21	(0.86, 1.71)	0.2680
Bone marrow involvement (yes vs. no)	0.96	(0.67, 1.40)	0.8509

Time to next treatment

Table 15: Time to Next Treatment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Subsequent Therapy (event)	44 (31.7%)	82 (58.2%)
Censored	95 (68.3%)	59 (41.8%)
Time to next treatment (months)[a]		
25% quantile (95% CI)	10.4 (5.8, 14.7)	4.9 (3.4, 6.0)
Median (95% CI)	NE (NE, NE)	11.6 (8.0, 13.3)
75% quantile (95% CI)	NE (NE, NE)	22.0 (16.4, NE)
6-months STF rate (95% CI)	0.82 (0.75, 0.88)	0.67 (0.58, 0.75)
12-months STF rate (95% CI)	0.69 (0.60, 0.77)	0.48 (0.38, 0.57)
18-months STF rate (95% CI)	0.66 (0.57, 0.73)	0.26 (0.17, 0.35)
24-months STF rate (95% CI)	0.64 (0.55, 0.72)	0.19 (0.10, 0.30)
P-value[b]	< 0.0001	
Hazard ratio (95% CI)[c]	0.37 (0.25, 0.53)	

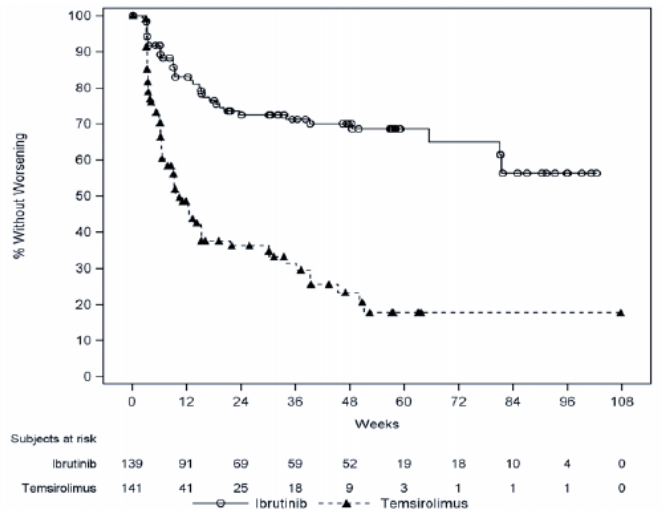
Time to worsening in the Lym subscale of FACT-Lym

Worsening was defined by a 5-point decrease from baseline. The overall compliance rates for the patient-reported outcomes measured (FACT-Lym and EQ-5D-5L) were <10% missing at most time points administered. The temsirolimus arm showed a lower compliance rate (by 5 to 10% compared with the ibrutinib arm) at most timepoints. The most common reason for the lower compliance rate was "administrative failure". Mean summary scores were similar for each treatment arm at baseline.

Table 16: Time to Worsening in FACT-Lym Lymphoma Subscale; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Worsening	37 (26.6%)	73 (51.8%)
Censored	102 (73.4%)	68 (48.2%)
Time to worsening (weeks)[a]		
25% quantile (95% CI)	19.4 (9.4, 65.4)	5.1 (3.4, 6.3)
Median (95% CI)	NE (81.1, NE)	9.7 (7.3, 15.3)
75% quantile (95% CI)	NE (NE, NE)	45.4 (30.3, NE)
12-weeks event-free rate (95% CI)	0.83 (0.75, 0.89)	0.49 (0.38, 0.58)
24-weeks event-free rate (95% CI)	0.72 (0.63, 0.80)	0.36 (0.26, 0.46)
36-weeks event-free rate (95% CI)	0.71 (0.62, 0.79)	0.31 (0.22, 0.41)
48-weeks event-free rate (95% CI)	0.70 (0.60, 0.78)	0.23 (0.14, 0.34)
72-weeks event-free rate (95% CI)	0.65 (0.53, 0.75)	0.18 (0.09, 0.29)
P-value[b]	< 0.0001	
Hazard ratio (95% CI)[c]	0.27 (0.18, 0.41)	

Figure 8: Time to Worsening in FACT-Lym Lymphoma Subscale; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



TPRO10: Summary of Meaningful Worsening and Improvement in Lymphoma Subscale Score; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Maximum increase in lymphoma subscale score		
N	130	123
Mean (SD)	8.62 (7.67)	4.68 (5.23)
Median	7.00	3.00
Range	(0.0; 40.0)	(0.0; 33.0)
5 or more	86	50
10 or more	50	25
Maximum decrease in lymphoma subscale score		
N	130	123
Mean (SD)	4.08 (6.65)	8.65 (8.28)
Median	0.00	7.00
Range	(0.0; 37.0)	(0.0; 34.0)
5 or more	37	73
10 or more	23	51

Ancillary analyses

- Sensitivity analyses for PFS

Table 9: Summary of PFS Analyses for Study PCI-32765MCL3001

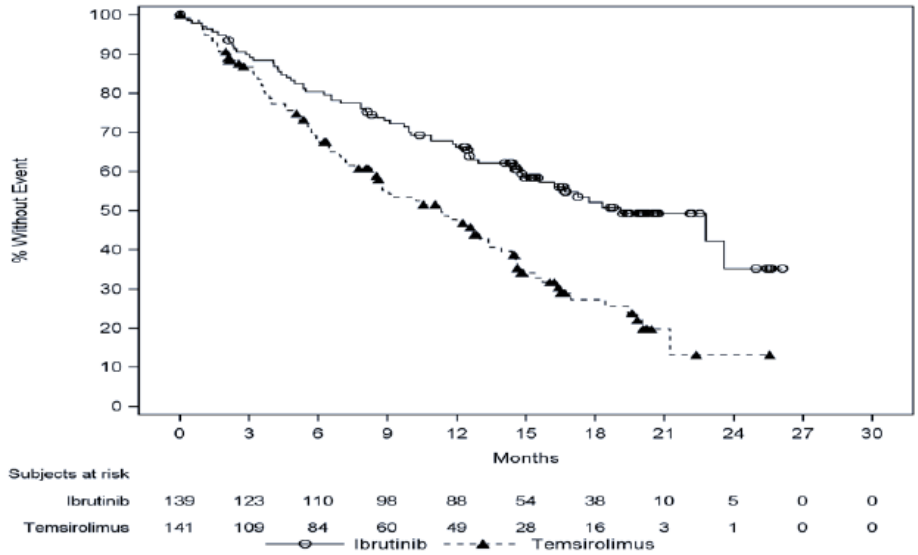
PFS Analysis / Population	Median PFS (months) Ibrutinib (95% CI)	Temsirolimus (95% CI)	Hazard Ratio (95% CI)	p-value
IRC determined date of progression / ITT Population (stratified log rank test)[a]	14.6 (10.4; NE)	6.2 (4.2; 7.9)	0.43 (0.32; 0.58)	<0.0001
IRC determined date of progression / ITT Population (unstratified log rank test)	14.6 (10.4; NE)	6.2 (4.2; 7.9)	0.43 (0.32; 0.58)	<0.0001
IRC determined date of progression at subsequent therapy start / ITT Population	14.6 (10.4; NE)	5.4 (4.0; 6.2)	0.40 (0.30; 0.54)	<0.0001
IRC determined date of progression censored at last disease assessment date prior to subsequent therapy / ITT Population	18.3 (11.8; NE)	6.2 (4.4; 8.3)	0.42 (0.30; 0.57)	<0.0001
Investigator-determined date of progression / ITT population	15.6 (10.6; NE)	6.2 (4.2; 7.8)	0.43 (0.32; 0.58)	<0.0001

PFS2 by investigators´assessment

TEFPFS201: PFS2 by Investigator Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Subject status		
Event	64 (46.0%)	87 (61.7%)
Censored	75 (54.0%)	54 (38.3%)
PFS2 (months)[a]		
25% quantile (95% CI)	8.1 (5.4, 10.9)	4.9 (3.5, 6.0)
Median (95% CI)	19.1 (14.9, NE)	11.3 (8.5, 13.4)
75% quantile (95% CI)	NE (23.6, NE)	19.4 (15.4, NE)
6-months PFS2 rate (95% CI)	0.80 (0.73, 0.86)	0.68 (0.59, 0.76)
12-months PFS2 rate (95% CI)	0.66 (0.58, 0.74)	0.47 (0.38, 0.55)
18-months PFS2 rate (95% CI)	0.52 (0.42, 0.61)	0.27 (0.19, 0.37)
24-months PFS2 rate (95% CI)	0.35 (0.18, 0.53)	0.13 (0.04, 0.28)
P-value[b]	< 0.0001	
Hazard ratio (95% CI)[c]	0.49 (0.36, 0.69)	

Figure 9: Kaplan-Meier Plot of PFS2 by Investigator Assessment; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)



Supportive studies

2.4.2.1. Study PCI-32765MCL2001; Phase 2, single arm

"A Phase 2, Multicenter, Single-Arm Study to Evaluate the Efficacy and Safety of Single- Agent Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Subjects With Mantle Cell Lymphoma Who Progress After Bortezomib Therapy"

Study period: Study initiated: 17 July 2012; Clinical cutoff: 29 April 2014; Database lock: 20 June 2014. Note, a CSR addendum representing the final analysis at study closure (31 May 2015, the last subject, last visit date) has been provided, including further investigator-assessed data only. Patients on ibrutinib treatment at study closure could be enrolled in the CAN3001 extension study.

Study centers: Belgium (n=1 study center), France (n=2), Israel (n=6), Poland (n=1), Russia (n=4), United Kingdom (n=2), and United States (n=22).

Key inclusion criteria

- Diagnosis of MCL confirmed by central review prior to enrollment.
- Received at least 1 prior rituximab-containing chemotherapy regimen.

- Received at least 2 cycles of bortezomib therapy (single-agent or in combination) and had documented progressive disease during or after bortezomib therapy based on Revised Response Criteria for Malignant Lymphoma. Documentation of progressive disease after bortezomib therapy must have been reviewed and approved by the Sponsor prior to the first dose of study drug.
- At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma
- Eastern Cooperative Oncology Group performance status score 0, 1, or 2.

Notable exclusion criteria

- More than 5 prior lines of therapy (separate lines of therapy were defined as single or combination therapies that were either separated by disease progression or by a >6 month treatment-free interval).
- History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.
- Required anticoagulation with warfarin or equivalent vitamin K

Study medication

Ibrutinib 560 mg orally once per day continuously during 21-day treatment cycles.

Endpoints

Primary endpoint: ORR, defined as the proportion of evaluable subjects who achieved CR or PR as assessed by the IRC based upon the Revised Response Criteria for Malignant Lymphoma.

Disease evaluations included CT, MRI, PET, and clinical evaluation performed every 9 weeks for up to 15 months from the start of study drug, and every 24 weeks thereafter. Whole body FDG-PET scan (skull base to the proximal femur) will be done at Screening. For subjects who are PET-positive at baseline, PET will be done at the time of maximal tumor reduction (eg, CR or PR with 2 consecutive CT scans showing no further tumor reduction). In addition, PET will be performed at suspected disease progression, if a new lesion was detected on CT.

Key secondary endpoints: Time to initial response/best response for subjects who achieved CR/PR, duration of response, PFS as determined by the IRC, OS.

Key statistical elements

Single arm design. The sample size for this study was based on the assumption that the ORR for ibrutinib would be 56%, which was the lowest observed response rate in all subgroups analyzed from the then ongoing Phase 2 study, PCYC-1104-CA. With 101 evaluable subjects, the study was expected to have 90% power to declare that ORR was 40% or higher at the 1-sided significance level of 0.025. No interim analysis. The final analysis for ORR was to be conducted using a clinical cutoff date approximately 1 year after enrollment of the last subject. End of study occurred approximately 2 years after the last subject was enrolled.

With amendment INT-2 (28 August 2013; 120 subjects = fully enrolled), the clinical cutoff for the primary analysis was changed from 6 months to approximately 1 year after the last subject was enrolled.

Results

At the primary analysis, the median time on study was 14.9 months.

Table 1: Study Treatment Completion/Withdrawal Information; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all-treated	120
Treatment ongoing	39 (32.5%)
Discontinued treatment	81 (67.5%)
Reason for discontinuation	
Progressive Disease or Relapse	53 (44.2%)
Adverse event	8 (6.7%)
Lost to follow-up	0
Investigator or Sponsor decision	3 (2.5%)
Pregnancy	0
Death	8 (6.7%)
Subject refuses further treatment with study drug per protocol	9 (7.5%)

Table 9: Major Protocol Deviations; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all treated	120
Subjects with major protocol deviation	16 (13.3%)
Protocol deviation coded term	
Entered But Did Not Satisfy Criteria	7 (5.8%)
Safety Assessment Deviation	7 (5.8%)
Received A Disallowed Concomitant Treatment	2 (1.7%)
Efficacy Assessment Deviation	1 (0.8%)

Demographics and baseline characteristics

Table 4: Baseline Disease Characteristics; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all treated	120
Time from initial diagnosis to first dose (months)	
N	120
Mean (SD)	53.72 (36.151)
Median	43.94
Range	(6.8; 189.6)
Time from end of last prior therapy to first dose (months)	
N	120
Mean (SD)	9.21 (13.184)
Median	3.10
Range	(0.5; 62.5)
Stage of MCL at study entry	
N	120
I	2 (1.7%)
II	9 (7.5%)
III	16 (13.3%)
IV	93 (77.5%)
Types of Histology	
N	120
Blastoid	11 (9.2%)
Diffuse	62 (51.7%)
Nodular	29 (24.2%)
Other	18 (15.0%)
Simplified MCL international prognostic index	
N	118
Low risk (1-3)	28 (23.7%)
Intermediate risk (4-5)	57 (48.3%)
High risk (6 – 11)	33 (28.0%)
Baseline lymphoma symptom[a]	
N	120
Yes	59 (49.2%)
B-symptoms	18 (15.0%)
Recurrent fevers	5 (4.2%)
Night sweat	14 (11.7%)
Weight loss	7 (5.8%)
Other MCL-related symptoms	55 (45.8%)
Itching	9 (7.5%)
Severe and persistent fatigue	30 (25.0%)
Physical discomfort due to enlarged lymph nodes	30 (25.0%)
Other	12 (10.0%)
ECOG performance status	
N	120
0	42 (35.0%)
1	67 (55.8%)
2	11 (9.2%)
Prior lines of therapy	
N	120
Mean (SD)	2.66 (1.267)
Median	2.00
Range	(1.0; 8.0)
1-2	63 (52.5%)
3-5	56 (46.7%)
>5	1 (0.8%)

All treated population, n=120. Subjects had a median age of 67.5 years (range: 35 to 85 years), with 62.5% of subjects ≥65 years of age. Most subjects (86.7%) were men and 94.2% were white. Thirty-one percent of patients were recruited in Europe, the rest in US. Median number of prior lines of therapy was 2.

Table 5: Extent of Disease at Baseline; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all treated	120
Number of lesions	
N	120
Mean (SD)	5.87 (3.507)
Median	5.00
Range	(1.0; 24.0)
Bulky disease (LD >= 5 cm)	63 (52.5%)
Bulky disease (LD >= 10 cm)	17 (14.2%)
Extranodal disease	72 (60.0%)
Bone marrow involvement[a]	50 (41.7%)

Table 7: Summary of Prior Treatment for Mantle Cell Lymphoma; All-treated Population (Study PCI-32765MCL2001)	
	Ibrutinib
Population: all treated	120
Prior cancer-related surgery	29 (24.2%)
Prior radiotherapy	28 (23.3%)
Prior systemic therapy	120 (100.0%)
Bortezomib	120 (100.0%)
Rituximab	120 (100.0%)
Alkylator	118 (98.3%)
Anthracycline	108 (90.0%)
Vinca alkyloid	100 (83.3%)
CHOP / R-CHOP [a]	48 (40.0%)
Stem cell transplant	40 (33.3%)
Lenalidomide	23 (19.2%)
Hyper CVAD	19 (15.8%)
Purine analog	16 (13.3%)

ORR by IRC, primary endpoint

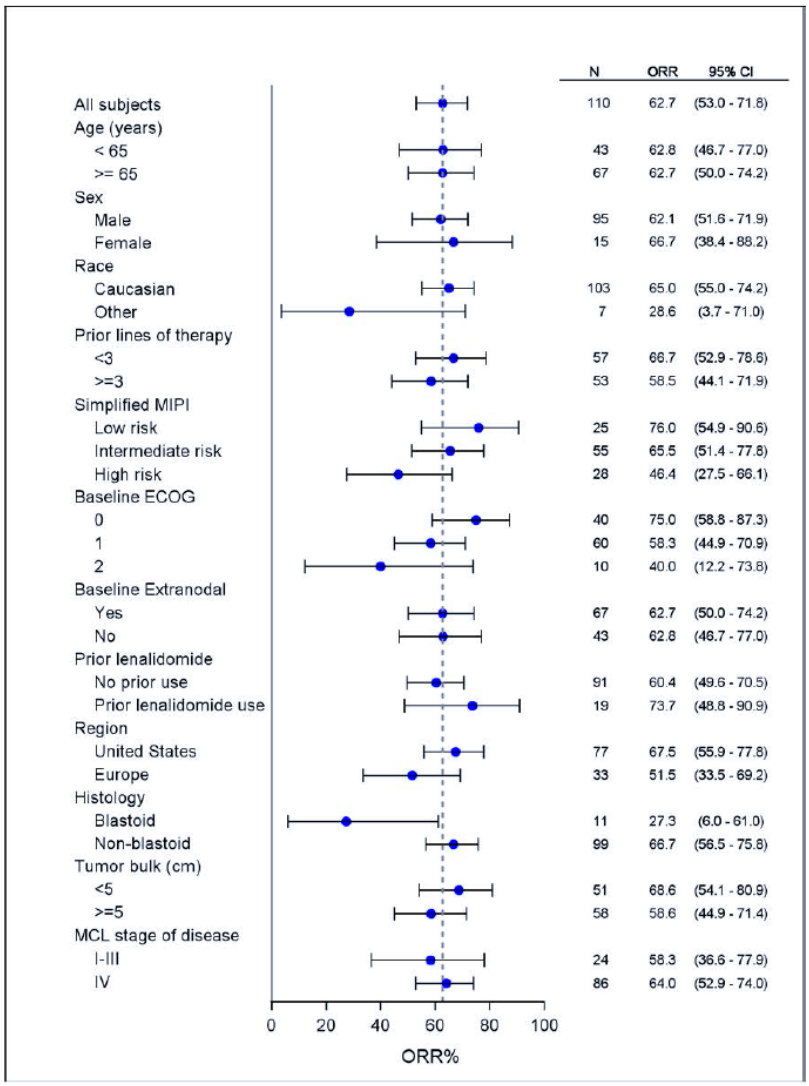
Table 12: Response Rate by IRC; Response Evaluable Population (Study PCI-32765MCL2001)			
	Ibrutinib		
	N (%)	95% CI	p-value [a]
Population: response evaluable	110		
Best Response			
Complete response (CR)	23 (20.9%)	(13.3%, 28.5%)	
Partial response (PR)	46 (41.8%)	(32.6%, 51.0%)	
Overall response (CR+PR)	69 (62.7%)	(53.7%, 71.8%)	< 0.001
Stable disease	16 (14.5%)	(8.0%, 21.1%)	
Progressive disease	25 (22.7%)	(14.9%, 30.6%)	

[a] Based on 40% response rate under the null hypothesis and normal approximation to binomial.

The ORR by investigator assessment of the response-evaluable population was 66.4% (95% CI: 57.5%, 75.2%) with a CR rate of 18.2% (95% CI: 11.0%, 25.4%). The overall concordance between IRC and investigator assessments of ORR was 90.0%. At the final analysis by investigator, with a median follow-up of 26.7 months, ORR was unchanged but the fraction of patients with CR had increased to 24.5%.

The ORR by IRC assessment of the all-treated population (n=120) was 57.5% (95% CI: 48.7%, 66.3%), which included a CR rate of 19.2% (95% CI: 12.1%, 26.2%).

Figure 4: Subgroup Analysis of Response Rate by IRC; Response Evaluable Population (Study PCI-32765MCL2001)



CIs are based on exact binomial distribution.

Secondary endpoints

- Time to initial/best response

Table 14: Time to Response and Best Response by IRC; All-treated (Study PCI-32765MCL2001)

	Ibrutinib
Population: all-treated[a]	69
Responder (complete or partial response)	69
Time to initial response (months)	
Mean (SD)	2.37 (1.045)
Median	2.07
Range	(1.3; 6.3)
Time to best response (months)	
Mean (SD)	3.62 (2.346)
Median	2.14
Range	(1.3; 10.6)

- Duration of response

Table 15: Duration of Response by IRC; All-treated (Study PCI-32765MCL2001)

	Ibrutinib
Population: all-treated[a]	69
Responder (complete or partial response)	
Progressed or died	23 (33.3%)
Censored	46 (66.7%)
Duration of response (months)[b]	
25th percentile (95% CI)	9.69 (4.17, 12.45)
Median (95% CI)	14.92 (12.35, NE)
75th percentile (95% CI)	NE (14.92, NE)

- Progression-free survival

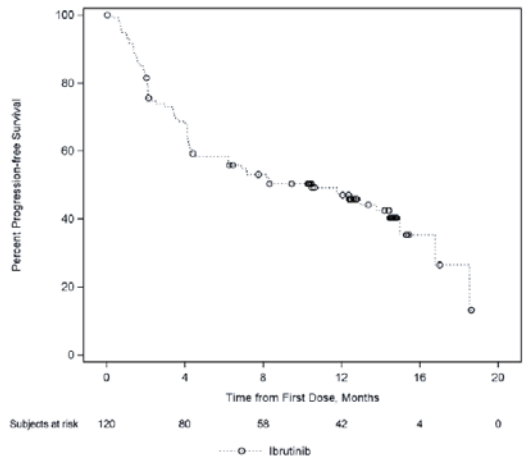
Table 16: Progression-free Survival by IRC; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all treated	120
Subject status	120
Progressed or died	68 (56.7%)
Censored	52 (43.3%)
Progression-free survival (PFS) (months)[a]	
25th percentile (95% CI)	2.17 (1.94, 4.11)
Median (95% CI)	10.48 (4.37, 14.98)
75th percentile (95% CI)	18.53 (14.98, NE)
6-months PFS rate (95% CI)	0.58 (0.49, 0.67)
12-months PFS rate (95% CI)	0.47 (0.38, 0.56)
18-months PFS rate (95% CI)	0.26 (0.11, 0.45)

Reasons for censoring (n=52) were study cutoff 75%, lost to follow-up 14%, and withdrew consent 12%.

The median PFS by investigator assessment was 10.1 months (95% CI: 6.2, 13.8 months).

Figure 5: Kaplan-Meier Curve of Progression-free Survival by IRC; All-treated Population (Study PCI-32765MCL2001)

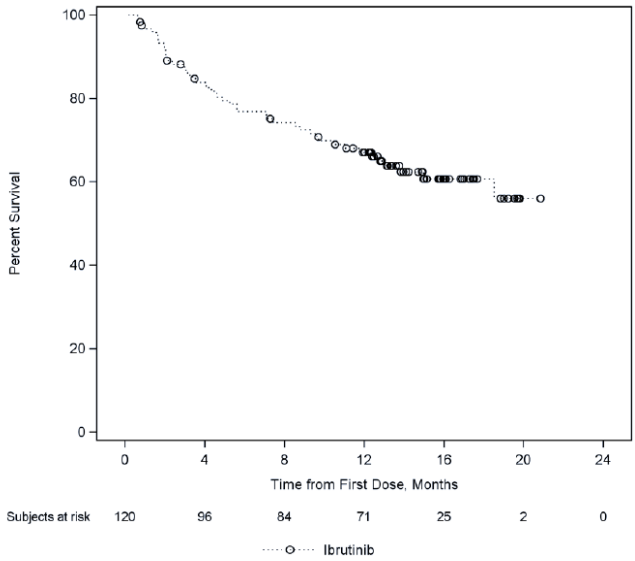


- Overall survival

Table 17: Overall Survival; All-treated Population (Study PCI-32765MCL2001)

	Ibrutinib
Population: all treated	120
Subject status	120
Died	44 (36.7%)
Censored	76 (63.3%)
Overall survival (OS) (months)[a]	
25th percentile (95% CI)	7.43 (4.07, 11.79)
Median (95% CI)	NE (18.53, NE)
75th percentile (95% CI)	NE (NE, NE)
6-months survival rate (95% CI)	0.77 (0.68, 0.83)
12-months survival rate (95% CI)	0.67 (0.58, 0.75)
18-months survival rate (95% CI)	0.61 (0.50, 0.69)
24-months survival rate (95% CI)	0.56 (0.43, 0.67)

Figure 6: Kaplan-Meier Curve of Overall Survival; All-treated Population (Study PCI-32765MCL2001)



Summary of efficacy across studies in r/r MCL

Table 3: Key Efficacy Assessments – Study MCL3001, Study MCL2001, and Study 1104

	Study MCL3001		Study MCL2001	Study 1104
	Ibrutinib	Temsirolimus	Ibrutinib	Ibrutinib
Progression-free Survival per IRC[a]				
Analysis set: ITT/All Treated[b]	139	141	120	111
Events	73 (52.5%)	111 (78.7%)	68 (56.7%)	57 (51.4%)
Median (95% CI), months	14.59 (10.41, NE)	6.21 (4.21, 7.85)	10.48 (4.37, 14.98)	13.90 (7.00, NE)
p-value	<0.0001			
Hazard Ratio (95% CI)	0.428 (0.316, 0.579)			
Overall Response Rate[d] per IRC				
Analysis set: ITT/All Treated /Response Evaluable[c]	139	141	110	111
ORR[d] per IRC (CR, PR)	100 (71.9%)	57 (40.4%)	69 (62.7%)	76 (68.5%)[e]
Relative Risk (95% CI)	1.78 (1.43, 2.23)[f]			
p-value[g]	<0.0001			
Overall Survival				
Analysis set: ITT/All Treated[b]	139	141	120	111
Deaths	59 (42.4%)	63 (44.7%)	44 (36.7%)	41 (36.9%)
Median (95% CI), months	NE (18.63, NE)	21.26 (13.01, NE)	NE (18.53, NE)	NE (13.24, NE)
p-value	0.1324			
Hazard Ratio (95% CI)	0.760 (0.531, 1.088)			

CI=confidence interval, CR=complete response, IRC=Independent Review Committee, ITT=intent-to-treat, NE=not estimable, PR=partial response.

[a] Study 1104 result is based on investigator assessment, as the primary analysis in the CSR is per investigator assessment.

[b] Study MCL3001 uses the ITT analysis set; Studies MCL2001 and 1104 use the all treated analysis set.

[c] Study MCL3001 uses the ITT analysis set; Study 1104 uses the all treated analysis set; Study MCL2001 uses the response evaluable analysis set.

[d] Response rate is estimated using the crude proportion of responders based on the best overall response.

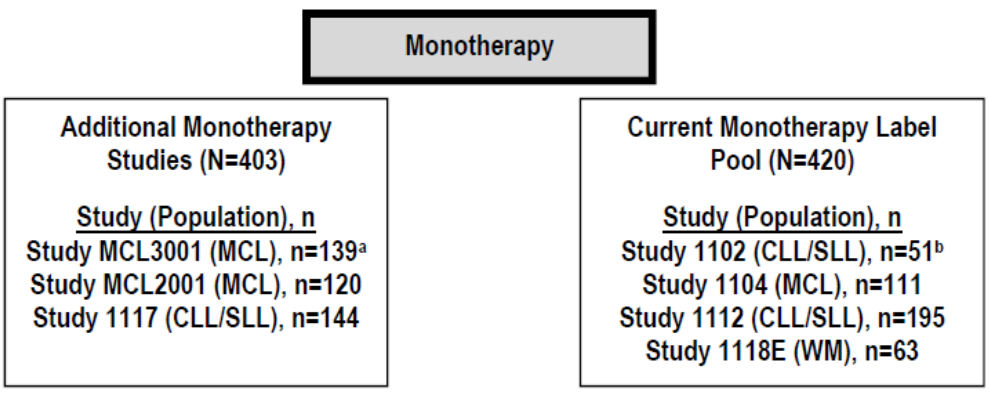
[e] The primary analysis of ORR by investigator was 67.6%.

[f] In the MCL3001 clinical study report, the odds ratio is reported: 3.98 (95% CI: 2.38, 6.65).

[g] Stratified Cochran Mantel Haenszel test.

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

Comparison of "Current monotherapy label pool" with "Additional monotherapy studies"



[a] Subjects treated with ibrutinib

[b] Subjects with relapsed or refractory CLL treated with 420 mg ibrutinib

Table 1 **Data Cutoff Dates for Current Monotherapy Label Pool Safety Analyses**

Study	Data Cutoff Dates for Safety Analyses			
	Primary CSR	Original MAA Filing	Current SmPC[a]	Current Type II variation
1102	28 Nov 2012	28 Nov 2012	28 Nov 2012	28 Nov 2012
1112	06 Nov 2013	06 Nov 2013	20 Jun 2014 (4-month update)	06 Nov 2013
1104	26 Dec 2012	15 May 2013 (4-month update)	03 Mar 2014 (final follow-up data)	26 Dec 2012
1118E	28 Feb 2014	28 Feb 2014	28 Feb 2014	28 Feb 2014

Exposure

Table 3: Extent of Exposure - Additional Monotherapy Studies and Current Monotherapy Label Pool; Safety Population

	Additional Monotherapy Studies (Studies MCL2001, MCL3001 and Study 1117)	Current Monotherapy Label Pool (Studies 1102, 1104, 1112 and 1118E)
Analysis set: safety population	403	420
Treatment duration (months)		
N	403	420
Mean (SD)	10.83 (6.643)	10.47 (5.812)
Median	11.10	9.38
Range	(0.0; 28.2)	(0.2; 28.7)
0 - <3 months	72 (17.9%)	45 (10.7%)
3 - <6 months	45 (11.2%)	37 (8.8%)
6 - <9 months	30 (7.4%)	111 (26.4%)
9 - <12 months	84 (20.8%)	95 (22.6%)
12 - <15 months	79 (19.6%)	50 (11.9%)
15 - <18 months	31 (7.7%)	28 (6.7%)
18 - <24 months	50 (12.4%)	40 (9.5%)
>=24 months	12 (3.0%)	14 (3.3%)
Relative dose intensity (%)		
N	402	420
Mean (SD)	95.0 (9.33)	94.0 (11.09)
Median	99.2	99.1
Range	(30; 100)	(33; 102)
<75 %	20 (5.0%)	28 (6.7%)
75%-<90%	43 (10.7%)	50 (11.9%)
≥ 90%	339 (84.3%)	342 (81.4%)

Demographics and baseline characteristics

Table 5: Demographics and Baseline Disease Characteristics - Additional Monotherapy Studies and Current Monotherapy Label Pool; Safety Population

	Additional Monotherapy Studies (Studies MCL2001, MCL3001 and Study 1117)	Current Monotherapy Label Pool (Studies 1102, 1104, 1112 and 1118E)
Analysis set: safety population	403	420
Region		
N	403	420
United States	167 (41.4%)	288 (68.6%)
Europe	194 (48.1%)	121 (28.8%)
ROW	42 (10.4%)	11 (2.6%)
Age (years)		
N	403	420
Mean (SD)	65.9 (9.55)	65.9 (10.03)
Median	66.0	67.0
Range	(35; 89)	(30; 86)
< 65	173 (42.9%)	174 (41.4%)
≥ 65	230 (57.1%)	246 (58.6%)
≥ 70	160 (39.7%)	164 (39.0%)
≥ 75	80 (19.9%)	86 (20.5%)
Sex		
N	403	420
Male	300 (74.4%)	299 (71.2%)
Female	103 (25.6%)	121 (28.8%)
Time from initial diagnosis to randomization/ first dose (months)		
N	396	420
Mean (SD)	39.2 (38.75)	87.4 (64.21)
Median	29.9	73.6
Range	(0; 299)	(2; 334)
Histology		
N	403	420
CLL/SLL	144 (35.7%)	246 (58.6%)
MCL	259 (64.3%)	111 (26.4%)
WM	0	63 (15.0%)
Lines of prior therapy		
N	403	420
Mean (SD)	2.3 (1.28)	3.3 (2.12)
Median	2.0	3.0
Range	(1; 9)	(1; 12)
< 3	246 (61.0%)	192 (45.7%)
≥ 3	157 (39.0%)	228 (54.3%)
Missing	0	0

Subject disposition

Table 7: Subject Disposition, Treatment Withdrawal and Time on Study Information - Additional Monotherapy Studies and Current Monotherapy Label Pool; Safety Population

	Additional Monotherapy Studies (Studies MCL2001, MCL3001 and Study 1117)	Current Monotherapy Label Pool (Studies 1102, 1104, 1112 and 1118E)
Analysis set: safety population	403	420
Still on treatment	205 (50.9%)	265 (63.1%)
Completed treatment	0	35 (8.3%)
Discontinued treatment	198 (49.1%)	120 (28.6%)
Reason for discontinuation		
Progression disease or relapse	126 (31.3%)	65 (15.5%)
Adverse event	35 (8.7%)	26 (6.2%)
Death	14 (3.5%)	9 (2.1%)
Lost to follow-up	0	1 (0.2%)
Pregnancy	0	0
Investigator or sponsor decision	7 (1.7%)	7 (1.7%)
Subject refuses further treatment	16 (4.0%)	9 (2.1%)
Other	0	3 (0.7%)
Time on study (months)[b]		
N	403	420
Mean (SD)	12.49 (6.182)	11.74 (5.386)
Median[c]	14.09	11.47
Range	(0.2; 28.2)	(0.3; 29.0)

2.4.3. Discussion on clinical efficacy

CLL studies

Ibrutinib is currently licensed "for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, and as a single agent for the treatment of adult patients with previously untreated CLL ". This submission aims at providing the results of the pivotal study CLL3001, a placebo controlled add-on study to bendamustine + rituximab (BR) in patients with R/R CLL or SLL, and other supportive studies as foreseen at the time of the approval and agreed as part of the post- authorisation programme of ibrutinib.

Design and conduct of clinical studies

The median/mean ages at enrolment were 64/64 and about 30% of patients were >70 years of age. The efficacy of ibrutinib in patients previously treated for CLL were further evaluated in a randomised, multicenter, double-blinded phase 3 study of IMBRUVICA in combination with BR versus placebo + BR (Study CLL3001). Patients (n = 578) were randomised 1:1 to receive either IMBRUVICA 420 mg daily or placebo in combination with BR until disease progression, or unacceptable toxicity. All patients received BR for a maximum of six 28-day cycles. Bendamustine was dosed at 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab was administered at a dose of 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 Cycles 2 through 6, Day 1. Ninety patients randomised to placebo + BR crossed over to receive IMBRUVICA following IRC confirmed progression. The median age was 64 years (range, 31 to 86 years), 66% were male, and 91% were Caucasian. All patients had a baseline ECOG performance status of 0 or 1. The median time since diagnosis was 6 years and the median number of prior treatments was 2 (range, 1 to 11 treatments). At baseline, 56% of patients had at least one tumour ≥ 5 cm, 26% had del11q.

CLL3001 enrolled patients with R/R CLL/SLL. About 50% of patients had received one line of prior therapy and about 25% were refractory to purine analogues. Due to the selected background therapy, patients with del.17p positive CLL/SLL were excluded.

The supportive Study 1108 provides supportive single arm evidence as regards the activity and safety of ibrutinib as add-on to BR. Study 1109, exploring the combination ofatumumab and ibrutinib, is of minor relevance for this submission whilst the single arm, monotherapy study 1117 provides further confirmation of the efficacy of ibrutinib in case of CLL with del 17p.

Efficacy data and additional analyses

Submitted data refer to an interim analysis conducted at a PFS event rate about 20 and 60%, i.e. at a higher event rate than originally planned for. Expressed as PFS HRs the treatment difference was about 0.02 at a p-value <0.001. The main difference in terms of PFS events was observed after end of induction therapy.

The reported ORRs (IRC) were 83% vs. 68%, p-value <0.0001.

At event rates of 9% and 14%, there is a trend towards improved survival HR 0.63, p-value 0.06.

An increase in MRD negativity was reported in the experimental arm, 13% vs. 5% p-value 0.001 (to be viewed as exploratory due to hierarchical testing procedure).

The interim analysis was conducted at a low event rate in the ibrutinib arm, meaning that the stability of the PFS event curve is ill defined. Based on prior monotherapy studies, however, it is accepted that ibrutinib show durable responses. A formal issue is that the interim was conducted at a higher event rate than planned (OC).

Submitted subgroup analyses are compatible with consistent add-on activity, but the low event rate in the ibrutinib arm undermines firm conclusions. ORR data grouped according to the co-variates used in the PFS subgroup analyses might provide some insights as regards possible heterogeneity (OC).

The main difference between study arms develops during the maintenance phase comparing ibrutinib in mono-therapy with placebo. This means that events of PD have different meaning in the two study arms. A PFS2 analysis has therefore been submitted. The event rates in this analysis were as expected low, 10 vs. 17%, HR 0.53, p-value 0.006 (exploratory). Based on the results of the interim analysis, the DMC recommended unblinding of the study

At this stage OS data cannot be used to support conclusions as regards long term benefit. The study was also opened to cross-over to ibrutinib in January 2014 when all patients were enrolled.

The prognostic value of MRD negativity relies on data from patients who have been off therapy for some months. Its value in patients on therapy is non-established. A comparison of ORR including MRD negativity after end of induction therapy might nevertheless be informative (OC) about the value of ibrutinib during the induction phase.

Mantle Cell Lymphoma studies

The final CSRs for study MCL3001 and MCL2001 have been provided in support of the current indication as foreseen at the time of the approval and agreed as part of the post- authorisation programme of ibrutinib in r/r MCL.

Design and conduct of clinical studies

The efficacy of ibrutinib in MCL was further studied in a randomised phase 3, open-label, multicenter study including 280 patients with MCL who received at least one prior therapy (Study MCL3001). Patients (n=280) were randomised 1:1 to receive either IMBRUVICA orally at 560 mg once daily for 21 days or temsirolimus intravenously at 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Treatment on both arms continued until disease progression or unacceptable toxicity. The median age was 68 years (range, 34; 88), 74% were male and 87% were Caucasian. The median time since diagnosis was 43 months, and median number of prior treatments was 2 (range: 1 to 9 treatments), including 51% with prior high-dose chemotherapy, 18% with prior bortezomib, 5% with prior lenalidomide, and 24% with prior stem cell transplant. At baseline, 53% of patients had bulky disease (≥ 5 cm), 21% had high-risk score by Simplified MIPI, 60% had extranodal disease and 54% had bone marrow involvement at screening. Progression-free survival (PFS) was assessed by IRC according to the revised International Working Group (IWG) for non-Hodgkin's lymphoma (NHL) criteria.

MCL2001 was a Phase 2, open-label, monotherapy study in r/r MCL after at least one prior rituximab-containing chemotherapy regimen and documented PD after at least 2 cycles of single-agent or combination bortezomib therapy (n=120).

Efficacy data and additional analyses

In the MCL3001 study, PFS by IRC, the primary outcome measure, showed a HR of 0.43 in favour of the ibrutinib arm, p<0.0001, with mature data in the temsirolimus arm (79%). The median PFS was 14.6 (10.4, NE) months in the ibrutinib arm compared to 6.2 (4.2, 7.9) months in the temsirolimus arm. Sensitivity analyses and secondary outcomes, as well as PFS2, were all supportive.

A smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with ibrutinib versus temsirolimus (HR 0.27, p < 0.0001).

In the MCL2001 study, ORR by IRC, the primary outcome measure, was 63% for the response-evaluable population, with a CR rate of 21%, and 57% for the all-treated population. At the final analysis by investigator, with a median follow-up of 26.7 months, ORR was unchanged but the fraction of patients with CR had increased from 18% at the time of the cut-off for the primary analysis to 24.5%. At the primary cutoff and with 33% events the median DOR by IRC was approximately 15 months. At the final analysis by investigator, with a median follow-up of 26.7 months, DOR had increased from 12.9 months at the time of the primary analysis to 21.3 months.

Looking at activity in terms of response rates with ibrutinib across the MCL studies, the ORR was 72% in MCL3001 (vs 40.4 % in the temsirolimus arm), 63% in MCL2001 and 68% in 1104.

Inspection of the KM curve for PFS in study MCL3001 reveals a slightly higher event rate in the ibrutinib arm vs the temsirolimus arm for the first approximately 2 months and a separate analysis for the first 3 months, with PD and deaths addressed separately, was provided.

A smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (27% versus 52%) and time to worsening of symptoms occurred more slowly with ibrutinib versus temsirolimus (HR 0.27, $p < 0.0001$). The rationale for the definition of clinically meaningful worsening in the Lym subscale of the FACT-Lym assessment as a 5-point decrease from baseline in the MCL3001 study was justified.

Due to small subject numbers in several groups and the uncontrolled setting in MCL2001, subgroup data should be interpreted with caution. The analyses may, however, indicate a potentially lower activity in high risk disease and in blastoid histology.

2.4.4. Conclusions on the clinical efficacy

The results of the submitted study CLL3001 demonstrate the efficacy of ibrutinib as add-on to the rituximab – bendamustine regimen as PFS favoured the ibrutinib arm with a HR for PFS estimated at 0.2 [95% CI; 0.15, 0.28] (median PFS not reached for ibrutinib arm). As the studies supporting the CLL indication granted at the time of the Marketing Authorisation included use of ibrutinib as single agent, the CLL indication is extended to the use of ibrutinib in combination with bendamustine and rituximab (BR).

The results from the MCL studies submitted, confirm the efficacy of ibrutinib in the approved indication of MCL as PFS with ibrutinib was 14.6 (10.4, NE) as compared to 6.2 (4.2, 7.9) months in the temsirolimus group with HR of 0.43 [95% CI: 0.32, 0.58].

Study resuts were included under section 5.1 of the SmPC. The indication section was revised to include the combination of ibrutinib with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy and to specify where appropriate the use of ibrutinib as a single agent.

2.5. Clinical safety

MCL3001

Table 7: Extent of Exposure; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Treatment duration (months)		
N	139	139
Mean (SD)	13.27 (8.31)	6.04 (6.80)
Median	14.39	3.02
Range	(0.0; 28.2)	(0.0; 27.0)
0 - <3 months	25 (18.0%)	66 (47.5%)
3 - <6 months	15 (10.8%)	26 (18.7%)
6 - <9 months	11 (7.9%)	12 (8.6%)
9 - <12 months	8 (5.8%)	12 (8.6%)
12 - <15 months	11 (7.9%)	5 (3.6%)
15 - <18 months	15 (10.8%)	5 (3.6%)
>=18 months	54 (38.8%)	13 (9.4%)
Total number of cycles		
N	139	139
Mean (SD)	19.7 (12.1)	9.4 (9.8)
Median	21.0	5.0
Range	(1; 41)	(1; 40)
Relative dose intensity (%)		
N	139	139
Mean (SD)	96.29 (8.15)	76.49 (21.44)
Median	99.85	81.82
Range	(30.3; 100.0)	(30.0; 100.0)
< 75%	3 (2.2%)	59 (42.4%)
>= 75% - < 90%	12 (8.6%)	29 (20.9%)
>= 90%	124 (89.2%)	51 (36.7%)

Adverse events

Overall Summary of Treatment-Emergent Adverse Events; Safety Analysis Set (Study CLL3001) - Study PCI-32765CLL3001

	Ibrutinib+BR	Placebo+BR
Analysis set: safety	287	287
Treatment-emergent adverse events	278 (96.9%)	279 (97.2%)
Grade >=3	241 (84.0%)	230 (80.1%)
Drug-related	240 (83.6%)	227 (79.1%)
Treatment-emergent serious adverse events	150 (52.3%)	125 (43.6%)
Grade >=3	130 (45.3%)	106 (36.9%)
Drug-related	87 (30.3%)	63 (22.0%)
Treatment-emergent adverse events leading to treatment discontinuation	41 (14.3%)	33 (11.5%)
Treatment-emergent adverse events with outcome of death	19 (6.6%)	18 (6.3%)

Note: Treatment-emergent adverse events with outcome of death may include deaths that occurred more than 30 days after last dose with the treatment-emergent AE as the reason for death.

MCL3001

Table 18: Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Any TEAE	138 (99.3%)	138 (99.3%)
Grade >= 3	94 (67.6%)	121 (87.1%)
Drug related	115 (82.7%)	133 (95.7%)
Any TESAE	67 (48.2%)	80 (57.6%)
Grade >= 3	63 (45.3%)	68 (48.9%)
Drug related	29 (20.9%)	53 (38.1%)
TEAE leading to treatment discontinuation	18 (12.9%)	41 (29.5%)
TEAE with outcome death	15 (10.8%)	11 (7.9%)

Table 19: Overall Summary of Treatment-emergent Adverse Events During the First 6 Months of Treatment; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Any TEAE	130 (93.5%)	138 (99.3%)
Grade >= 3	73 (52.5%)	119 (85.6%)
Drug related	103 (74.1%)	133 (95.7%)
Any TESAE	50 (36.0%)	66 (47.5%)
Grade >= 3	47 (33.8%)	56 (40.3%)
Drug related	21 (15.1%)	43 (30.9%)
TEAE leading to treatment discontinuation	12 (8.6%)	36 (25.9%)
TEAE with outcome death	8 (5.8%)	11 (7.9%)

Serious adverse event / deaths / other significant events - Study PCI-32765CLL3001

The overall incidence of Grade 3 or higher drug-related TEAEs was 62.4% in the ibrutinib+BR treatment group and 53.7% in the placebo+BR treatment group. Grade 5 drug-related events were observed in 2.8% of subjects in the ibrutinib+BR treatment group and in 3.1% of subjects in the placebo+BR treatment group.

Grade 3 or Higher Treatment-Emergent Adverse Events with Subject Incidence of ≥2% in Either Group by Preferred Term and Maximum Toxicity Grade; Safety Analysis Set - Study PCI-32765CLL3001

	Ibrutinib+BR			Placebo+BR		
	Grade 3-5	Grade 3+4	Grade 5	Grade 3-5	Grade 3+4	Grade 5
Analysis set: safety	287	287	287	287	287	287
Subjects with any grade 3 or higher treatment-emergent adverse events	241 (84.0%)	222 (77.4%)	19 (6.6%)	230 (80.1%)	212 (73.9%)	18 (6.3%)
Preferred term						
Neutropenia	154 (53.7%)	154 (53.7%)	0	145 (50.5%)	145 (50.5%)	0
Thrombocytopenia	43 (15.0%)	43 (15.0%)	0	43 (15.0%)	43 (15.0%)	0
Febrile neutropenia	34 (11.8%)	34 (11.8%)	0	24 (8.4%)	23 (8.0%)	1 (0.3%)
Pneumonia	21 (7.3%)	21 (7.3%)	0	21 (7.3%)	20 (7.0%)	1 (0.3%)
Neutrophil count decreased	15 (5.2%)	15 (5.2%)	0	12 (4.2%)	12 (4.2%)	0
Anaemia	10 (3.5%)	10 (3.5%)	0	23 (8.0%)	23 (8.0%)	0
Hypertension	10 (3.5%)	10 (3.5%)	0	4 (1.4%)	4 (1.4%)	0
Leukopenia	10 (3.5%)	10 (3.5%)	0	12 (4.2%)	12 (4.2%)	0
Pyrexia	10 (3.5%)	10 (3.5%)	0	5 (1.7%)	5 (1.7%)	0
Tumour lysis syndrome	10 (3.5%)	10 (3.5%)	0	10 (3.5%)	10 (3.5%)	0
Fatigue	9 (3.1%)	9 (3.1%)	0	10 (3.5%)	10 (3.5%)	0
White blood cell count decreased	9 (3.1%)	9 (3.1%)	0	0	0	0
Atrial fibrillation	8 (2.8%)	8 (2.8%)	0	2 (0.7%)	2 (0.7%)	0
Bronchitis	7 (2.4%)	7 (2.4%)	0	10 (3.5%)	10 (3.5%)	0
Hyperuricaemia	7 (2.4%)	7 (2.4%)	0	0	0	0
Lymphopenia	7 (2.4%)	7 (2.4%)	0	1 (0.3%)	1 (0.3%)	0
Platelet count decreased	7 (2.4%)	7 (2.4%)	0	5 (1.7%)	5 (1.7%)	0
Sepsis	7 (2.4%)	6 (2.1%)	1 (0.3%)	4 (1.4%)	1 (0.3%)	3 (1.0%)
Bronchopneumonia	6 (2.1%)	6 (2.1%)	0	3 (1.0%)	2 (0.7%)	1 (0.3%)
Diarrhoea	6 (2.1%)	6 (2.1%)	0	4 (1.4%)	4 (1.4%)	0
Upper respiratory tract infection	6 (2.1%)	6 (2.1%)	0	0	0	0
Autoimmune haemolytic anaemia	0	0	0	7 (2.4%)	7 (2.4%)	0

Note: A subject with multiple severity ratings for a given AE was counted only once under the maximum toxicity grade. Adverse events are presented by descending frequency of PT for Ibrutinib; those with the same frequency are presented alphabetically.

Deaths - Study PCI-32765CLL3001

There were altogether 19 (6.6%, ibrutinib) and 18 TEAE (6.3%, placebo arm) with an outcome of death.

Apart from 2 cases of MDS in the ibrutinib arm all were single reports. There was one case of ventricular flutter and one case of sudden death.

In the placebo arm, two cases of PD were reported as TEAE leading to death (vs. 1 in the ibrutinib arm). With respect to infections 7 cases (sepsis 3, septic shock 1, febrile neutropenia 1, bronchopneumonia 1, pneumonia 1).

Incidence of Treatment-Emergent Serious Adverse Events, 2% or more - Study PCI-32765CLL3001

	Ibrutinib+BR			Placebo+BR		
	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5
Analysis set: safety	287			287		
Subjects with any treatment-emergent adverse events	150 (52.3%)	112 (39.0%)	18 (6.3%)	125 (43.6%)	88 (30.7%)	18 (6.3%)
Preferred term						
Febrile neutropenia	27 (9.4%)	27 (9.4%)	0	22 (7.7%)	21 (7.3%)	1 (0.3%)
Pneumonia	20 (7.0%)	18 (6.3%)	0	21 (7.3%)	18 (6.3%)	1 (0.3%)
Pyrexia	9 (3.1%)	4 (1.4%)	0	7 (2.4%)	4 (1.4%)	0
Atrial fibrillation	8 (2.8%)	5 (1.7%)	0	2 (0.7%)	1 (0.3%)	0
Neutropenia	6 (2.1%)	6 (2.1%)	0	6 (2.1%)	6 (2.1%)	0
Sepsis	6 (2.1%)	5 (1.7%)	1 (0.3%)	4 (1.4%)	1 (0.3%)	3 (1.0%)
Tumour lysis syndrome	6 (2.1%)	6 (2.1%)	0	1 (0.3%)	1 (0.3%)	0
Anaemia	3 (1.0%)	1 (0.3%)	0	7 (2.4%)	4 (1.4%)	0

Treatment-emergent haemorrhagic events of any grade were reported for 31.0% of subjects in the ibrutinib+BR treatment group and 14.6% of subjects in the placebo+BR treatment group.

Incidence of Treatment-Emergent Major Haemorrhage Events by Preferred Term and Maximum Toxicity Grade; Safety Analysis Set - Study PCI-32765CLL3001

	Ibrutinib+BR			Placebo+BR		
	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5
Analysis set: safety	287			287		
Subjects with any treatment-emergent adverse events	11 (3.8%)	6 (2.1%)	2 (0.7%)	5 (1.7%)	5 (1.7%)	0
Preferred term						
Gastrointestinal haemorrhage	2 (0.7%)	1 (0.3%)	0	0	0	0
Uterine haemorrhage	2 (0.7%)	0	0	0	0	0
Aortic aneurysm rupture	1 (0.3%)	0	1 (0.3%)	0	0	0
Haematemesis	1 (0.3%)	0	0	0	0	0
Haematochezia	1 (0.3%)	1 (0.3%)	0	0	0	0
Haemorrhage intracranial	1 (0.3%)	1 (0.3%)	0	0	0	0
Haemorrhagic stroke	1 (0.3%)	1 (0.3%)	0	0	0	0
Muscle haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0
Post procedural haemorrhage	1 (0.3%)	0	1 (0.3%)	0	0	0
Purpura	1 (0.3%)	1 (0.3%)	0	0	0	0
Vitreous haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0
Duodenal ulcer haemorrhage	0	0	0	1 (0.3%)	1 (0.3%)	0
Epistaxis	0	0	0	1 (0.3%)	1 (0.3%)	0
Haemoptysis	0	0	0	1 (0.3%)	1 (0.3%)	0
Immune thrombocytopenic purpura	0	0	0	1 (0.3%)	1 (0.3%)	0
Vessel puncture site haematoma	0	0	0	1 (0.3%)	1 (0.3%)	0

Note: A subject with multiple severity ratings for a given AE was counted only once under the maximum toxicity grade.
Note: Major hemorrhage includes serious or grade >= 3 hemorrhage and CNS hemorrhage at any grade among bleeding events identified by haemorrhage SMQ excluding laboratory terms.
Subjects with missing toxicity grades are included in the All Grades column but not shown separately.
Adverse events are presented by descending frequency of PT within All Grades for Ibrutinib; those with the same frequency are presented alphabetically.

No major haemorrhagic events resulted in a dose reduction, but 3 events in the ibrutinib+BR treatment group (uterine haemorrhage, vitreous haemorrhage, and haematochezia) were managed with a drug interruption and 1 event (haemoptysis) in the placebo+BR treatment group; and 2 events in the ibrutinib+BR treatment group and none in the placebo+BR treatment group led to treatment discontinuation (haemorrhage intracranial and haemorrhagic stroke).

Hepatic Adverse Events - Study PCI-32765CLL3001

TEAEs in the SOC of Hepatobiliary Disorders of any grade were reported for 3.8% of subjects in the ibrutinib+BR treatment group and 4.2% of subjects in the placebo+BR treatment group. Grade 3 or 4 events were reported for 6 (2.1%) subjects in the ibrutinib+BR treatment group; no events were fatal.

In the placebo+BR treatment group, 4 (1.4%) subjects had Grade 3 or 4 events; and 1 subject had fatal hepatobiliary events (cholestasis and hepatocellular injury).

Serious adverse event / deaths / other significant events - Study MCL3001

MCL3001

Table 20: Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects in Either Arm by Preferred Term; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Subjects with any TEAE	138 (99.3%)	138 (99.3%)
Preferred term		
Diarrhoea	40 (28.8%)	43 (30.9%)
Cough	31 (22.3%)	31 (22.3%)
Fatigue	31 (22.3%)	40 (28.8%)
Muscle spasms	26 (18.7%)	4 (2.9%)
Upper respiratory tract infection	26 (18.7%)	16 (11.5%)
Anaemia	25 (18.0%)	60 (43.2%)
Decreased appetite	25 (18.0%)	26 (18.7%)
Thrombocytopenia	25 (18.0%)	78 (56.1%)
Pyrexia	23 (16.5%)	29 (20.9%)
Neutropenia	22 (15.8%)	36 (25.9%)
Nausea	20 (14.4%)	30 (21.6%)
Oedema peripheral	18 (12.9%)	31 (22.3%)
Rash	18 (12.9%)	24 (17.3%)
Back pain	16 (11.5%)	15 (10.8%)
Conjunctivitis	16 (11.5%)	7 (5.0%)
Dyspnoea	16 (11.5%)	17 (12.2%)
Vomiting	16 (11.5%)	10 (7.2%)
Nasopharyngitis	15 (10.8%)	16 (11.5%)
Blood creatinine increased	14 (10.1%)	17 (12.2%)
Headache	13 (9.4%)	17 (12.2%)
Pneumonia	13 (9.4%)	17 (12.2%)
Constipation	12 (8.6%)	21 (15.1%)
Epistaxis	12 (8.6%)	33 (23.7%)
Platelet count decreased	12 (8.6%)	23 (16.5%)
Pruritus	12 (8.6%)	18 (12.9%)
Asthenia	11 (7.9%)	27 (19.4%)
Hypokalaemia	11 (7.9%)	24 (17.3%)
Respiratory tract infection	8 (5.8%)	15 (10.8%)
Insomnia	6 (4.3%)	15 (10.8%)
Weight decreased	6 (4.3%)	18 (12.9%)
Stomatitis	4 (2.9%)	29 (20.9%)
Hyperglycaemia	3 (2.2%)	26 (18.7%)
Oral herpes	3 (2.2%)	15 (10.8%)
Mucosal inflammation	2 (1.4%)	21 (15.1%)
Hypercholesterolaemia	1 (0.7%)	18 (12.9%)
Hypertriglyceridaemia	0	25 (18.0%)

Table 21: Incidence of Grade 3 or Higher Treatment-emergent Adverse Events Occurring in 2% or More Subjects in Either Arm by Preferred Term

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Subjects with any Grade 3 or higher TEAE	94 (67.6%)	121 (87.1%)
Preferred term		
Neutropenia	18 (12.9%)	23 (16.5%)
Thrombocytopenia	13 (9.4%)	59 (42.4%)
Anaemia	11 (7.9%)	28 (20.1%)
Pneumonia	11 (7.9%)	9 (6.5%)
Hypokalaemia	8 (5.8%)	12 (8.6%)
Neutrophil count decreased	7 (5.0%)	5 (3.6%)
Fatigue	6 (4.3%)	10 (7.2%)
Abdominal pain	5 (3.6%)	2 (1.4%)
Atrial fibrillation	5 (3.6%)	2 (1.4%)
Hyperkalaemia	5 (3.6%)	1 (0.7%)
Sepsis	5 (3.6%)	5 (3.6%)
Back pain	4 (2.9%)	1 (0.7%)
Diarrhoea	4 (2.9%)	6 (4.3%)
Dyspnoea	4 (2.9%)	5 (3.6%)
Hypertension	4 (2.9%)	2 (1.4%)
Multi-organ failure	4 (2.9%)	0
Pleural effusion	4 (2.9%)	0
Renal failure	4 (2.9%)	4 (2.9%)
Febrile neutropenia	3 (2.2%)	2 (1.4%)
Haemorrhage	3 (2.2%)	1 (0.7%)
Lymphocyte count increased	3 (2.2%)	1 (0.7%)
Syncope	3 (2.2%)	3 (2.2%)
Upper respiratory tract infection	3 (2.2%)	1 (0.7%)
Hypophosphataemia	2 (1.4%)	4 (2.9%)
Platelet count decreased	2 (1.4%)	19 (13.7%)
Asthenia	1 (0.7%)	3 (2.2%)
Decreased appetite	1 (0.7%)	4 (2.9%)
General physical health deterioration	1 (0.7%)	3 (2.2%)
Hyperglycaemia	1 (0.7%)	10 (7.2%)
Hyponatraemia	1 (0.7%)	6 (4.3%)
Mucosal inflammation	1 (0.7%)	6 (4.3%)
Oral pain	1 (0.7%)	3 (2.2%)
Pyrexia	1 (0.7%)	3 (2.2%)
Tumour lysis syndrome	1 (0.7%)	3 (2.2%)
Urinary tract infection	1 (0.7%)	3 (2.2%)
Cataract	0	4 (2.9%)
Gastroenteritis	0	3 (2.2%)
Hypercholesterolaemia	0	3 (2.2%)
Hypertriglyceridaemia	0	13 (9.4%)
Lymphopenia	0	5 (3.6%)
Oedema peripheral	0	3 (2.2%)
Pneumonitis	0	3 (2.2%)
Respiratory tract infection	0	3 (2.2%)
Stomatitis	0	5 (3.6%)

Deaths – MCL3001

Table 22: Death Within 30 Days After Last Dose of Study Treatment; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Death within 30 days after last dose	24 (17.3%)	15 (10.8%)
Primary cause of death		
Progressive disease	15 (10.8%)	7 (5.0%)
Adverse event	9 (6.5%)	8 (5.8%)
Unknown	0	0
Other	0	0

Table 23: Incidence of Treatment-emergent Adverse Events Leading to Death by Preferred Term; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Subjects with any TEAE leading to death	15 (10.8%)	11 (7.9%)
Preferred term		
Sepsis	3 (2.2%)	1 (0.7%)
Multi-organ failure	2 (1.4%)	0
Renal failure	2 (1.4%)	1 (0.7%)
Septic shock	2 (1.4%)	1 (0.7%)
Pulmonary embolism	1 (0.7%)	0
Pulmonary oedema	1 (0.7%)	0
Respiratory failure	1 (0.7%)	1 (0.7%)
Splenic rupture	1 (0.7%)	0
Subdural haematoma	1 (0.7%)	0
Transitional cell carcinoma	1 (0.7%)	0
Cardiac arrest	0	1 (0.7%)
Cardiac failure acute	0	1 (0.7%)
Cardiopulmonary failure	0	1 (0.7%)
General physical health deterioration	0	2 (1.4%)
Ischaemic stroke	0	1 (0.7%)
Pneumonia	0	1 (0.7%)

Of the 15 subjects in the ibrutinib arm who were reported with a TEAE leading to death, 6 subjects had progressive disease as their primary cause of death and are counted in that category in Table 22. Of the 11 subjects in the temsirolimus arm who were reported with a TEAE leading to death, 3 subjects had progressive disease as their primary cause of death and are counted in that category in Table 22.

During the first 6 months of treatment, 8 subjects (5.8%) in the ibrutinib arm and 11 subjects (7.9%) in the temsirolimus arm had a TEAE with an outcome of death. When adjusted for exposure differences between the treatment arms, the incidence rate for TEAEs leading to death was 0.811 per 100 patient-months for the ibrutinib arm and 1.299 for the temsirolimus arm.

SAEs

Table 24: Incidence of Treatment-Emergent Serious Adverse Events Occurring in 2% or More Subjects in Either Arm by System Organ Class and Preferred Term; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Subjects with any Serious TEAE	67 (48.2%)	80 (57.6%)
System organ class		
Preferred term		
Infections and infestations	25 (18.0%)	40 (28.8%)
Pneumonia	12 (8.6%)	9 (6.5%)
Sepsis	4 (2.9%)	5 (3.6%)
Urinary tract infection	1 (0.7%)	3 (2.2%)
Respiratory, thoracic and mediastinal disorders	18 (12.9%)	14 (10.1%)
Dyspnoea	6 (4.3%)	5 (3.6%)
Pleural effusion	3 (2.2%)	0
Pneumonitis	0	3 (2.2%)
Blood and lymphatic system disorders	12 (8.6%)	10 (7.2%)
Thrombocytopenia	5 (3.6%)	3 (2.2%)
Anaemia	3 (2.2%)	5 (3.6%)
General disorders and administration site conditions	11 (7.9%)	16 (11.5%)
Multi-organ failure	4 (2.9%)	0
Pyrexia	3 (2.2%)	7 (5.0%)
Fatigue	2 (1.4%)	3 (2.2%)
General physical health deterioration	2 (1.4%)	5 (3.6%)
Gastrointestinal disorders	10 (7.2%)	13 (9.4%)
Abdominal pain	4 (2.9%)	1 (0.7%)
Diarrhoea	2 (1.4%)	4 (2.9%)
Stomatitis	0	3 (2.2%)
Cardiac disorders	8 (5.8%)	9 (6.5%)
Atrial fibrillation	5 (3.6%)	2 (1.4%)
Renal and urinary disorders	7 (5.0%)	6 (4.3%)
Renal failure	3 (2.2%)	4 (2.9%)
Metabolism and nutrition disorders	5 (3.6%)	8 (5.8%)
Tumour lysis syndrome	1 (0.7%)	3 (2.2%)

The 4 patients with multiorgan failure noted in the ibrutinib arm were all assessed with progressive disease concurrently or immediately prior to the multi-organ failure event.

For the pleural effusion cases, 2 subjects had a concurrent infection (1 pneumonia, 1 tuberculosis) and the other subject had a history of “pleurisy” and tuberculosis with no clear etiology for the event. All subjects resumed treatment for at least 6 months with the pleural effusion event reported as recovered/resolved.

Other events of special interest

- Major bleeding

TSFAE21A: Incidence of Treatment-emergent Major Bleeding Events by Toxicity Grade and Preferred Term; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib			Temsirolimus		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: safety	139			139		
Subjects with any Major Bleeding TEAE	14 (10.1%)	10 (7.2%)	1 (0.7%)	9 (6.5%)	7 (5.0%)	0
Preferred term						
Haemorrhage	4 (2.9%)	3 (2.2%)	0	1 (0.7%)	1 (0.7%)	0
Epistaxis	2 (1.4%)	1 (0.7%)	0	3 (2.2%)	2 (1.4%)	0
Post procedural haemorrhage	2 (1.4%)	2 (1.4%)	0	1 (0.7%)	0	0
Subdural haematoma	2 (1.4%)	0	1 (0.7%)	0	0	0
Cystitis haemorrhagic	1 (0.7%)	1 (0.7%)	0	0	0	0
Haematuria	1 (0.7%)	1 (0.7%)	0	0	0	0
Purpura	1 (0.7%)	1 (0.7%)	0	0	0	0
Vitreous haemorrhage	1 (0.7%)	1 (0.7%)	0	0	0	0
Gastritis haemorrhagic	0	0	0	1 (0.7%)	0	0
Gastrointestinal haemorrhage	0	0	0	2 (1.4%)	2 (1.4%)	0
Intestinal haemorrhage	0	0	0	1 (0.7%)	1 (0.7%)	0
Lower gastrointestinal haemorrhage	0	0	0	1 (0.7%)	1 (0.7%)	0

When adjusted for exposure, the event rate for any major bleeding TEAE was 0.786 events per 100 patient-months for the ibrutinib arm and 1.077 events per 100 patient-months for the temsirolimus arm. A major bleeding event was reported for 8 subjects (5.8%) in the ibrutinib arm and for 6 subjects (4.3%) in the temsirolimus arm during the first 6 months of drug treatment. One subject in the ibrutinib arm died with a cause of death reported as subdural hematoma.

- Tumour lysis syndrome

Tumor lysis syndrome was reported for 1 subject (0.7%, Grade 3) in the ibrutinib arm and for 3 subjects (2.2%, all Grade 3-4) in the temsirolimus arm.

- Infections

Treatment-emergent adverse events from the Infections and infestations SOC were reported for 73 subjects (52.5%) in the ibrutinib arm and for 93 subjects (66.9%) during the first 6 months of drug treatment.

Infections were reported as a cause of death for 5 subjects (3.6%; 3 subjects with sepsis and 2 subjects with septic shock) in the ibrutinib arm and for 3 subjects (2.2%; 1 subjects each with sepsis, septic shock, and pneumonia) in the temsirolimus arm.

- Atrial fibrillation/flutter

Atrial fibrillation was reported for 6 subjects (4.3%) in the ibrutinib arm and for 3 subjects (2.2%) in the temsirolimus arm during the first 6 months of drug treatment. The EAIRs for atrial fibrillation were similar between the ibrutinib arm (0.337 events per 100 patient-months) and the temsirolimus arm (0.358 events per 100 patient-months.

- Other malignancies

TSFAE29: Summary of Other Malignancies by Type and Preferred Term; Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: safety	139	139
Subjects with any other malignancies	5 (3.6%)	4 (2.9%)
Type		
Preferred term		
Non-melanoma skin cancer	2 (1.4%)	2 (1.4%)
Basal cell carcinoma	1 (0.7%)	1 (0.7%)
Squamous cell carcinoma	1 (0.7%)	2 (1.4%)
Melanoma skin cancer	0	0
Non-skin cancer (malignant)	3 (2.2%)	2 (1.4%)
Prostate cancer	1 (0.7%)	0
Salivary gland cancer	1 (0.7%)	0
Transitional cell carcinoma	1 (0.7%)	0
Acute myeloid leukaemia	0	1 (0.7%)
Adenocarcinoma gastric	0	1 (0.7%)

- Ocular events

Serious Grade 3-4 events were reported for 2 subjects in the ibrutinib arm (1 subject with diabetic retinopathy and 1 subject with vitreous hemorrhage) and 1 subject in the temsirolimus arm with cataract.

The EAIR for the Eye disorder SOC was 1.919 events per 100 patient-months for the ibrutinib arm and 3.403 events per 100 patient-months for the temsirolimus arm. The EAIR for conjunctivitis was 0.968 events per 100 patient-months for the ibrutinib arm and 0.878 events per 100 patient-months for the temsirolimus arm.

Treatment-emergent adverse events (all grades) from the Eye disorders SOC were reported for 17 subjects (12.2%) from each treatment arm during the first 6 months of drug treatment. Conjunctivitis was reported for 11 subjects (7.9%) in the ibrutinib arm and for 5 subjects (3.6%) in the temsirolimus arm during the first 6 months of drug treatment.

- Hypertension

The EAIR for hypertension were 0.571 events per 100 patient-months for the ibrutinib arm and 0.614 events per 100 patient-months for the temsirolimus arm.

Hypertension was reported for 6 subjects (4.3%) in the ibrutinib arm and for 3 subjects (2.2%) in the temsirolimus arm during the first 6 months of drug treatment.

- Hepatic AEs

Three subjects (2.2%) in the ibrutinib treatment arm met the laboratory criteria for potential drug-induced liver injury (DILI) based on ALT/AST, alkaline phosphatase, and total bilirubin laboratory abnormalities (Hy's Law). However, one event occurred in the setting of septic shock and disease progression, and one in the context of hepatitis B reactivation (day 340, 11 days after the last dose of ibrutinib) with obviously negative rechallenge. No clear alternative aetiology is reported for the 3rd event but the patient had a negative rechallenge.

The EAIR for the Hepatobiliary disorders SOC was 0.338 events per 100 patient-months for the ibrutinib arm and 0.478 events per 100 patient-months for the temsirolimus arm.

Treatment-emergent adverse events from the Hepatobiliary disorders SOC were reported for 4 subjects (2.9%) from the ibrutinib arm and for 3 subjects (2.2%) from the temsirolimus arm during the first 6 months of drug treatment.

- AEs in relation to age (<65 versus ≥65 years)

The incidences of any grade TEAE, drug-related TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death were similar (<10% difference) between the age groups for both the ibrutinib and temsirolimus treatment arms.

For the ibrutinib arm, incidences were higher (>10% difference) for subjects ≥65 years for Grade ≥3 TEAEs (72.1% versus 60.4%), any serious TEAE (52.3% versus 41.5%), and drug-related serious TEAEs (25.6% versus 13.2%).

- Treatment-related lymphocytosis

Treatment-related lymphocytosis was reported for 52 subjects (38.2%) in the ibrutinib arm and for 31 subjects (22.6%) in the temsirolimus arm. The median time to lymphocytosis was 3.14 weeks for subjects in the ibrutinib arm and 2.86 weeks in the temsirolimus arm. Most events in the ibrutinib arm resolved (43 of the 52 subjects) with a median duration of 6.14 weeks.

Medical resource utilisation (not corrected for treatment duration)

Table 29: Descriptive Summary of MRU; Intent-to-treat Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib	Temsirolimus
Analysis set: intent-to-treat	139	141
Number of hospitalizations		
N	83	91
Mean (SD)	3.1 (4.6)	2.8 (4.3)
Median	2.0	2.0
Range	(1; 34)	(1; 31)
Days of hospitalization		
N	83	91
Mean (SD)	19.7 (20.5)	20.3 (22.4)
Median	12.0	13.0
Range	(0; 82)	(0; 116)
Number of emergency room visits		
N	5	5
Mean (SD)	1.2 (0.4)	1.2 (0.4)
Median	1.0	1.0
Range	(1; 2)	(1; 2)
Days of emergency room visits		
N	5	5
Mean (SD)	1.8 (1.3)	1.6 (1.3)
Median	1.0	1.0
Range	(1; 4)	(1; 4)
Blood product transfusions		
N	139	141
Yes	25 (18.0%)	56 (39.7%)
No	114 (82.0%)	85 (60.3%)
Use of hematopoietic growth factors		
N	139	141
Yes	17 (12.2%)	36 (25.5%)
No	122 (87.8%)	105 (74.5%)

Safety in special populations

Overall Summary of Treatment-Emergent Adverse Events by Age Group - Study PCI-32765CLL3001

	Ibrutinib+BR		Placebo+BR	
	<65	>=65	<65	>=65
Analysis set: safety	144	143	160	127
Treatment-emergent adverse events	138 (95.8%)	140 (97.9%)	154 (96.3%)	125 (98.4%)
Grade >=3	115 (79.9%)	126 (88.1%)	126 (78.8%)	104 (81.9%)
Drug-related	115 (79.9%)	125 (87.4%)	119 (74.4%)	108 (85.0%)
Treatment-emergent serious adverse events	69 (47.9%)	81 (56.6%)	59 (36.9%)	66 (52.0%)
Grade >=3	54 (37.5%)	76 (53.1%)	48 (30.0%)	58 (45.7%)
Drug-related	40 (27.8%)	47 (32.9%)	22 (13.8%)	41 (32.3%)
Treatment-emergent adverse events leading to treatment discontinuation	14 (9.7%)	27 (18.9%)	15 (9.4%)	18 (14.2%)
Treatment-emergent adverse events with outcome of death	5 (3.5%)	14 (9.8%)	10 (6.3%)	8 (6.3%)

Note: Treatment-emergent adverse events with outcome of death may include deaths that occurred more than 30 days after last dose with the treatment-emergent AE as the reason for death.

	Ibrutinib+BR						Placebo+BR					
	<65			≥65			<65			≥65		
	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5
General disorders and administration site conditions	68 (47.2%)	9 (6.3%)	1 (0.7%)	92 (64.3%)	16 (11.2%)	4 (2.8%)	83 (51.9%)	12 (7.5%)	4 (2.5%)	81 (63.8%)	11 (8.7%)	1 (0.8%)

Discontinuation due to adverse events
Treatment discontinuation - Study PCI-32765CLL3001

	Ibrutinib+BR			Placebo+BR		
	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5
Analysis set: safety	287			287		
Subjects with any treatment-emergent adverse events	41 (14.3%)	31 (10.8%)	1 (0.3%)	33 (11.5%)	22 (7.7%)	2 (0.7%)
Preferred term						
Pneumonia	4 (1.4%)	4 (1.4%)	0	0	0	0
Atrial fibrillation	3 (1.0%)	3 (1.0%)	0	0	0	0
Neutropenia	3 (1.0%)	2 (0.7%)	0	8 (2.8%)	7 (2.4%)	0
Thrombocytopenia	2 (0.7%)	2 (0.7%)	0	2 (0.7%)	1 (0.3%)	0

Dose reductions

	Ibrutinib+BR			Placebo+BR		
	All Grades	Grade 3+4	Grade 5	All Grades	Grade 3+4	Grade 5
Analysis set: safety	287			287		
Subjects with any treatment-emergent adverse events	27 (9.4%)	14 (4.9%)	0	21 (7.3%)	17 (5.9%)	0
Preferred term						
Neutropenia	10 (3.5%)	7 (2.4%)	0	11 (3.8%)	11 (3.8%)	0
Balance disorder	2 (0.7%)	0	0	0	0	0
Neutrophil count decreased	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0

TEAEs leading to treatment discontinuation – Study MCL3001

TEAEs leading to treatment discontinuation were reported for 12.9% of subjects in the ibrutinib arm and 29.5% of subjects in the temsirolimus arm. Serious TEAEs leading to treatment discontinuation were reported for 8.6% of subjects in the ibrutinib arm and 14.4% of subjects in the temsirolimus arm.

TEAEs leading to treatment discontinuation in more than one patient were thrombocytopenia (3) abdominal pain (2) and pneumonia (2) in the ibrutinib arm, and fatigue (7), thrombocytopenia (4), pneumonitis (4), neutropenia (3), oedema peripheral (3), asthenia (3), pneumonia (2), confusional state (2), decreased appetite (2), mucosal inflammation (2), pyrexia (2) and rash (2) in the temsirolimus arm.

TEAEs leading to dose reduction – Study MCL3001

TEAEs leading to dose reduction were reported for 3.6% of patients on the ibrutinib arm and 43.2% of patients on the temsirolimus arm. In the ibrutinib arm, no event was reported in more than 1 patient.

Exposure-adjusted Incidence Rates – Study MCL3001

An exposure-adjusted incidence rate (EAIR) analysis was performed to explore the influence of differences in drug exposure (median exposures: ibrutinib arm = 14.39 months; temsirolimus arm = 3.02 months) in summarising TEAEs that occurred up to 30 days from the last dose of study drug. An EAIR is reported as the incidence rate per 100 patient-months at risk.

Table 27: Overall Summary of Exposure-Adjusted Incidence Rates (EAIRs) (Exposure at First Event); Safety Analysis Set (Study PCI-32765MCL3001)

	Ibrutinib			Temsirolimus		
	n	100 Patient-months at Risk[a]	EAIR[b]	n	100 Patient-months at Risk[a]	EAIR[b]
Analysis set: safety	139			139		
Any TEAE	138	2.0	70.018	138	0.4	358.700
Grade >= 3	94	11.3	8.309	121	2.2	54.977
Drug related	115	4.4	26.316	133	0.5	242.116
Any TESAE	67	14.5	4.613	80	6.5	12.250
Grade >= 3	63	15.0	4.195	68	7.0	9.661
Drug related	29	15.9	1.820	53	7.3	7.272
TEAE leading to treatment discontinuation	18	18.5	0.975	41	8.4	4.896
TEAE with outcome death	15	18.5	0.811	11	8.5	1.299

Key: EAIR = exposure-adjusted incidence rate; TEAE= treatment-emergent adverse event; TESAE= treatment-emergent serious adverse event

[a] Patient-months at risk is the sum of the exposure times at the occurrence of the first TEAE for each subject. A patient's duration of exposure is given either by the time when the event has occurred (non-censored data), or by the total duration of treatment if the patient does not show the adverse event in question (censored data).

[b] EAIR represents the number of subjects with the event divided by 100 patient-months at risk for that event. If a patient has multiple occurrences of an event, the patient is counted only once in the numerator.

The most frequently reported SOCs by EAIR (per 100 patient-months) were Infections and infestations (ibrutinib: 11.68 all grades, 1.64 Grade ≥3; temsirolimus: 30.34 all grades, 5.69 Grade ≥3), Gastrointestinal disorders (ibrutinib: 8.19 all grades, 0.79 Grade ≥3; temsirolimus: 33.36 all grades, 3.38 Grade ≥3), General disorders and administration site conditions (ibrutinib: 6.62 all grades, 0.84 Grade ≥3; temsirolimus: 26.92 all grades, 3.77 Grade ≥3), and Respiratory, thoracic, and mediastinal disorders (ibrutinib: 5.95 all grades, 0.90 Grade ≥3; temsirolimus: 19.01 all grades, 2.28 Grade ≥3).

2.5.1. Discussion on clinical safety

In the CLL studies there was an overall moderate degree of ADR related to the add-on of ibrutinib; in terms of AEs leading to treatment discontinuations, 14% vs. 12% and in terms of dose reductions 9% vs. 7%. The ADR the profile in the combination arm looks essentially as expected based on the combination of the profiles of BR and ibrutinib alone. Thus the components were administered at the same dos intensity as used for ibrutinib and BR alone.

Regarding the data in MCL, it should be noted that treatment duration was substantially different between the study arms in MCL3001, median 14.4 months for the ibrutinib arm and 3 months for the temsirolimus arm (21 vs 5 cycles), with obvious impact on AE rates. Nevertheless, all TEAE categories (grade≥3, TESAE etc), except for outcome with death, were numerically more commonly reported in the temsirolimus arm. TEAEs leading to treatment discontinuation were reported in 12.9% of patients in the ibrutinib arm and 29.5% in the temsirolimus arm. When the analysis was restricted to the first 6 months of treatment, the differences between study arms were larger, and TEAEs with outcome of death numerically slightly lower in the ibrutinib arm. The latter outcome was also supported by an exposure time-adjusted analysis.

No new ADRs were identified, except muscle spasm and hypertension that were recently added as new ADRs through the type II variation for a broader first line indication in CLL.

The median time to atrial fibrillation/flutter was shorter in the Additional monotherapy studies (61 days; n=31) as sompared to the Current monotherapy label pool (91 days; n=29).

Based on the additional data provided with this submission the MAH proposes a revised list of ADRs for inclusion in SmPC 4.8. Except from revision of incidence information for some ADRs, dehydration, dry mouth and anemia are suggested to be removed. This is considered acceptable.

2.5.2. Conclusions on clinical safety

The safety of ibrutinib as observed in the submitted studies is in line with the already known profile and no new or unexpected findings were revealed. The list of ADRs under SmPC section 4.8 was revised in terms of changes to the incidence for some ADRs, and the removal of dehydration, dry mouth and anaemia.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

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

2.6. Risk management plan

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

The PRAC considered that the RMP version 5.1 (dated 10 November 2015) is acceptable, as described in the PRAC endorsed PRAC Rapporteur revised assessment report dated 18 February 2016.

The CHMP endorsed this advice without changes.

The PRAC and CHMP also endorsed RMP version 6.0.1 (dated 12 July 2016), combining the RMP versions 6.0 (dated 24 June 2016) and 5.1, approved within variations II-24/G (positive CHMP opinion received on 21 July 2016) and II-17/G, respectively, with the following contents.

Safety concerns

Table – Summary of the Safety concerns

Important Identified Risks	Leukostasis Haemorrhage Tumour lysis syndrome Hepatotoxicity (including hepatic failure) Non-melanoma skin cancer Interstitial lung disease
Important Potential Risks	Drug-drug interaction Anaemia Neutropenia Thrombocytopenia Infections Cardiac arrhythmia Severe GI disorders Other malignancies (excluding non-melanoma skin cancer) Hypersensitivity Teratogenicity Eye disorders Renal failure Hypertension
Missing Information	Off-label use in paediatric patients Use during breastfeeding Use in patients with severe cardiac disease Use in patients with severe renal impairment Use in patients with severe hepatic impairment Long term use (>2 years)

Pharmacovigilance plan

Table – Table of Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan

Study / activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
PCYC-PMR-2060-03 In Vitro Studies on the Effect of Ibrutinib on Platelet Function (category 3)	To evaluate the effect of ibrutinib on platelet aggregation as assessed by light transmission aggregometry.	Haemorrhage	Started	4th Quarter 2016

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCYC-PMR-2060-04 Enhanced pharmacovigilance to evaluate the risks of hemorrhage with the administration of IMBRUVICA® (ibrutinib): A post-marketing requirement (category 3)	To study of the risk of serious bleeding from clinical trials and all postmarketing sources	Haemorrhage	Started	4th Quarter 2018
PCI-32765LYM1003 A drug-drug interaction study of Ibrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancy (category 3)	To assess steady-state PK of repeated oral doses of ibrutinib alone in patients with B-cell malignancies and when combined with a moderate and strong CYP3A inhibitor.	Drug-drug interaction	Started	1st Quarter 2018
PCYC-1112-CA Yearly updates, including del17p/TP53 subgroups identified at baseline, for the randomised, multicentre, open-label; Subjects with CLL who have failed at least 1 prior line of therapy; Assess PFS by IRC trial. (category 1)	Yearly updates of trial results for progression and death.	Overall safety profile	Yearly updates	2nd Quarter 2016 2nd Quarter 2017 4th Quarter 2017
PCI-32765 CLL1007 An exploratory study to assess the pharmacokinetics and safety of a supratherapeutic dose of ibrutinib followed by a randomized, double-blind, placebo- and positive-controlled, single-dose, four-way crossover study to evaluate the effects of ibrutinib on cardiac repolarization in healthy subjects (category 3)	To assess the effect of ibrutinib on ECG parameters	Cardiac arrhythmia	Planned	Final Report Submission: 4th Quarter 2016
PCI-1103-CA [a] A Long-Term Safety Study of Bruton's Tyrosine Kinase (Btk) Inhibitor PCI-32765 in B Cell Lymphoma and Chronic Lymphocytic Leukemia (category 3)	Determine the long term safety and tolerability of a fixed daily dose of ibrutinib	Long term use (>2 years)	Started	Interim report 2nd Quarter 2016
PCI-32765 CAN3001[a] A Phase 3b, Multicenter, Open-label, PCI-32765 (Ibrutinib) Long-term Extension Study (category 3)	To determine the long term safety of ibrutinib	Long term use (>2 years)	Started	Interim report 2nd Quarter 2016

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
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 (category 3)	Evaluate efficacy and safety of ibrutinib in combination with BR vs. BR alone	Overall safety profile	Started	3rd Quarter 2020 final
PCI-32765CLL1005 Open-Label, Sequential-Design Drug Interaction Study of the Effect of Omeprazole on the Pharmacokinetics of Ibrutinib in Healthy Adults (category 3)	Determine the effect of ibrutinib on proton pump inhibitors.	Drug-drug interaction	Started	3rd Quarter 2016
Following the mouse range-finder study: TOX11482 A 26-week carcinogenicity study of ibrutinib by oral gavage in CByB6F1/Tg rasH2 hemizygous mice (category 3)	To evaluate the potential of ibrutinib to induce preneoplastic and neoplastic lesions.	Other malignancies (excluding non-melanoma skin cancer)	Planned	1st Quarter 2018
PCYC-1116-CA An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil) – 2 year safety update (category 3)	To further characterise the long term safety of ibrutinib	Non-melanoma skin cancer Other malignancies (excluding non-melanoma skin cancer) Long term use (>2 years)	Started	2nd Quarter 2018
AMES assays of major human metabolites M21 and M34 (category 3)	Assess mutagenicity potential of major human metabolites	Long term use (>2 years)	Started	Final report: 1st Quarter 2017
[a] Trial only collects grade 3 or 4 AEs and not all AEs				

Risk minimisation measures

Table – Summary table of the risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks:		
Leukostasis	Wording in SmPC section 4.4 and 4.8.	None
Haemorrhage	Wording in SmPC section 4.4.	None
Tumour lysis syndrome	Wording in SmPC section 4.4 and 4.8.	None
Hepatotoxicity (including hepatic failure)	Wording in SmPC section 4.8 and 4.9.	None
Non-melanoma skin cancer	Wording in SmPC section 4.4 and 4.8.	None
Interstitial lung disease	Wording in SmPC section 4.4 and 4.8.	None
Important Potential Risks:		
Drug-drug interactions	Wording in SmPC section 4.4 and 4.5.	None
Anaemia	Wording in SmPC section 4.2 and 4.4.	None
Neutropenia	Wording in SmPC section 4.2, 4.4 and 4.8.	None
Thrombocytopenia	Wording in SmPC section 4.2, 4.4 and 4.8.	None
Infections	Wording in SmPC section 4.4.	None
Cardiac arrhythmia	Wording in SmPC section 4.4.	None
Severe GI AEs	Wording in SmPC section 4.8.	None
Other malignancies (excluding non-melanoma skin cancer)	None proposed.	None
Hypersensitivity	Wording in SmPC section 4.3 and 4.8.	None
Teratogenicity	Wording in SmPC section 4.4 and 4.6.	None
Eye disorders	Wording in SmPC 4.8.	None
Renal failure	Wording in SmPC 4.2.	None
Hypertension	Wording in SmPC 4.8.	None
Missing Information:		
Use in paediatric patients	Wording in SmPC 4.2.	None
Use during breastfeeding	Wording in SmPC 4.6.	None
Use in patients with severe cardiac disease	Wording in SmPC 4.2.	None
Use in patients with severe renal impairment	Wording in SmPC 4.2.	None
Use in patients with severe hepatic impairment	Wording in SmPC 4.2.	None
Long term use (>2 years)	None proposed.	None

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Annex II have been updated. In addition, a minor editorial change was made to section 4.5 of the SmPC. The Package Leaflet is updated accordingly.

2.7.1. User consultation

No user consultation on the Package Leaflet was conducted as the changes to the Package Leaflet were considered minor. This is acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects
CLL3001 enrolled patients with R/R CLL/SLL. About 50% of patients had received one line of prior therapy and about 25% were refractory to purine analogues. Due to the selected background therapy, patients with del.17p positive CLL/SLL were excluded. The median/mean ages at enrolment were 64/64 and about 30% of patients were >70 years of age.

Submitted data refer to an interim analysis conducted at a PFS event rate about 20 and 60%, i.e. at a higher event rate than originally planned for. Expressed as PFS HRs the treatment difference was about 0.02 at a p-value <0.001. The main difference in terms of PFS events was observed after end of induction therapy. The reported ORRs (IRC) were 83% vs. 68%, p-value <0.0001. A PFS2 analysis has been submitted. The event rates in this analysis were as expected low, 10 vs. 17%, HR 0.53, p-value 0.006 (exploratory). Based on the results of the interim analysis, the DMC recommended unblinding of the study.

At event rates of 9% and 14%, there is a trend towards improved survival with HR 0.63, p-value 0.06. An increase in MRD negativity was reported in the experimental arm, 13% vs. 5% p-value 0.001 (to be viewed as exploratory due to hierarchical testing procedure).

The supportive Study 1108 provides supportive single arm evidence as regards the activity and safety of ibrutinib as add-on to BR. Study 1109, exploring the combination ofatumumab and ibrutinib, is of minor relevance for this submission whilst the single arm, monotherapy study 1117 provides further confirmation of the efficacy of ibrutinib in case of CLL with del 17p.

The final CSRs for study MCL3001 and MCL2001 have been provided in support of the current indication in r/r MCL. MCL3001 was a Phase 3, open-label, randomised monotherapy study comparing ibrutinib with temsirolimus in r/r MCL after at least one prior rituximab-containing chemotherapy regimen (n=280, 1:1 randomisation). MCL2001 was a Phase 2, open-label, monotherapy study in r/r MCL after at least one prior rituximab-containing chemotherapy regimen and documented PD after at least 2 cycles of single-agent or combination bortezomib therapy (n=120).

In the MCL3001 study, PFS by IRC, the primary outcome measure, showed a HR of 0.428 in favour of the ibrutinib arm, p<0.0001, with mature data in the temsirolimus arm (79%). Sensitivity analyses and secondary outcomes, as well as PFS2, were all supportive.

In the MCL2001 study, ORR by IRC, the primary outcome measure, was 63% for the response-evaluable population, with a CR rate of 21%, and 57% for the all-treated population. At the final analysis by investigator, with a median follow-up of 26.7 months, ORR was unchanged but the fraction of patients with CR had increased from 18% at the time of the cutoff for the primary analysis to 24.5%. At the primary cutoff and with 33% events the median DOR by IRC was approximately 15 months. At the final analysis by investigator, with a median follow-up of 26.7 months, DOR had increased from 12.9 months at the time of the primary analysis to 21.3 months.

Looking at activity in terms of response rates with ibrutinib across the MCL studies, the ORR was 72% in MCL3001, 63% in MCL2001 and 68% in 1104.

Overall the data submitted confirm the benefit observed with ibrutinib in the approved indications.

Uncertainty in the knowledge about the beneficial effects

The interim analysis was conducted at a low event rate in the ibrutinib arm in the CLL study, therefore the PFS event curve is not well established, however based on prior monotherapy studies, however, it is accepted that ibrutinib shows durable responses. At this stage OS data cannot be used to support conclusions as the study was open to cross-over to ibrutinib at the time of patients' enrolment.

Risks

Unfavourable effects

There was an overall moderate degree of ADR related to the add-on of ibrutinib; in terms of AEs leading to treatment discontinuations, 14% vs. 12% and in terms of dose reductions 9% vs. 7%. The ADR profile in the combination arm looks essentially as expected based on the combination of the profiles of BR and ibrutinib alone. Thus the components were administered at the same dose intensity as used for ibrutinib and BR alone.

It should be noted that treatment duration was substantially different between the study arms in MCL3001, median 14.4 months for the ibrutinib arm and 3 months for the temsirolimus arm (21 vs 5 cycles), with obvious impact on AE rates. Nevertheless, all TEAE categories (grade≥3, TESAE etc), except for outcome with death, were numerically more commonly reported in the temsirolimus arm. TEAEs leading to treatment discontinuation were reported in 12.9% of patients in the ibrutinib arm and 29.5% in the temsirolimus arm. When the analysis was restricted to the first 6 months of treatment, the differences between study arms were larger, and TEAEs with outcome of death numerically slightly lower in the ibrutinib arm. The latter outcome was also supported by an exposure time-adjusted analysis.

No new ADRs were identified, except muscle spasm and hypertension that were proposed as new ADRs in the ongoing type II variation for a broader first line indication in CLL.

The median time to atrial fibrillation/flutter was shorter in the additional monotherapy studies (61 days; n=31) as compared to the current monotherapy label pool (91 days; n=29).

Based on the additional data provided with this submission the MAH proposes a revised list of ADRs for inclusion in SmPC 4.8. Except from revision of incidence information for some ADRs, dehydration, dry mouth and anemia are suggested to be removed, which is considered acceptable.

Uncertainty in the knowledge about the unfavourable effects
There were no further uncertainties resulting from the assessment of the submitted studies.

Benefit Risk

Importance of favourable and unfavourable effects
The results from studies conducted in the CLL indication were considered of high clinical relevance. The results provided reconfirm the importance of the benefits of ibrutinib in the CLL and MCL approved indications as discussed in the original application.

Clinically relevant results were observed in patients with MCL treated with ibrutinib monotherapy in the original application for a marketing authorisation and although the pivotal study was a single arm study, the dramatic activity seen in terms of ORR, and DOR was considered unprecedented historically and sufficiently important in this heavily pre-treated patient population to support approval. Having now these results confirmed by the comparison of ibrutinib to temsirolimus is an additional reassurance to their importance.

The safety data are in line with the so far known safety profile. Subject to additional scrutiny through this assessment, some modifications of the ADRs incidences were implemented in the PI. Long term safety data are still lacking and will be provided through agreed study updates in the RMP.

Discussion on the Benefit-Risk Balance

The results of the pivotal study CLL3001, a placebo controlled add-on study to bendamustine + rituximab (BR) in patients with R/R CLL or SLL -which was part of the post-authorisation studies for Imbruvica- led to an extension of indication to add the combination of ibrutinib with bendamustine and rituximab to the CLL indications. These are of high clinical relevance to CLL patients, consistent across subgroups and supported by evidence as regards the activity and safety of ibrutinib as add-on to BR from supportive single arm data. The benefit – risk profile of adding ibrutinib to bendamustine + rituximab is considered favourable in patients with R/R CLL.

The final CSRs for study MCL3001 and MCL2001 have been provided in support of the current indication in r/r MCL. From a safety perspective, potentially important issues have been extensively discussed and revisions of the SPC have been agreed whilst in the overall pattern the safety profile of ibrutinib is unchanged.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB
C.I.4	C.I.4 - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Extension of Indication for use of Imbruvica in combination with bendamustine and rituximab in patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and the Annex II are updated. The Package Leaflet is updated in accordance. In addition, a clarification is made that the indications in mantle cell lymphoma (MCL) and Waldenstroem's macroglobulinaemia (WM) refer to use of ibrutinib as single agent. In addition, the Marketing authorisation holder (MAH) introduced minor editorial changes throughout the product information. The RMP is updated accordingly (RMP version 6.1).

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Submission of the final study report of study MCL3001	1Q 2016

Similarity with authorised orphan medicinal products

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