19 June 2025
EMA/CHMP/200822/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Imbruvica

International non-proprietary name: Ibrutinib

Procedure No. EMEA/H/C/003791/II/0092

Note

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

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

AE	adverse event
ASCT	autologous stem cell transplant(ation)
BCNU	bis-chloroethylnitrosourea (carmustine)
BEAM	BCNU, etoposide, Ara-C, and melphalan
BTK	Bruton's tyrosine kinase
CCO	clinical cutoff
CI	confidence interval
COVID-19	coronavirus disease 2019
CR	complete response
CrCL	creatinine clearance
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EoI	end of induction immunochemotherapy
FAS	full analysis set
FFS	failure-free survival
G-CSF	granulocyte colony stimulating factor
GDPR	General Data Protection Regulation
HR	hazard ratio
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	intent-to-treat
IV	Intravenous
LDH	lactate dehydrogenase
LLC	limited liability company

MCL	mantle cell lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MUE	median unbiased estimate(or)
NE	non-evaluable
ORR	overall response rate
OS	overall survival
pASCT	post autologous stem cell transplantation
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
PO	per os (oral administration)
PR	partial response
Q1, Q3	first quartile, third quartile
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAP	rituximab, dexamethasone, cytarabine, and cisplatin
SAP	statistical analysis plan
SC	Subcutaneous
SCE	Summary of Clinical Efficacy
SD	stable disease
TBI	total body irradiation
tSPRT	truncated sequential probability ratio test
THAM	TBI, Ara-C, and melphalan

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V.

submitted to the European Medicines Agency on 18 December 2024 an application for a variation.

The following variation was requested:

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

Extension of indication to include IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are eligible for autologous stem cell transplantation (ASCT), based on results from study MCL3003. This is a randomized, 3-arm, parallel-group, open-label, international, multicenter Phase 3 study. The purpose of Study MCL3003 is to compare 3 alternating courses of R CHOP/R-DHAP followed by ASCT (control Arm A), versus the combination with ibrutinib in induction and maintenance (experimental Arm A+I), or the experimental arm without ASCT (experimental Arm I) in participants with previously untreated MCL who are eligible for ASCT. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Version 23.1 of the RMP was also submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included the EMA Decisions P/0149/2013 (Capsule, hard) and P/0298/2017 (Film-coated tablet) on the granting of a product-specific 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 application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek scientific advice from 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

Timetable	Actual dates
Submission date	18 December 2024
Start of procedure:	26 January 2025
CHMP Rapporteur Assessment Report	21 March 2025
PRAC Rapporteur Assessment Report	28 March 2025
PRAC members comments	2 April 2025
CHMP Co-Rapporteur Assessment	2 April 2025
PRAC Outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 April 2025
Request for supplementary information (RSI)	25 April 2025
PRAC Rapporteur Assessment Report	26 May 2025
PRAC members comments	28 May 2025
Updated PRAC Rapporteur Assessment Report	2 June 2025
CHMP Rapporteur Assessment Report	4 June 2025
PRAC Outcome	6 June 2025
CHMP members comments	10 June 2025
Updated CHMP Rapporteur Assessment Report	12 June 2025
Opinion	19 June 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Mantle cell lymphoma (MCL) is a relatively rare subtype of lymphoid malignancy and has been recognized as a distinct entity in the Revised European-American Lymphoma (REAL) classification since 1994.

The initially sought indication was:

IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are eligible for autologous stem cell transplantation (ASCT).

The approved indication is:

IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously

untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT)"

Epidemiology

MCL is a mature B-cell Non-Hodgkin lymphoma (NHL) that accounts for about 6% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000 recently. Median age of patients at diagnosis is about 70 years. Approximately three-quarters of patients with MCL are male.

Biologic features

MCL is a subtype of B-cell non-Hodgkin lymphomas associated with increased cellular proliferation, a reduced response to DNA damage, and enhanced cell survival caused by impaired apoptosis. MCL is characterised by chromosomal translocation t(11;14)(q13:q32) that juxtaposes the cyclin D1 locus with the immunoglobulin heavy chain gene locus. This results in overexpression of the cyclin D1 (CCDN1) gene and increased proliferation.

MCL is also characterised by disturbances in pathways and factors that regulate apoptosis. MCL cells avoid apoptosis through expression of BCL2, upregulation of the PI3 kinase (PI3K)/AKT pro-survival signalling pathway, activation of nuclear factor-kB (NF-kB), and loss-of-function TP53 mutations.

Clinical presentation, diagnosis and stage

MCL is a heterogenous subtype of B-cell NHL, which remains incurable and typically has a more aggressive disease course compared to indolent NHL. MCL is characterised by involvement of the lymph nodes, spleen, blood, and bone marrow.

The diagnosis is made on a biopsy of a lymph node, tissue, bone marrow, or blood phenotype. Most tumours have a classic morphology of small-medium sized cells with irregular nuclei. Immunophenotyping is commonly used with the MCL cells being CD20+, CD5+, and positive for Cyclin D1. The hallmark chromosomal translocation t(11:14) (q13;32) that causes overexpression of cyclin D1 can be shown in most cases.

Although some patients obtain prolonged remission after first-line chemoimmunotherapy, many will need several treatment lines. Median OS for patients with MCL was recently presented to be about 5 years, in a non-selected nationwide cohort (n=1367, diagnosed 2006-2018 in Sweden) in which access to BTKi and CAR-T therapy was limited and a majority of patients did not receive rituximab maintenance (Jerkeman et al 2023).

Prognosis of MCL is affected by the clinical presentation, disease stage, and pathologic features. The Mantle Cell Lymphoma International Prognostic Index (MIPI) score prospectively divides patients into low-, intermediate-, and high-risk groups based on age, LDH, white blood cell count, and performance status.

Blastoid and pleomorphic subtypes, as well as high Ki-67 proliferation index ≥50%, are poor prognostic features. In addition, mutated p53 is associated with poor prognosis in MCL patients treated with conventional therapy including transplant.

Management

Newly diagnosed patients with MCL have so far typically been categorised into 2 subpopulations defined by their suitability and eligibility for intensive treatment including autologous stem cell transplant (ASCT).

- For most of the younger patients (< 65 years) and **transplant-eligible** patients, an intensive treatment approach including induction therapy followed by ASCT with rituximab maintenance therapy has represented the present standard of care treatment (ESMO GL 2017). Combination regimens such as R-CHOP/R-DHAP are currently among the standards of care for induction therapy. The inclusion of rituximab maintenance after ASCT in guidelines is based on the LyMa trial (Le Gouill et al 2017) in which rituximab maintenance therapy, administered for 3 years after ASCT, improved OS in fit patients with previously untreated MCL.

In the current US-based National Comprehensive Cancer Network (NCCN) GL (version 1.2025 — Dec 20, 2024) it is stated that the results of the Triangle study (study MCL3003) suggest that alternating R-CHOP + ibrutinib/R-DHAP followed by maintenance ibrutinib + rituximab is an effective induction therapy for patients <66 years of age and consolidation therapy with ASCT could be avoided in this group of patients. However, since first-line consolidation with ASCT has demonstrated promising outcomes in a number of studies and is considered as an appropriate option for consolidation therapy the NCCN GL also include ASCT followed by maintenance ibrutinib + rituximab as an option for patients with a CR following aggressive induction therapy.

- In **transplant-ineligible** patients, several chemoimmunotherapy combinations followed by rituximab maintenance are currently used. These include BR (rituximab-bendamustine), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), and also VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone).

Despite intensive approach with ASCT, no curative treatment is available for MCL. Hence, there is an unmet medical need for more effective treatments with different mechanisms of action that provide alternative treatment options for patients with newly diagnosed MCL.

2.1.2. About the product

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys 481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity.

BTK, a member of the Tec kinase family, is an important signaling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B cell malignancies, including MCL, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and CLL. BTK's pivotal role in signaling through the B cell surface receptors results in activation of pathways necessary for B cell trafficking, chemotaxis and adhesion. In preclinical studies, it has been observed that ibrutinib inhibits malignant B-cell proliferation and survival *in vivo.*

Previously approved indications:

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

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

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

No scientific advice has been requested to the CHMP. The MAH discussed a potential regulatory submission to extend the indications of ibrutinib based on the results from the 8th interim analysis (CCO date of 22 May 2022) of Study MCL3003 with the FDA and the Swedish MPA in 2022.

2.1.4. General comments on compliance with GCP

According to the MAH, Study MCL3003 was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the protocol.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The MAH has provided an updated ERA (according to the new guideline) in support of the extension of existing Mantle Cell Lymphoma (MCL) indication of Imbruvica to include the combination of ibrutinib with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) for the treatment of adult patients with previously untreated MCL who are eligible for ASCT (autologous stem cell transplantation). The ERA from the original MAA was updated with regard to predicted environmental concentration (PEC) using a new refined Fpen and resulting risk ratios.

PBT assessment

The log D_{OW} of ibrutinib was determined to be 3.8 (pH 5); 4.0 (pH 7) and 4.0 (pH 4.0). which is below the action limit of 4.5, and therefore, ibrutinib is not a potential PBT substance. However, since the log D_{OW} is higher than 3, a fish bioconcentration study was performed. This study demonstrated that bioconcentration factor (BCF) ranged from 13.5 to 68.0 L/kg which is below BCF values of <2000 L/kg. therefore ibrutinib does not bioconcentrate in aquatic systems.

Phase II Tier A: updated risk ratios (PEC/PNEC)

The previously submitted predicted environmental concentration in surface water $PEC_{SURFACEWATER}$ of ibrutinib for MCL, CLL and WM was based on a default market penetration factor (FPEN). The predicted environmental concentration in $PEC_{SURFACEWATER}$ of ibrutinib is based on the maximum proposed dose of 560 mg/day and a refined FPEN of 0.00026 (based on IARC data). The resulting $PEC_{SURFACEWATER}$ is 0.72 µg

Risk characterisation ratios (RCR) were calculated for each compartment as the ratio of the PEC/PNEC as follows:

Parameter	PEC	PNEC	RCR (action limit)
Surface water	0.072 µg/L	1.55 µg/L	0.047 (<1)
Groundwater	0.018 µg/L	0.155 µg/L	0.117 (<1)
Microorganism	0.072 µg/L	100000 µg/L	0.00001 (<0.1)
Sediment	0.047 µg/L	2.37	0.020 (<1)
Collembola	0.001 µg/L	17 mg/kg	0.0001 (<1)
Earthworm	0.001 mg/kg	5.20 mg/kg	0.0002 (<1)
Terrestrial plants	0.001 µg/L	0.028	0.034 (<1)
N-transformation			<25% effect compared to control

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. An updated ERA was provided. The predicted environmental concentration in $PEC_{SURFACEWATER}$ of ibrutinib is based on the maximum proposed dose of 560 mg/day and a refined FPEN of 0.00026 (based on IARC data). The resulting $PEC_{SURFACEWATER}$ is 0.72 µg. The risk ratios (PEC/PNEC) were subsequently re-calculated which resulted in risk ratios remaining below the action limits. Hence, the clinical use of Imbruvica (in combination with R-CHOP) for the indication of MCL is not expected to pose a risk for the environment.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated ERA submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of ibrutinib.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial was performed in accordance with GCP as claimed by the MAH.

- Tabular overview of the clinical study

Study / Phase / Status	Design/crossing	Treatment	N	Efficacy Endpoints	Median Time on Study
Study 54179060MCL3003 (TRIANGLE, MCL3003) Phase 3 Ongoing	Randomized (1:1:1), 3-arm, open-label, international multicenter trial comparing standard treatment versus standard treatment (with or without ASCT) combined with ibrutinib in induction and maintenance (2 years) in patients with previously untreated MCL	**Arm A+I (experimental):** Alternating 3 cycles R-CHOP[a]+ibrutinib[e] (Cycles 1, 3, 5)/3 cycles R-DHAP[b] (Cycles 2, 4, 6) induction, followed by THAM or BEAM[c] and ASCT, and 2 years ibrutinib maintenance [d,f]	**ITT:** N=292/870 **FAS**: N=272/809	**Primary**: FFS **Secondary**: OS, PFS, CRR, ORR, PR to CR conversion rate	54.9 months (range: 0-91)
		Arm I (experimental): Alternating 3 cycles R-CHOP[a]+ibrutinib[e] (Cycles 1, 3, 5)/3 cycles R-DHAP[b] (Cycles 2, 4, 6) induction, followed by 2 years ibrutinib maintenance[d,f]	**ITT:** N=290/870 **FAS**: N=268/809		
		Arm A (control): Alternating 3 cycles R-CHOP[a] (Cycles 1, 3, 5)/3 cycles R-DHAP[b] (Cycles 2, 4, 6) induction followed by THAM or BEAM[c] and ASCT[d]	**ITT:** N=288/870 **FAS**: N=269/809		

2.3.2. Pharmacokinetics

No new clinical pharmacological data are provided in the current submission.

2.3.3. Pharmacodynamics

No new clinical pharmacological data are provided in the current submission.

2.3.4. PK/PD modelling

No new clinical pharmacological data are provided in the current submission.

2.3.5. Discussion on clinical pharmacology

The mechanism of action of ibrutinib has been previously well characterised. However, the Phase 3 study TRIANGLE did not include PK sampling of ibrutinib which is considered a limitation in this submission. The potential concern from a PK-perspective is that the co-administered drugs during parts of the induction phase (R-CHOP) could cause drug-drug interactions (DDIs) with ibrutinib. The main risk for a DDI is from an object-perspective since ibrutinib is a CYP3A4 substrate.

The SmPC of Imbruvica states that co-administration with strong CYP3A4 inhibitors and moderate / strong CYP3A4 inducers should only be considered when the potential benefits clearly outweigh the potential risks. In this case, high doses of prednisolone induce CYP3A4 which may lead to lower ibrutinib exposure which could, in theory, lead to lack of efficacy. This concerns the induction phase where ibrutinib is to be co-administered with prednisolone, but not the monotherapy phase where ibrutinib is not co-administered with prednisolone. Despite the potential DDI resulting in lower ibrutinib exposure during the induction phase with coadministration of R-CHOP, the data from the TRIANGLE study suggest sufficient activity (see Discussion of Clinical Efficacy) for the dosing regimen proposed in the target population.

2.3.6. Conclusions on clinical pharmacology

2.4. There was no additional pharmacology information submitted with this application, however as discussed above, potential DDI concerns were alleviated as per the clinical effect observed.Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies are provided in the current submission.

The rationale for the use of ibrutinib 560 mg once daily dose in combination with induction immunochemotherapy, followed by ibrutinib maintenance therapy at the same dose, in previously untreated MCL patients was based on the currently registered ibrutinib dose as a single agent for the treatment of adult patients with relapsed or refractory MCL.

- The rationale for the dosing of ibrutinib in **combination with R-CHOP** was based on results from a Phase 1b study designed to determine the RP2D and preliminary efficacy data of ibrutinib in combination with R-CHOP in subjects with previously untreated B-cell lymphoma (including MCL; Younes 2014). Participants received the standard R-CHOP regimen every 21 days in combination with ibrutinib 280 mg, 420 mg, or 560 mg daily. While the maximum tolerated dose was not reached, the RP2D for ibrutinib was 560 mg daily. According to the MAH, the combination regimen was generally well tolerated with no new safety signals identified.
- As data for the ibrutinib in **combination with R-DHAP** were not available at study start, ibrutinib was not to be administered during the R-DHAP cycles in Study MCL3003.

The rationale for 24 months of **ibrutinib maintenance** treatment in Study MCL3003 was based on preliminary results from the LyMa trial (Le Gouill 2014) in which rituximab maintenance therapy, administered after ASCT, substantially improved PFS and EFS in young and fit patients with previously untreated MCL. Based on these findings, it was hypothesized that a fixed duration of maintenance therapy with ibrutinib may result in even deeper and more durable remissions when administered after induction immunotherapy (with or without subsequent ASCT).

2.4.2. Main study: Pivotal Study MCL3003 (Triangle)

Overview

MCL3003 is a randomized, 3-arm, parallel-group, open-label, international, multicenter Phase 3 study, conducted by the Klinikum der Universität München, Germany (hereafter referred to as study sponsor) on behalf of the European MCL Network (a network of 15 national and multinational lymphoma study groups) in 13 European countries and in Israel, and financially supported by the MAH.

The MAH was not involved in the study design and the conduct of the study, however the study is the main basis for the proposed extension of indication, proposed to encompass the use of ibrutinib together with ASCT maintenance (Arm A+I) or without ASCT (Arm I).

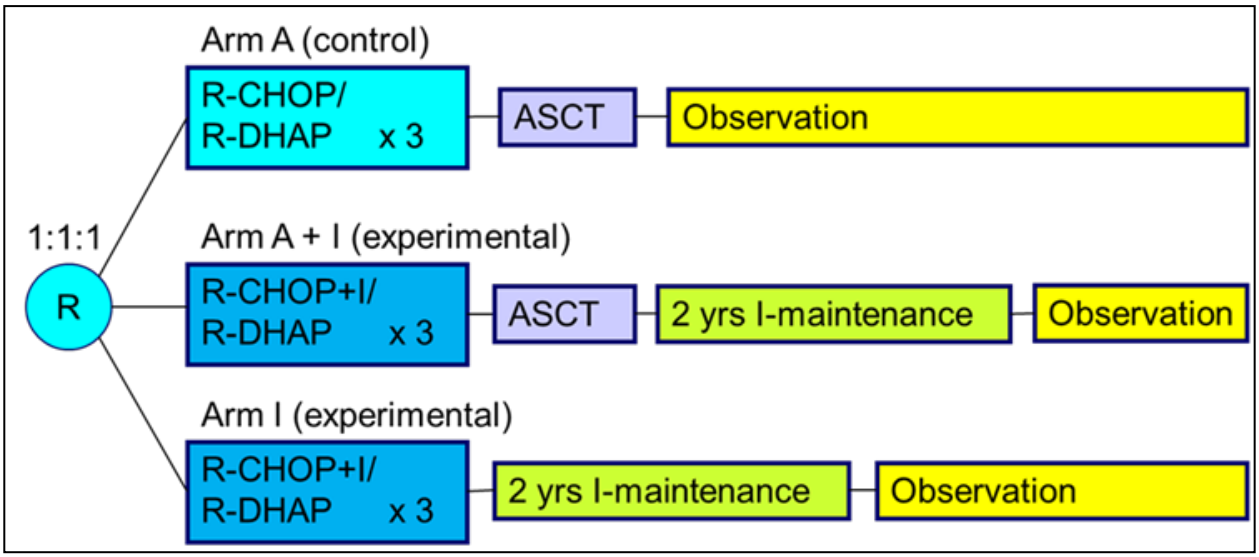


Figure 1 Study MCL3003: Schematic Overview of the Study Design

Methods

Study participants

Key Inclusion criteria (according to protocol version 1.9)

- Histologically confirmed diagnosis of MCL according to WHO classification 2008
- Previously untreated MCL
- Suitable for high-dose treatment including high-dose Ara-C
- Stage II-IV (Ann Arbor)
- Age ≥ 18 years and ≤ 65 years
- ECOG/WHO performance status ≤ 2
- Absolute neutrophil count (ANC) ≥1000 cells/uL
- Platelets ≥100,000 cells/uL
- Transaminases (AST and ALT) ≤3 x upper limit of normal (ULN) and total bilirubin ≤2x ULN unless due to known Gilbert-Meulengracht-Syndrome
- Creatinine ≤2 mg/dL or calculated creatinine clearance ≥50 mL/min
- Written informed consent form according to ICH/EU GCP and national regulations

Key Exclusion criteria (according to protocol version 1.9)

- Major surgery within 4 weeks prior to randomization.
- History of stroke or intracranial hemorrhage within 6 months prior to randomization.
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists
- Requires treatment with strong CYP3A4/5 inhibitors.
- Known CNS involvement of MCL
- Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon except prephase therapy outlined in this trial protocol

- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)
- Pulmonary (chronic lung disease with hypoxemia)
- Severe, not sufficiently controlled diabetes mellitus
- Prior organ, bone marrow or peripheral blood stem cell transplantation

Treatments

Table 1 Definition of Treatment Arms in Study MCL3003

Arm	Treatment Regimen (21-day cycles)	Group
A	Alternating 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by high-dose therapy (THAM or BEAM) and ASCT	Control
A+I	Alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by high-dose therapy (THAM or BEAM) and ASCT, and 2 years ibrutinib maintenance	Experimental
I	Alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by 2 years ibrutinib maintenance	Experimental

R-CHOP

Rituximab 375 mg/m^2 IV (D0 or 1), cyclophosphamide 750 mg/m^2 IV (D1), doxorubicin 50 mg/m^2 IV (D1), vincristine 1,4 mg/m^2 (max 2 mg) IV (D1), predniso(lo)ne 100 mg oral (D1 to D5)

R-DHAP

Rituximab 375 mg/m^2 IV (D0 or 1), dexamethasone 40 mg oral (D1 to D4), Ara-C 2x 2 g/m^2 q12h IV (D2), cisplatin 100 mg/m^2 (alternatively oxaliplatin 130 mg/m^2) IV (D1). G-CSF 5 µg/kg SC was mandatory in R-DHAP from D6 daily until recovery of WBC >2.5 G/l (alternatively pegfilgrastim could be applied once at D6)

High-dose therapy THAM or BEAM

Each site decided before trial activation which ASCT conditioning regimen (THAM or BEAM) would be chosen for all patients.

THAM= total body irradiation (TBI) 10 Gy (D -7 to -5), Ara-C 2x 1,5 g/m^2 q12h IV (D -4 to -3), melphalan 140 mg/m^2 IV (D -2)

BEAM= BCNU 300 mg/m^2 IV (D -7), etoposide 2x 100 mg/m^2 q12h IV (D -6 to -3), Ara-C 2x 200 mg/m^2 q12h IV (D -6 to -3), melphalan 140 mg/m^2 IV (D -2)

Ibrutinib

Induction:

560 mg oral (D1 to D19) in combination with R-CHOP cycle 1, 3, and 5.

Maintenance:

560 mg oral (daily) for 2 years. According to the protocol version 1.9, ibrutinib maintenance should start after regeneration of peripheral blood count after the end of the last cycle of induction therapy (earliest maintenance start at week 18) or ASCT (earliest maintenance start at week 22).

Rituximab maintenance

As evidence supporting rituximab maintenance treatment was not yet established at the start of the study, rituximab maintenance was not considered a study treatment in Study MCL3003. However, in the original protocol (protocol version 1.1, dated 18 December 2015) it was stated that "*if the recently completely recruited LyMa trial proves a benefit of rituximab maintenance after an ASCT, rituximab maintenance will be added to all 3 study arms depending on national guidelines*".

Since the final results from the LyMa trial (Le Gouill 2017) demonstrated prolonged OS for the rituximab maintenance group after ASCT in patients with previously untreated MCL, this approach has been included in national treatment guidelines in the EU. Thus, following the implementation in the national guidelines for a participating country, rituximab maintenance was to be administered to participants as per the recommendations of the site's study group, and the decision on rituximab maintenance had to be consistent for all 3 study arms to avoid treatment-related bias.

Objectives and Outcomes/endpoints

Study MCL3003 was designed to establish 1 of the 3 treatment arms as the future standard of care (per the academic study sponsor's original protocol) based on the primary endpoint Failure-free survival (FFS).

More specifically, the sponsor´s intention was to investigate whether adding ibrutinib to the current standard treatment for younger patients with MCL eligible for transplant (which includes induction immunochemotherapy followed by ASCT), would lead to superior outcomes. In addition, the study was designed to determine whether the current standard despite the short- and long-term toxicity remains superior to the same regimen in which ibrutinib is added in induction and maintenance treatment but without ASCT. Finally, the study evaluated whether the addition of ibrutinib to the current standard is superior to the same regimen but without ASCT.

Table 2 Primary and Secondary Efficacy Objectives and Endpoints for Study MCL3003

Objectives	**Endpoints**
Primary	
To establish 1 of 3 treatment arms, - R-CHOP/R-DHAP followed by ASCT (control Arm **A**), - R-CHOP+ibrutinib /R-DHAP followed by ASCT and followed by ibrutinib maintenance (experimental Arm **A+I**), and - R-CHOP+ibrutinib /R-DHAP followed by ibrutinib maintenance (experimental Arm **I**)	FFS (the time from randomization to stable disease at EoI, PD, or death from any cause, whichever comes first)

Objectives	Endpoints
as future standard based on the comparison of FFS assessed by central medical EU MCL Network case evaluation of investigator assessment	
Secondary	
To compare the efficacy of the 3 treatment arms in terms of secondary efficacy endpoints	OS (the time from randomization to death) PFS (the time to progression or death from any cause) calculated from: o randomization o EoI in patients with CR or PR at EoI o the staging 4 to 6 weeks after the EoI assessment (ie, at month 6 evaluation [pASCT])[a] in participants with CR or PR at this point CRR and ORR during the study,[b] response rate and CRR at EoI and 4 to 6 weeks after EoI, ie, at Month 6 evaluation (pASCT) PR to CR conversion rate during follow-up after EoI (for participants with PR at the EoI)

[a] For comparability of efficacy across the 3 arms, participants in Arm I had an evaluation 4 to 6 weeks after EoI, to align with the evaluation 3 to 5 weeks after ASCT for Arm A and Arm A+I (the pASCT timepoint). Hereafter, "pASCT" will be used to refer to this timepoint for all 3 arms.

[b] These endpoints reflect the best response rates and were not pre-specified in the protocol but were included in the SAP as supportive secondary endpoints.

In case of either stable disease at the end of induction immunochemotherapy (EoI) or progressive disease at any time (proven by CT scan), study treatment had to be stopped, but the participant was expected to remain in the study for further follow-up. Any salvage therapy according to institutional standard could be used after stopping study treatment upon the discretion of the treating physician.

EOI evaluation was performed 3 weeks after completion of the last cycle of chemotherapy.

Sample size

SAP version 5 states that up to 870 patients from up to 250 international sites were planned to be enrolled. The maximal trial duration would be up to 10 years with up to 5 years of recruitment. The trial may stop earlier based on the result of pre-planned interim analyses.

Randomisation and Blinding (masking)

After verification of eligibility (registration checklist) patient registration and randomisation were planned to be performed via EDC system. Participants planned to be randomized into the 3 treatment groups.

allocation ratio was done 1:1:1 unless one treatment group would have been closed; allocation ratio would then be changed to 1:1. Randomisation was stratified according to prespecified regional study groups and Mantle Cell Lymphoma International Prognostic Index (MIPI) risk groups at study entry.

The investigational product was to be labelled and handled as open-label material.

Statistical methods

Sample size and timing of interim analyses

The following assumptions were used to estimate the sample size and the trial duration:

- Randomization period up to 5 years
- Additional follow-up period up to 5 years
- Randomization rate 174 per year
- Allocation ratio 1:1:1
- Drop-out rate 5% of randomized patients
- Three pairwise log-rank tests for FFS with local one-sided significance level 0.05/3; overall significance level 5%
- FFS curve for control arm A as estimated from the experimental arm of the preceding MCL Younger trial of the European MCL Network (clinical cut-off date April 7, 2013, section 15.1.4 (CTP_Version 1.1_18. Dec 2015)
- Power 95% to detect a FFS superiority of A vs. I (hazard ratio 0.60, 5-year FFS: 64.8% vs. 48.5%)
- Power 90% to detect a FFS superiority of A+I vs. A and of A+I vs. I (hazard ratio 0.60, 5-year FFS: 77.1% vs. 64.8%)
- Regular interim analyses to allow early stopping for efficacy or futility by truncated sequential probability ratio tests truncated at 230 events for A vs. I and at 190 events for A+I vs. A and A+I vs. I

Regular pre-planned interim analyses with respect to the primary outcome FFS were planned to be performed for each pairwise comparison to allow early stopping for efficacy or futility. The multiple testing correction for interim analyses was performed using truncated sequential probability ratio tests (Whitehead 1985). For the truncated sequential probability ratio test, the number of interim analyses or the number of events at each interim analysis did not have to be specified in advance. However, regular interim analyses in an approximately half-yearly schedule triggered by the regular meetings of the European MCL Network that took place twice a year were planned. The stopping boundaries were calculated based on the number of events achieved at the time of each interim analysis in line with tSPRT methodology using the Planning and Evaluation of Sequential Trials (PEST) Version 3 software (PEST 1993). The Christmas tree adjustment was used to adjust for the discrete nature of interim analyses.

Based on the truncated sequential probability ratio test, it was concluded that a maximum of 230 events would be needed for the one-sided comparison A vs. I and a maximum of 190 events for comparisons A+I vs. A and A+I vs. I. The planned sample size was approximately 870 participants.

The truncated sequential probability ratio test was also performed for the post-hoc two-sided analyses stated in SAP version 5. It was concluded that the comparison of I vs. A would require at maximum 230 events. Corresponding fixed-sample test (without interim analyses) would require 218 events. The

comparison A+I vs. A and A+I vs. I would require maximum number of events of 190. Corresponding fixed-sample test (without interim analyses) would require 178 events.

SAP version 5 states that up to 870 patients from up to 250 international sites were planned to be enrolled. The maximal trial duration would be up to 10 years with up to 5 years of recruitment. The trial may stop earlier based on the result of pre-planned interim analyses.

Endpoints

The analysis of the primary objective were to be performed according to the intention to treat. Thus, all randomised patients were planned to be included in the primary analysis irrespective of eligibility and evaluated according to the treatment arms they were randomly allocated to. No exclusion or censoring was planned to be done in case of protocol violations.

However, it was not possible to adhere to the initially defined primary analysis population according to ITT. The applicant describes the circumstances as follows in the clinical overview:

"*Per the European General Data Protection Regulation (GDPR), a study participant must provide explicit permission for the participant's data to be included in a dossier for global HA submissions. As the results from Study MCL3003 were not originally intended by the study sponsor to be included in a dossier for global HA submissions, and due to the timing of the GDPR regulation becoming effective (25 May 2018), such explicit permission was not required to be requested within the original study ICF.*

Therefore, the ICF was updated in 2023 and of the 870 participants randomized to the study (ITT analysis set: Arm A+I: 292; Arm I: 290; Arm A: 288), 809 participants (272, 268, and 269 for Arm A+I, Arm I and Arm A, respectively) have either provided explicit permission in the ICF for their data to be included in a dossier for global HA submissions or were deceased. These 809 participants (93% of the ITT analysis set) are referred to throughout the submission documents as the FAS."

Consequently, post-hoc SAP version 5 (dated 5 September 2024) states that all analyses prepared by the applicant would contain all randomized participants who had provided explicit consent for their data to be used by the applicant for health authority submissions and participants who are deceased (Full Analysis Set). The safety analysis set would include all participant of the FAS who received at least 1 dose of study intervention.

<u>Analysis methods for primary efficacy endpoint</u>

The primary endpoint FFS, was defined according to protocol, as the time from randomisation to stable disease at end of induction immuno-chemotherapy, progressive disease, or death from any cause, whichever came first. The primary endpoint was FFS assessed by central medical EU MCL Network case evaluation of investigator assessment. Three pairwise one-sided statistical hypothesis tests (A vs. I, A+I vs. A, and A+I vs. I) were planned to be performed using the log-rank statistic for FFS.

The hypotheses of these three log-rank tests are described as follows:

- FFS comparison Control arm A (R-CHOP/R-DHAP followed by ASCT) vs. Experimental arm I (R-CHOP+ibrutinib/R-DHAP followed by ibrutinib maintenance)
    - H0: A is not superior to I
    - H1: A is superior to I
- FFS comparison Experimental arm A+I (R-CHOP+ibrutinib/R-DHAP followed by ASCT and ibrutinib maintenance) vs. Control arm A (R-CHOP/R-DHAP followed by ASCT)
    - H0: A+I is not superior to A

- H1: A+I is superior to A

- FFS comparison Experimental arm A+I (R-CHOP+ibrutinib/R-DHAP followed by ASCT and ibrutinib maintenance) vs. Experimental arm I (R-CHOP+ibrutinib/R-DHAP followed by ibrutinib maintenance)
    - H0: A+I is not superior to I
    - H1: A+I is superior to I

For each pairwise test, the local one-sided significance level was planned to be 0.05/3 =0,0167 such that a global significance level of 5% would be maintained (Bonferroni-correction for multiple testing).

The formal decision for the new standard would be taken based on the results for the three pairwise statistical tests. According to protocol, for the primary analysis, p-values and hazard ratios for the treatment effects would be calculated correcting for the sequential design.

Post-hoc SAP version 5 (dated 5 September 2024) specified additional post-hoc analyses to support regulatory assessment of the proposed indication. The following hypotheses were planned to be performed to support the initial primary analyses that were specified in the protocol.

FFS two-sided comparison based on log-rank test of hypotheses I vs. A; A+I vs A and A+I vs I with alpha at 0.05/3 (0.0167) for each comparison.

- FFS one-sided comparison based on log-rank test of hypotheses I vs. A; A+I vs A and A+I vs I with alpha at 0.025/3 (0.0083) for each comparison.

Post-hoc SAP version 5 state the following as primary estimator:

- Median unbiased estimator (MUE) of hazard ratio with one-sided 98.33% CI was planned to be the primary estimator (correcting for sequential analyses) according to the prespecified primary analysis in the protocol. Overrunning analyses would incorporate data collected after the formal decision of each sequential test. Kaplan-Meier method would be used to estimate the distribution of FFS for each treatment group.
- One-sided unstratified log-rank test for statistical significance at the 1.667% level (after Bonferroni correction for pairwise treatment group comparison) would be conducted, correcting for sequential analyses. Post hoc analysis based on the two-sided log-rank test for statistical significance at the 1.667% level (one-sided log-rank test for statistical significance at the 0.83% level) would also be conducted.
- Unstratified Cox's regression model with study treatment (Treatment groups) as the sole explanatory variable would be performed to provide hazard ratio with one-sided 98.33% CIs.

Censoring rules, handling of missing data and Intercurrent events

According to protocol, patients alive without failure at latest contact were planned to be censored at the latest tumour assessment date. Patients without any lymphoma restaging during or at end of induction were planned to be censored at the date of randomisation.

According to SAP version 5, derivation of FFS would use the following data: date of randomisation, end of induction response, date of first progression, date of death, date of end of induction staging, last date without progression. Patients with stable disease at the end of induction therapy or with progressive disease or death at any time from any cause have an FFS event. If two or more FFS events occurred, the earlier event would count for FFS evaluation. In patients with complete or partial response at the end of induction therapy and without progression or death, FFS would be censored at

the last adequate disease assessment date. Patients without any lymphoma disease evaluation during or at the end of induction were planned to be censored one day after randomization.

As the TRIANGLE protocol was written prior to the adoption of (ICHE9[R1] 2019), estimands were not defined and explicitly pre-specified in the protocol. However, because this is currently expected by regulators and other stakeholders, estimands were defined explicitly in the SAP for the primary endpoint and the key secondary endpoints of PFS and OS. Intercurrent event Treatment discontinuation due to AE or reasons other than AE or worsening of disease would be handled using treatment policy. Use of subsequent anticancer therapy would be handled with both treatment policy and hypothetical strategy in which participants would not use any subsequent anti-cancer therapies, as they would not have been available.

Sensitivity analyses

The protocol stated that after the decision of the confirmatory statistical test, secondary efficacy endpoints would be compared between the three treatment groups. As secondary sensitivity analysis for the primary analyses of FFS, a modified intention-to-treat cohort would be used including randomised patients with confirmed MCL who started induction immuno-chemotherapy according to the randomly allocated treatment arm.

According to post-hoc SAP version 5, the following was stated

Sensitivity estimator 1

- A stratified Cox regression model with study treatment as the sole explanatory variable, with the MIPI risk group as stratification factor, was planned to be performed for FFS.

In case stratified log-rank test and stratified Cox regression model causes any convergence issue due to small number of events, stratified log-rank and stratified Cox regression model would be conducted by combining the stratum level with convergence issue.

Sensitivity estimator 2

- A stratified Cox regression model with study treatment as the sole explanatory variable, with Rituximab maintenance status (Yes or No) as stratification factor, was planned to be performed for FFS.

Of note, as per protocol, study group was specified as one of the stratification factors in the randomization of the study. Due to the large number of categories in study group stratification factor, Rituximab maintenance status is used as a substitute stratification factor in this sensitivity analysis

- An unstratified Cox's regression model with study treatment (Treatment groups) as the sole explanatory variable was planned to be performed to analyse FFS by investigator.

Subgroup analyses

According to the protocol, subgroup analyses would be performed according to MIPI, Ki-67 index, remission status (CR vs. PR) at end of induction immuno-chemotherapy, and remission status 3 months after end of induction immuno-chemotherapy. For subgroup analyses, statistical tests would be done in multivariable regression models on the interaction term of treatment group and the subgroup indicator including the main effects treatment group and subgroup indicator.

Sex, MIPI risk group, Ki-67 index, Cytology (MCL), p53 expression and Rituximab maintenance are defined as subgroups in post-hoc SAP. The subgroup analyses were planned to be performed using the multivariate Cox regression model that include treatment group and subgroup indicator as main effects and treatment-by-subgroup interaction in the model.

Changes from protocol specified analyses

The following post-hoc analyses were stated in the SAP version 5

- Estimands were specified for FFS, PFS and OS
- PFS calculated from randomisation will be considered as the primary PFS endpoint and the other 2 will be considered supportive.
- Additional analyses of the 2-sided tests at an overall 5% significance level (individual 1.67% significance level) and 1-sided test at an overall 2.5% significance level (individual 0.833% significance level) based on the log-rank test statistic were not pre-specified in the protocol. These analyses were specified in the SAP to support the primary analysis.
- FFS stratified by MIPI; FFS stratified by Rituximab status; FFS by investigator assessment were specified in SAP version 5 as sensitivity analyses.
- FFS; censored at the last disease assessment showing evidence of neither stable disease at EoI therapy nor evidence of PD before subsequent anticancer therapy.\\

Results

Participant flow

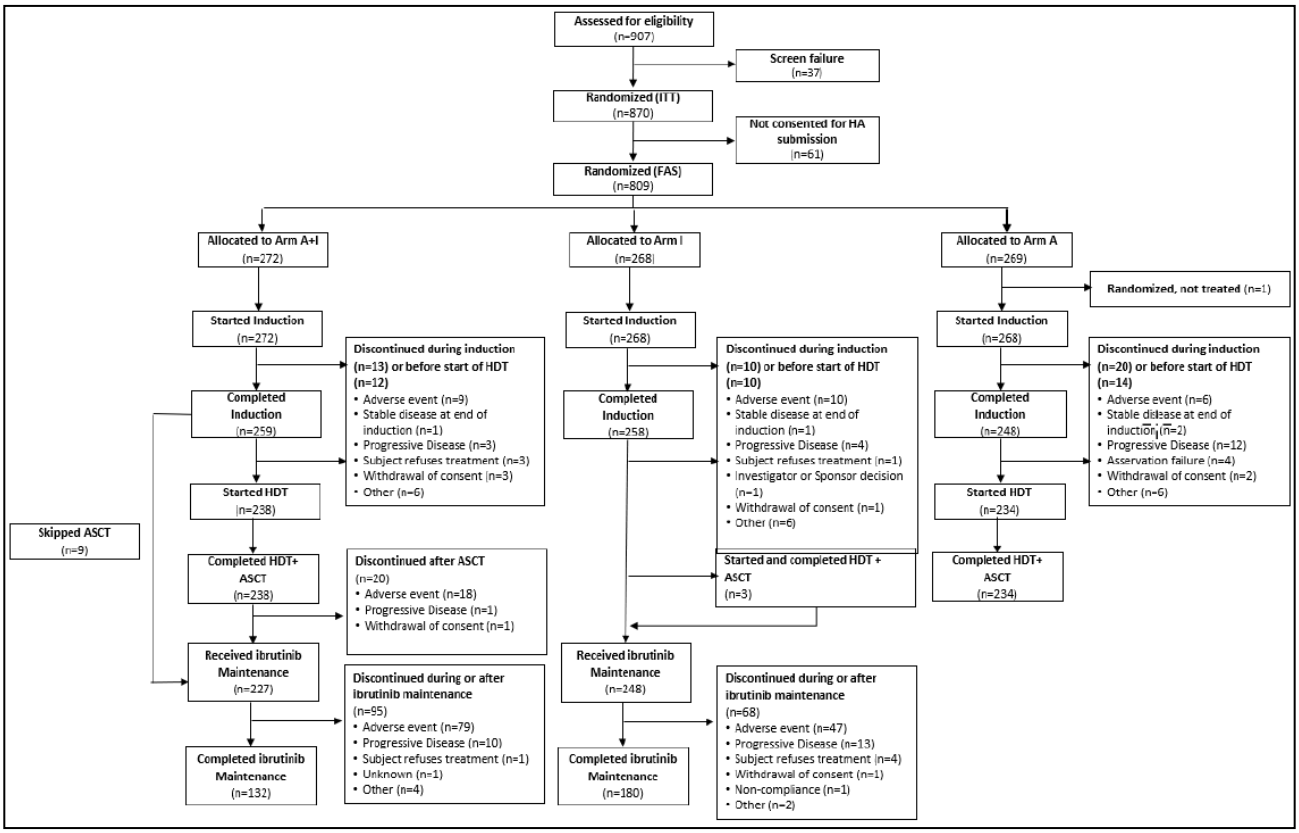


Figure 2 Consort diagram of the Treatment disposition of participants in study MCL3003

Table 3 Treatment Disposition FAS Study MCL3003

	A+I	I	A	Total
Analysis set: Full	272	268	269	809
Subjects randomized but not treated	0	0	1 (0.4%)	1 (0.1%)
Subjects who received study treatment	272 (100.0%)	268 (100.0%)	268 (99.6%)	808 (99.9%)
Subjects who completed treatment	132 (48.5%)	180 (67.2%)	234 (87.0%)	546 (67.5%)
Subjects who are still on treatment	0	0	0	0
Subjects who discontinued study treatment	140 (51.5%)	88 (32.8%)	34 (12.6%)	262 (32.4%)
Adverse event	106 (39.0%)	57 (21.3%)	6 (2.2%)	169 (20.9%)
Asservation failure	0	0	4 (1.5%)	4 (0.5%)
Death	0	1 (0.4%)	0	1 (0.1%)
Investigator or sponsor decision	0	1 (0.4%)	0	1 (0.1%)
Non compliance	0	1 (0.4%)	0	1 (0.1%)
Other [a]	10 (3.7%)	3 (1.1%)	6 (2.2%)	19 (2.3%)
Progressive disease	14 (5.1%)	17 (6.3%)	12 (4.5%)	43 (5.3%)
Stable disease at end of induction	1 (0.4%)	1 (0.4%)	2 (0.7%)	4 (0.5%)
Subject refuses treatment	4 (1.5%)	5 (1.9%)	2 (0.7%)	11 (1.4%)
Unknown	1 (0.4%)	0	0	1 (0.1%)
Withdrawal of consent	4 (1.5%)	2 (0.7%)	2 (0.7%)	8 (1.0%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, MCL=Mantle Cell Lymphoma.
[a] Other includes eg, non-MCL diagnosis at baseline and errors.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

Table 4 Subject Disposition FAS Study MCL3003

	A+I	I	A	Total
Analysis set: Full	272	268	269	809
Completed	34 (12.5%)	33 (12.3%)	60 (22.3%)	127 (15.7%)
Still ongoing	230 (84.6%)	229 (85.4%)	206 (76.6%)	665 (82.2%)
Discontinued study participation	8 (2.9%)	6 (2.2%)	3 (1.1%)	17 (2.1%)
Reason for discontinuation				
Withdrawal of consent	8 (2.9%)	6 (2.2%)	3 (1.1%)	17 (2.1%)
Lost to follow-up	0	0	0	0
Other reason	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

Recruitment

Study Period: 25 July 2016 (date first participant signed informed consent) to 09 May 2024 (CCO and date of last observation recorded as part of the database for this CSR).

Number of Study Centers and Countries/Territories: This study was conducted at 165 sites that enrolled participants in 13 European countries and in Israel: Czech Republic (4 sites), Germany (49 sites), Italy (31 sites), Portugal (1 site), the Netherlands (22 sites), Belgium (5 sites), Denmark (6

sites), Finland (1 site), Norway (4 sites), Sweden (8 sites), Poland (7 sites), Spain (14 sites), Switzerland (8 sites), and Israel (5 sites).

Conduct of the study

Protocol amendments

Changes in the conduct of the study were implemented by 7 protocol amendments.

Table 5 A selection of the substantial amendments of the study protocol

Protocol amendment Protocol version and date	Substantial / non-substantial	Description of changes
01 1.2 12 May 2016	Substantial	General editorial amendments throughout Revisions to: • THAM dose: study day of administration • Schedule of treatments and assessments: corrections and clarifications • Clinical safety; addition of sub-section interstitial lung disease • Myeloablative treatment • Interruption of ibrutinib therapy if patients experience specific gastrointestinal events • Assessments completed in cases of progressive disease during study treatment • SAE reporting timeline • Quality complaint reporting timeline • EoT assessment updated to EoI assessment for maintenance period
02 1.3 07 February 2017	Substantial	General editorial amendments throughout Revisions to: • Inclusion criteria: specifically, approved contraceptive methods • Pharmacokinetics of ibrutinib; supportive data from in vitro studies • Treatment related lymphocytosis • Clinical safety; updated the safety data profile to present data from 1,944 subjects rather than 1,637, addition of reported events of hypertension, secondary primary malignancies and non-melanoma skin cancer

Protocol amendment Protocol version and date	Substantial / non-substantial	Description of changes
		• Risk-benefit assessment • Interruption of R-CHOP/R-DHAP/ ibrutinib therapy in the event of insufficient blood level recovery, persistent Grade >2 AEs, hematological or treatment associated toxicity • Timing of scheduled assessments to allow scheduled assessments and treatments to be performed within a timeframe of ±4 days except for the last intake of ibrutinib and the first day of the following R-DHAP which should be at least 3 days to ensure an adequate drug washout • SAE reporting criteria
03 1.4 24 May 2018	Substantial	General editorial amendments throughout Revisions to: • Inclusion criteria: specifically approved contraceptive methods up to 12 months following rituximab therapy • Exclusion criteria: positive test results for HBV, hepatitis B and C infections • Clinical safety; updated safety data pool, addition of reported events of bleeding-related events, infections, and cardiac arrhythmias • Interruption of ibrutinib therapy if patients experience specific cardiac events. Associated study drug disposition and compliance. • Stem cell mobilization and harvest • Survival follow-up assessment of salvage therapy
04 1.6 19 November 2019	Substantial	General editorial amendments throughout Revisions to: • Study flow chart and schedule of assessments; follow-up assessments • Ibrutinib maintenance therapy: ibrutinib maintenance therapy could be resumed at full dose even if dose reduced during induction • Tumor and response assessments; bone marrow biopsies • Timing of baseline examinations

Protocol amendment Protocol version and date	Substantial / non-substantial	Description of changes
		• Assessments completed during observation, without treatment • eCRF reporting
05 1.7 10 August 2020	Substantial	General editorial amendments throughout Revisions to: • Clinical safety; updated safety data pool, addition of reported events of leukostasis, hypertension, cerebrovascular accidents • Blood sample collections
06 1.8 10 June 2021	Substantial	General editorial amendments throughout Revisions to: • Non-clinical data on ibrutinib • Pharmacokinetics of ibrutinib; use of CYP3A inhibitors in subjects with hematological malignancies • Clinical safety; infections, cardiac arrhythmias, rash, cerebrovascular accidents
07 1.9 12 April 2023	Substantial	General editorial amendments throughout Revisions to: • Management of cardiac toxicity during ibrutinib therapy with instructions to withhold ibrutinib therapy in the event of new or worsening Grade 2 cardiac failure or cardiac arrhythmias.

With regard to COVID-19-related changes in study conduct, the sponsor provided guidance on how to manage study visits in view of COVID-19-related restrictions considering the "Guidance on the Management of Clinical Trials during the COVID-19 pandemic" Version No. 1 dated 20/03/2020 by the EMA and the European Commission. To maintain data quality and integrity, the following actions were also taken (i) remote monitoring visits were implemented whenever local COVID-19 restrictions prevented in-person monitoring visits, (ii) safety analyses of COVID-19-related TEAEs and deaths were included, and (iii) AEs were coded using MedDRA version 26.1, which includes specific terms for COVID-19 related AEs.

Protocol deviations

A summary of major protocol deviations, defined as any deviation that directly impacted participants rights, safety, or wellbeing, or the integrity and/or results of the clinical study, is provided in table below.

Table 6 Summary of Subjects with Major Protocol Deviations, FAS, Study MCL3003

	A+I	I	A	Total
Analysis set: Full	272	268	269	809
Subjects with major protocol deviations	23 (8.5%)	28 (10.4%)	11 (4.1%)	62 (7.7%)
Developed withdrawal criteria but not withdrawn	0	0	0	0
Entered but did not satisfy criteria	18 (6.6%)	12 (4.5%)	8 (3.0%)	38 (4.7%)
Received a disallowed concomitant treatment	1 (0.4%)	5 (1.9%)	1 (0.4%)	7 (0.9%)
Received wrong treatment or incorrect dose	4 (1.5%)	8 (3.0%)	1 (0.4%)	13 (1.6%)
Other	2 (0.7%)	4 (1.5%)	2 (0.7%)	8 (1.0%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
Note: Subjects may appear in more than one category.

Baseline data

Demographics and Baseline Characteristics

Table 7 Demographics and Baseline Characteristics, FAS, Study MCL3003

	A+I	I	A	Total
Analysis set: Full	272	268	269	809
Age, years				
N	272	268	269	809
Median	57.0	57.0	57.0	57.0
Range	(36; 68)	(27; 65)	(31; 65)	(27; 68)
26-50	52 (19.1%)	58 (21.6%)	48 (17.8%)	158 (19.5%)
51-64	206 (75.7%)	202 (75.4%)	204 (75.8%)	612 (75.6%)
>=65	14 (5.1%)	8 (3.0%)	17 (6.3%)	39 (4.8%)
Sex				
N	272	268	269	809
Female	70 (25.7%)	54 (20.1%)	64 (23.8%)	188 (23.2%)
Male	202 (74.3%)	214 (79.9%)	205 (76.2%)	621 (76.8%)
Race				
N	272	268	269	809
Asian	1 (0.4%)	0	0	1 (0.1%)
Black or African American	1 (0.4%)	0	0	1 (0.1%)

	A+I	I	A	Total
White	263 (96.7%)	268 (100.0%)	264 (98.1%)	795 (98.3%)
Other	7 (2.6%)	0	5 (1.9%)	12 (1.5%)
Study Group				
N	272	268	269	809
Czech Republic: CLSG	6 (2.2%)	6 (2.2%)	4 (1.5%)	16 (2.0%)
Nordic Lymphoma Group	34 (12.5%)	34 (12.7%)	33 (12.3%)	101 (12.5%)
Germany, GLA/GLSG	91 (33.5%)	87 (32.5%)	88 (32.7%)	266 (32.9%)
Israelian Study group	0	0	0	0
Italy: FIL	66 (24.3%)	64 (23.9%)	65 (24.2%)	195 (24.1%)
Netherlands/Belgium	30 (11.0%)	31 (11.6%)	32 (11.9%)	93 (11.5%)
Poland	10 (3.7%)	11 (4.1%)	11 (4.1%)	32 (4.0%)
Portugal	2 (0.7%)	1 (0.4%)	1 (0.4%)	4 (0.5%)
Spain	23 (8.5%)	23 (8.6%)	24 (8.9%)	70 (8.7%)
Switzerland	10 (3.7%)	11 (4.1%)	11 (4.1%)	32 (4.0%)

ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, SD=standard deviation, Q1=first quartile, Q3=third quartile.
Note: N's for each parameter reflect non-missing values.
Note: Baseline results include values collected outside of the 28-day screening window.
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

Table 8 Baseline Disease Characteristics, FAS, Study MCL3003

	A+I	I	A	Total
Analysis set: Full	272	268	269	809
MIPI Risk Group[a]				
N	272	268	269	809
Low risk	155 (57.0%)	152 (56.7%)	153 (56.9%)	460 (56.9%)
Intermediate risk	76 (27.9%)	76 (28.4%)	75 (27.9%)	227 (28.1%)
High risk	41 (15.1%)	40 (14.9%)	41 (15.2%)	122 (15.1%)

	A+I	I	A	Total
ECOG Performance Status				
N	272	267	266	805
0	199 (73.2%)	187 (70.0%)	191 (71.8%)	577 (71.7%)
1	71 (26.1%)	75 (28.1%)	71 (26.7%)	217 (27.0%)
2	2 (0.7%)	5 (1.9%)	4 (1.5%)	11 (1.4%)
Ki-67				
N	244	239	235	718
<30%	168 (68.9%)	161 (67.4%)	157 (66.8%)	486 (67.7%)
>=30%	76 (31.1%)	78 (32.6%)	78 (33.2%)	232 (32.3%)
Not done	28	29	34	91
p53 expression				
N	161	177	170	508
<=50%	138 (85.7%)	149 (84.2%)	149 (87.6%)	436 (85.8%)
>50%	23 (14.3%)	28 (15.8%)	21 (12.4%)	72 (14.2%)
Not done	111	91	99	301
Cytology (MCL)				
N	244	246	238	728
Blastoid/Pleomorphic	32 (13.1%)	29 (11.8%)	27 (11.3%)	88 (12.1%)
Classic/Small cell	212 (86.9%)	217 (88.2%)	211 (88.7%)	640 (87.9%)
Not done	28	22	31	81
Rituximab maintenance				
N	272	268	269	809
Yes	163 (59.9%)	160 (59.7%)	168 (62.5%)	491 (60.7%)
No	109 (40.1%)	108 (40.3%)	101 (37.5%)	318 (39.3%)
Diagnosis				
N	272	268	269	809
MCL	269 (98.9%)	266 (99.3%)	267 (99.3%)	802 (99.1%)

	A+I	I	A	Total
Other	3 (1.1%)	2 (0.7%)	2 (0.7%)	7 (0.9%)
Ann Arbor stage				
N	272	268	267	807
I	0	0	1 (0.4%)	1 (0.1%)
II	11 (4.0%)	16 (6.0%)	8 (3.0%)	35 (4.3%)
III	21 (7.7%)	26 (9.7%)	22 (8.2%)	69 (8.6%)
IV	240 (88.2%)	226 (84.3%)	236 (88.4%)	702 (87.0%)
Bone marrow involvement				
N	266	261	261	788
Yes	203 (76.3%)	200 (76.6%)	209 (80.1%)	612 (77.7%)
No	57 (21.4%)	57 (21.8%)	49 (18.8%)	163 (20.7%)
Unknown	6 (2.3%)	4 (1.5%)	3 (1.1%)	13 (1.6%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, MIPI=Mantle Cell Lymphoma International Prognostic Index, ECOG=Eastern Cooperative Oncology Group,

[a]Patients were stratified by mantle cell lymphoma international prognostic index (MIPI) score (low risk [<5.7] vs. intermediate risk [>=5.7 and <6.2] vs. high risk [>=6.2) in MCL3003.
Note: Baseline results include values collected outside of the 28-day screening window.
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

Comparison of Baseline data FAS vs ITT Population

Table 9 Baseline Demographic and Disease Characteristics for FAS vs ITT Population

Variable	Arm A		Arm A+I		Arm I	
	ITT, N=288	FAS, N=269	ITT, N=292	FAS, N=272	ITT, N=290	FAS, N=268
Age (years)*, Median (IQR)	57 (52 - 61)	57 (53 - 61)	57 (52 - 61)	57 (52 - 61)	57.5 (52 - 61)	57 (52 - 61)
Sex, Male n (%)	218 (76%)	205 (76%)	216 (74%)	202 (74%)	228 (79%)	214 (80%)
Race						
White or Caucasian n (%)	283 (98%)	264 (98%)	283 (97%)	263 (97%)	290 (100%)	268 (100%)
Other n (%)	5 (2%)	5 (2%)	9 (3%)	7 (3%)	0 (0%)	0 (0%)
Ann Arbor Stage						
I n (%)	0 (0%)	1/267 (0%)	0 (0%)	0/272 (0%)	0 (0%)	0/268 (0%)
II n (%)	11/285 (4%)	8/267 (3%)	12/290 (4%)	11/272 (4%)	18/289 (6%)	16/268 (6%)
III n (%)	24/285 (8%)	22/267 (8%)	21/290 (7%)	21/272 (8%)	29/289 (10%)	26/268 (10%)
IV n (%)	250/285 (88%)	236/267 (88%)	257/290 (89%)	240/272 (88%)	242/289 (84%)	226/268 (84%)
B-symptoms, Present n (%)	72/285 (25%)	58/266 (22%)	78/290 (27%)	58/271 (21%)	87/285 (31%)	66/263 (25%)
ECOG						
0 n (%)	213 (74%)	191 (72%)	213 (73%)	199 (73%)	208 (72%)	187 (70%)
1 n (%)	70 (24%)	71 (27%)	77 (26%)	71 (26%)	77 (27%)	75 (28%)
2 n (%)	5 (2%)	4 (2%)	2 (1%)	2 (1%)	5 (2%)	5 (2%)
LDH, > ULN n (%)	123 (43%)	114 (43%)	120 (41%)	105 (39%)	105 (36%)	93 (35%)
Leukocytes (WBC, G/L), Median (IQR)	7.34 (5.50 – 10.91)	7.4 (5.7- 12.1)	7.09 (5.28 – 11.11)	7.0 (5.2 – 11.0)	7.4 (5.77 – 11.92)	7.8 (6.0 – 12.6)
MIPI score						
Low n (%)	168 (58%)	153 (57%)	168 (58%)	155 (57%)	168 (58%)	152 (57%)
Intermediate n (%)	79 (27%)	75 (28%)	80 (27%)	76 (28%)	77 (27%)	76 (28%)
High n (%)	41 (14%)	41 (15%)	44 (15%)	41 (15%)	45 (16%)	40 (15%)
Ki-67 index, ≥30% n (%)	81/249 (33%)	78/235 (33%)	81/262 (31%)	76/244 (31%)	82/259 (32%)	78/239 (33%)
p53 expression, >50% n (%)	21/183 (11%)	21/170 (12%)	25/175 (14%)	23/161 (14%)	31/189 (16%)	28/177 (16%)

ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; LDH=lactate dehydrogenase; MCL=mantle cell lymphoma; MIPI=Mantle Cell Lymphoma International Prognostic Index; ULN=upper limit of normal

*Notes for ITT population: 1 patient aged 68 years and 1 patient aged 66 years were randomized in Arm A+I.

ECOG=Eastern Cooperative Oncology Group; IQR=interquartile range; LDH=lactate dehydrogenase; MCL=mantle cell lymphoma; MIPI=Mantle Cell Lymphoma International Prognostic Index; ULN=upper limit of normal

*Notes for ITT population: 1 patient aged 68 years and 1 patient aged 66 years were randomized in Arm A+I.

Concomitant therapy

The most common concomitant medications received were: Immunostimulants (Arm A+I: 96.7%, Arm I: 95.8%, Arm A:95.9%), Antibacterials for systemic use (Arm A+I: 96.4%, Arm I: 93.6%; Arm A: 97.0%), and Antiemetics (Arm A+I: 91.6.%, Arm I: 90.2%, Arm A: 88.1%).

Concomitant medications with a difference ≥10% between any arm included: Antivirals for systemic use (higher in Arm A+I (90.2%) and Arm A (81.3%) compared with Arm I (67.9%)), Antimycotics for systemic use (higher in Arm A+I (66.9%) and Arm A (66.0%) compared with Arm I (42.6%)).

The use of antithrombotic agents (including factor X inhibitors and platelet aggregation inhibitors other than heparin) was common and similar between the treatment arms (54.5%, 46.8%, and 51.5% in Arm A+I, Arm I and Arm A, respectively). No participant in the ibrutinib-containing arms received a vitamin K antagonist.

The percentage of participants who received any type of transfusion (blood products) during the study was 26.5%, 18.1%, and 20.5% in participants from Arm A+I, Arm I, and Arm A, respectively.

Numbers analysed

Table 10 Data sets analysed

	Arm A+I	Arm I	Arm A	Total
Randomized (Dreyling 2024 [a])	292	290	288	870
FAS	272	268	269	809
Safety Analysis Set	275*	265*	268	808

FAS: all randomized participants who have provided explicit consent for their data to be included by the Applicant for global HA submissions and participants who are deceased.

*Three participants who were randomly assigned to Arm I, received ASCT, therefore are considered as part of Arm A+I for safety analysis and reporting.

Outcomes and estimation

Primary endpoint FFS

The presented primary analysis of study MCL3003 is based on the FAS (n=809) with CCO date of 09 May 2024 and a median time on study for all participants of 54.9 months. In the table below, both the one-sided Primary analysis *(as pre-specified in the original protocol)* and the two-sided Additional analyses are presented.

Table 11 Summary of FFS, FAS, Study MCL3003

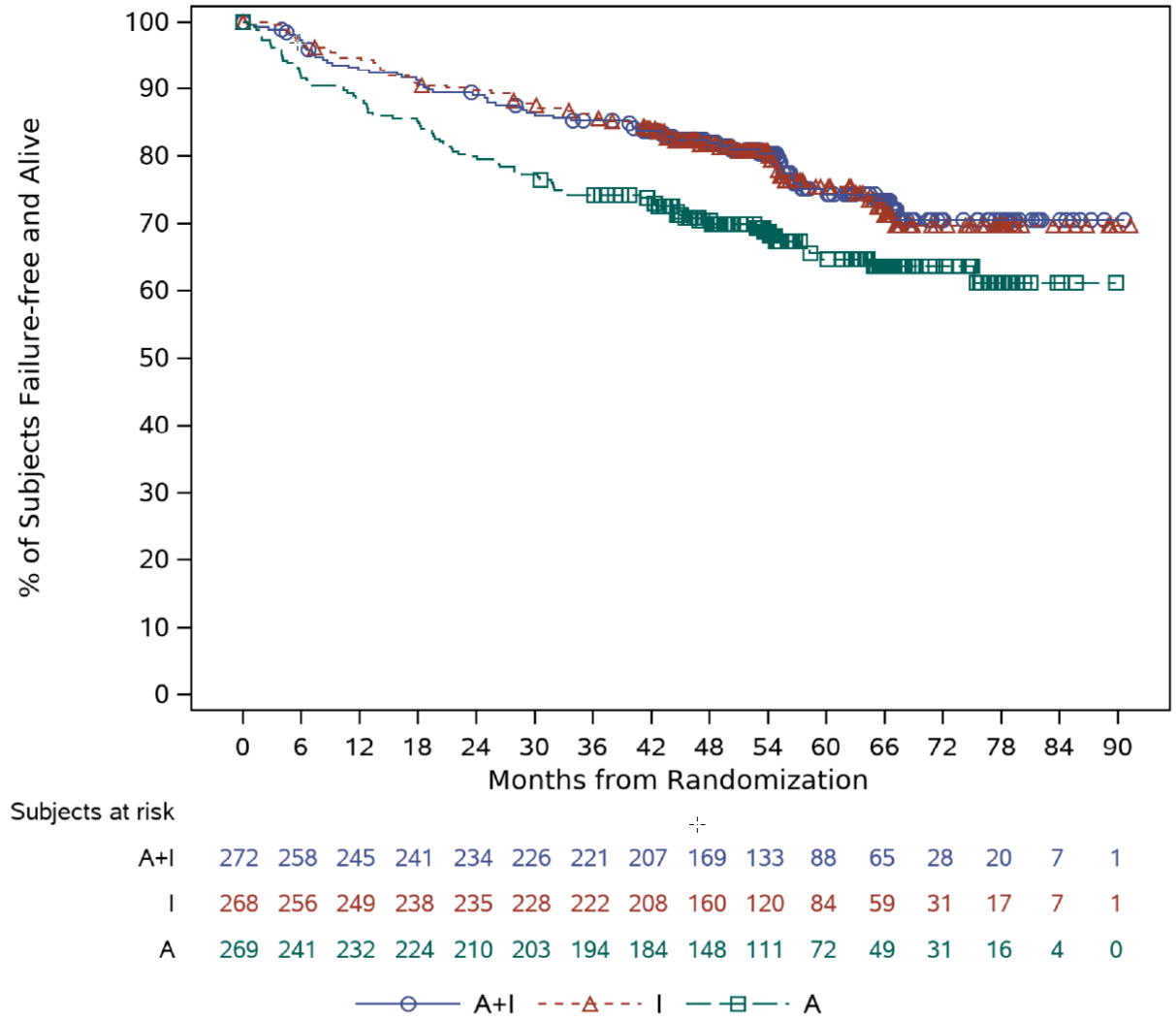
	A+I N=272	I N=268	A N=269	A+I vs A	A vs I	I vs A[b]	A+I vs I
Primary Analysis[a]							
FFS Events	**61 (22.4%)**	**61 (22.8%)**	**87 (32.3%)**				
SD at EoI	**1 (0.4%)**	**1 (0.4%)**	**5 (1.9%)**				
Failure-free Survival (months)							
Median (95% CI)	**NE (NE, NE)**	**NE (NE, NE)**	**NE (NE, NE)**				
48-month FFS rate (95% CI)	**0.819 (0.767, 0.861)**	**0.818 (0.765, 0.860)**	**0.703 (0.643, 0.755)**				
54-month FFS rate (95% CI)	**0.803 (0.748, 0.848)**	**0.807 (0.753, 0.851)**	**0.687 (0.626, 0.741)**				
60-month FFS rate (95% CI)	**0.743 (0.676, 0.798)**	**0.754 (0.688, 0.808)**	**0.646 (0.578, 0.707)**				
MUE HR (1-sided 98.33% CI)				**0.644 (0, 0.934)**	**1.546 (0, 2.206)**	**-**	**0.948 (0, 1.417)**
p-value (1-sided)				**0.0065**	**0.9883**	**-**	**0.3912**

Cox HR (1-sided 98.33% CI)	**0.633 (0, 0.904)**	**1.565 (0, 2.233)**	**-**	**0.983 (0, 1.445)**
p-value (1-sided)	**0.0029**	**0.9966**	**-**	**0.4612**
***Additional Analyses*[b]**				
MUE HR (2-sided 98.33% CI)	**0.640 (0.430, 0.963)**	**-**	**0.646 (0.434, 0.974)**	**1.059 (0.663, 1.802)**
p-value (2-sided)	**0.0091**	**-**	**0.0112**	**0.7782**
Cox HR (2-sided 98.33% CI)	**0.633 (0.425, 0.945)**	**-**	**0.639 (0.428, 0.953)**	**0.983 (0.637, 1.516)**
p-value (2-sided)	**0.0058**	**-**	**0.0068**	**0.9224**

[a] Primary analyses based on 1-sided 1.67% (5%/3) significance level using the tSPRT boundary-based approach. [b] Additional analyses based on 2-sided 1.67% (5%/3) significance level using the tSPRT boundary-based approach.

Table 12 Details on FFS events, FAS, Study MCL3003

	A+I	I	A
Analysis set: Full	272	268	269
FFS Events	61 (22.4%)	61 (22.8%)	87 (32.3%)
Stable Disease at the End of Induction Therapy	1 (0.4%)	1 (0.4%)	5 (1.9%)
Disease Progression	40 (14.7%)	49 (18.3%)	60 (22.3%)
Death	20 (7.4%)	11 (4.1%)	22 (8.2%)
Censored	211 (77.6%)	207 (77.2%)	182 (67.7%)



Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.

Figure 3 Kaplan-Meier Curves of FFS, FAS, Study MCL3003

Table 13 Reasons for censoring in each treatment arm in the FFS analysis

TEFFFS01AMCL: Failure-free Survival, Reason for Censoring by Central Medical MCL Network; Full Analysis Set (Study 54179060MCL3003)

	A+I	I	A
Analysis set: Full	272	268	269
Censored	211	207	182
Reason for Censoring			
No postbaseline disease assessment	5 (2.4%)	4 (1.9%)	6 (3.3%)
Study cut-off	201 (95.3%)	199 (96.1%)	176 (96.7%)
Withdrew consent	5 (2.4%)	4 (1.9%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
Note: Percentages are calculated with the number of censored subjects as denominator.

Sensitivity and Supplementary analyses of FFS

Table 14 Overview of Sensitivity and Supplementary Analyses for FFS in Study MCL3003

	A+I vs A	I vs A	A+I vs I
SENSITIVITY ANALYSES			
1: Cox regression model, stratified by MIPI risk group			
Median (months) (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Cox HR (98.33% CI)	0.626 (0.420, 0.935)	0.627 (0.420, 0.936)	0.993 (0.644, 1.532)
p-value (2-sided)	0.0048	0.0049	0.9693
2: Cox regression model, stratified by rituximab maintenance			
Median (months) (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Cox HR (98.33% CI)	0.587 (0.393, 0.876)	0.587 (0.393, 0.878)	1.016 (0.659, 1.568)
p-value (2-sided)	0.0013	0.0013	0.9284
3: FFS per investigator assessment			
Median (months) (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (75.14, NE)
Cox HR (98.33% CI)	0.633 (0.424, 0.945)	0.641 (0.430, 0.956)	0.975 (0.631, 1.508)
p-value (2-sided)	0.0059	0.0072	0.8900
SUPPLEMENTARY ANALYSIS			
1: Applying hypothetical strategy to handling of use of subsequent anticancer therapies			
Median (months) (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

	A+I vs A	I vs A	A+I vs I
Cox HR (98.33% CI)	0.642 (0.429, 0.961)	0.623 (0.414, 0.936)	1.022 (0.658, 1.588)
p-value (2-sided)	0.0080	0.0050	0.9071

Source Table 9 SCE

FFS comparison for FAS vs ITT Population

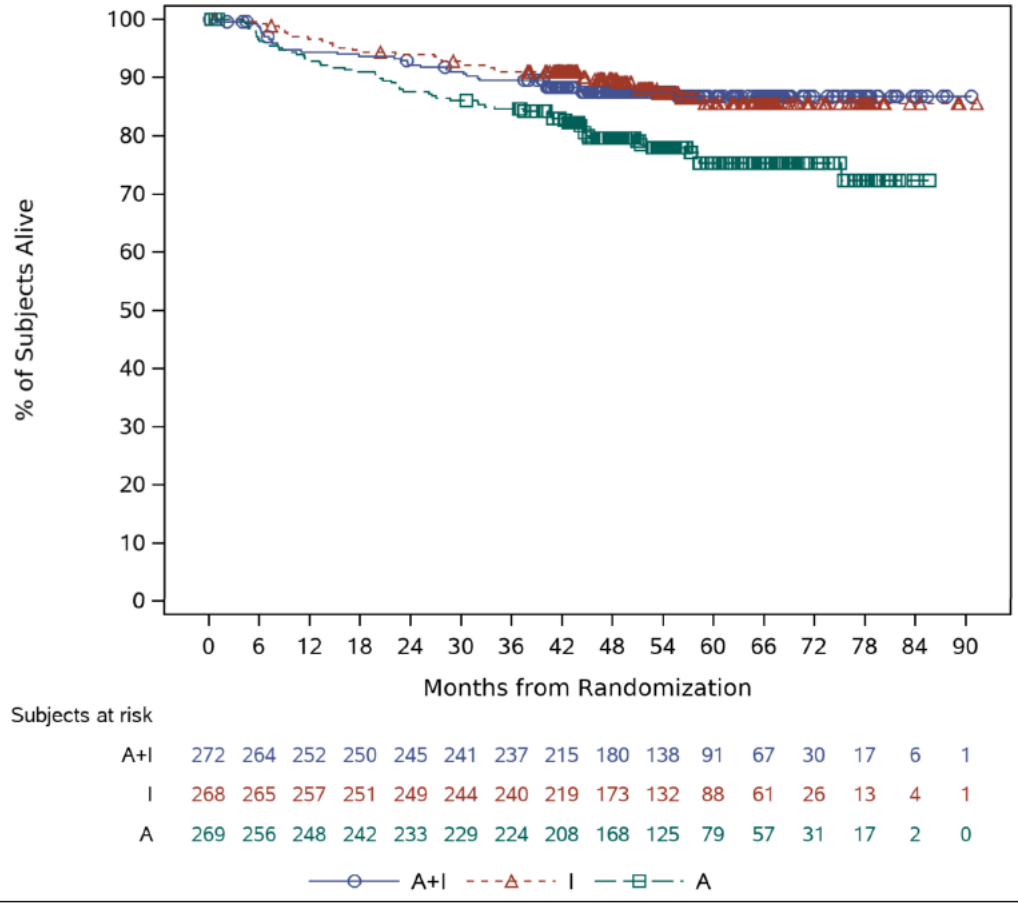
Table 15 Pairwise FFS Testing in ITT Population (Dreyling Lancet Publication) and FAS

	ITT (n=870)	**FAS (n=809)**
	HR (1-sided 98.3% CI) **1-sided p-value**	**MUE HR (1-sided 98.33% CI)** **1-sided p-value**
A+I vs A	0.52 (0.00, 0.86) p-value: 0.0008	0.644 (0, 0.934) p-value: 0.0065
A vs I	1.77 (0.00, 3.76) p-value: 0.9979	1.546 (0, 2.206) p-value: 0.9883
A+I vs I	Pairwise comparison for the superiority test of Arm A+I vs Arm I still ongoing at the time of 22 May 2022 CCO, to be reported later	0.948 (0, 1.417) p-value: 0.3912

CCO=clinical cutoff; CI=confidence interval; FAS=full analysis set; FFS=failure-free survival; HR=hazard ratio; ITT=intent-to-treat; MUE=median unbiased estimate(or). Note: based on median follow-up of 31 months for the ITT analysis set (Dreyling 2024]) and 54.9 months for the FAS.

Secondary endpoints

Overall survival



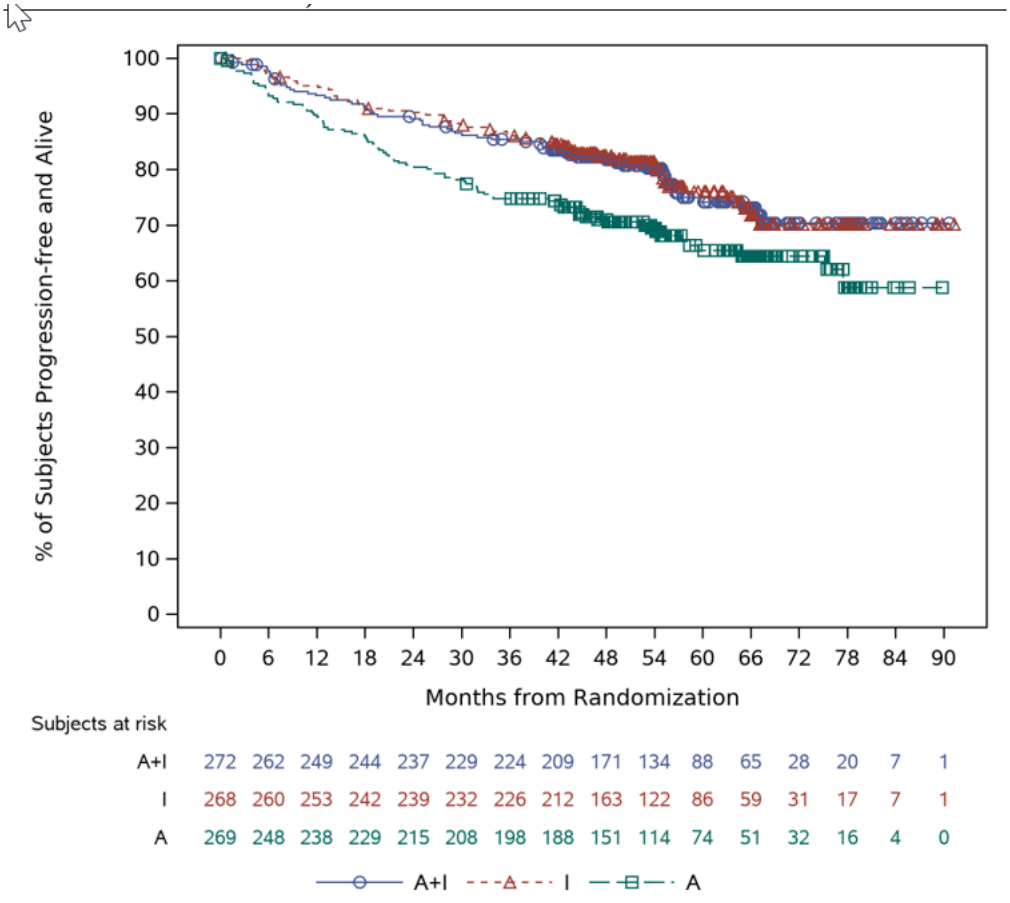
Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.

Figure 4 Kaplan-Meier Curves of OS, FAS, Study MCL3003

Table 16 Summary of OS, FAS, Study MCL3003

	A+I N=272	I N=268	A N =269	A+I vs A	I vs A	A+I vs I
Death	34 (12.5%)	33 (12.3%)	60 (22.3%)			
Censored	238 (87.5%)	235 (87.7%)	209 (77.7%)			
Overall Survival (months)						
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)			
48-month survival rate (95% CI)	0.875 (0.828, 0.909)	0.896 (0.852, 0.928)	0.796 (0.741, 0.840)			
54-month survival rate (95% CI)	0.875 (0.828, 0.909)	0.873 (0.824, 0.910)	0.779 (0.722, 0.826)			
60-month survival rate (95% CI)	0.867 (0.818, 0.904)	0.856 (0.800, 0.897)	0.753 (0.690, 0.805)			
Cox HR (95% CI)				0.542 (0.356, 0.826)	0.522 (0.341, 0.799)	1.040 (0.644, 1.679)
p-value (2-sided)				0.0038	0.0023	0.8721

Progression-free survival



Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.

Figure 5 Kaplan-Meier Curves of PFS, FAS, Study MCL3003

Table 17 Summary of PFS, FAS, Study MCL3003

	A+I N=272	I N=268	A N =269	A+I vs A	A vs I	I vs A	A+I vs I
Primary Analysis[a]							
PFS Events	62 (22.8%)	60 (22.4%)	87 (32.3%)				
Disease Progression	42 (15.4%)	49 (18.3%)	63 (23.4%)				
Death	20 (7.4%)	11 (4.1%)	24 (8.9%)				
Progression-free Survival (months)							
Median (95%CI)	NE (NE, NE)	NE (NE, NE)	NE (77.44, NE)				
48-month PFS rate (95% CI)	0.817 (0.765, 0.859)	0.824 (0.772, 0.865)	0.710 (0.651, 0.761)				
54-month PFS rate (95% CI)	0.802 (0.747, 0.846)	0.813 (0.759, 0.856)	0.694 (0.633, 0.747)				
60-month PFS rate (95% CI)	0.741 (0.675, 0.797)	0.760 (0.696, 0.813)	0.655 (0.587, 0.714)				
MUE HR (1-sided 98.33% CI)				0.661 (0, 0.953)	1.561 (0, 2.229)	-	1.009 (0, 1.492)
p-value (1-sided)				0.0084	0.9903	-	0.5187
Cox HR (1-sided 98.33% CI)				0.651 (0, 0.928)	1.580 (0, 2.258)	-	1.021 (0, 1.501)
p-value (1-sided)				0.0047	0.9970	-	0.5449
Additional Analyses[b]							
MUE HR (2-sided 98.33% CI)				0.656 (0.441, 0.981)	-	0.640 (0.430, 0.969)	1.076 (0.681, 1.803)
p-value (2-sided)				0.0122	-	0.0103	0.7092
Cox HR (2-sided 98.33% CI)				0.651 (0.437, 0.969)	-	0.633 (0.424, 0.946)	1.021 (0.662, 1.574)
p-value (2-sided)				0.0093	-	0.0060	0.9102

[a] Primary analyses based on 1-sided 1.67% (5%/3) significance level using the tSPRT boundary-based approach.
[b] Additional analyses based on 2-sided 1.67% (5%/3) significance level using the tSPRT boundary-based approach.

CR, ORR and PR to CR Conversion Rate

Table 18 CR and ORR Rate, FAS, Study MCL3003

Analysis set: Full	A+I 272	I 268	A 269	A+I vs A	I vs A	A+I vs I
Complete Response Rate[a]						
Complete Response Rate, n (%)	196 (72.1%)	180 (67.2%)	174 (64.7%)			
Relative risk (2-sided 95% CI)[c]				1.114 (0.993, 1.250)	1.038 (0.919, 1.173)	1.073 (0.959, 1.200)
p-value[d]				0.0788	0.5851	0.2250
Overall Response Rate[b]						
Overall Response Rate (CR, PR), n (%)	260 (95.6%)	258 (96.3%)	248 (92.2%)			
Relative risk (2-sided 90% CI)[c]				1.037 (0.993, 1.083)	1.044 (1.001, 1.089)	0.993 (0.959, 1.028)
p-value[d]				0.1085	0.0627	0.8284
Best Overall Response, n (%)						
Complete Response (CR)	196 (72.1%)	180 (67.2%)	174 (64.7%)			
Partial Response (PR)	64 (23.5%)	78 (29.1%)	74 (27.5%)			
Stable Disease (SD)	1 (0.4%)	1 (0.4%)	3 (1.1%)			
Progressive Disease (PD)	4 (1.5%)	3 (1.1%)	11 (4.1%)			
Not Evaluable (NE)	7 (2.6%)	6 (2.2%)	7 (2.6%)			

[a] CRR is defined as the proportion of subjects who achieve a best response of CR.
[b] ORR is defined as the proportion of subjects with a best response of CR or PR.
[c] Relative Risk >1 favors I vs. A, A+I vs. A, or A+I vs. I.
[d] p-value is from the Fisher's exact test.

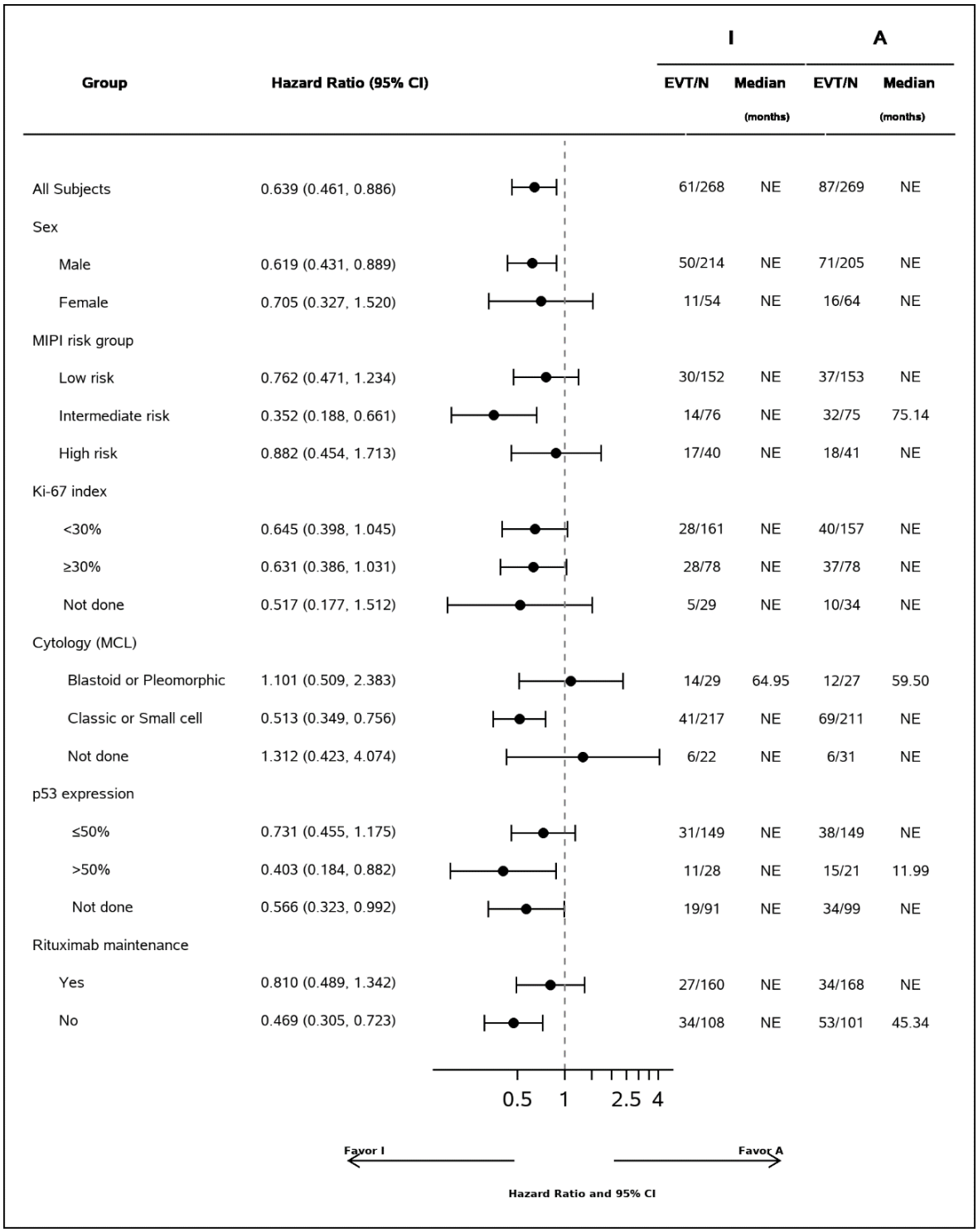
Note: Subjects with missing post-randomization data and non-evaluable responses are considered non-responders.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group as the denominators.

Table 19 PR and CR Conversion Rate during Follow-up after End of Induction, FAS, Study MCL3003

	A+I	I	A	A+I vs. A	I vs. A	A+I vs. I
Analysis set: Full	272	268	269			
Subjects with PR at EOI	145	138	150			
PR to CR conversion rate, n (%)	81 (55.9%)	60 (43.5%)	76 (50.7%)			
Relative risk (Two-sided 95% CI)[a]				1.103 (0.890, 1.366)	0.858 (0.670, 1.099)	1.285 (1.012, 1.632)
p-value[b]				0.4144	0.2389	0.0434

Key: + = censored observation, PR = Partial Response, CR = Complete Response, ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, CI=confidence interval, EOI = End of Induction.
[a] Relative Risk >1 favors I vs. A, A+I vs. A, or A+I vs. I.
[b] p-value is from the Fisher's exact test.
Note: Subjects with missing post-randomization data and non-evaluable responses are considered non-responders.
Note: Percentages are calculated with the number of subjects in the full analysis set in each treatment group with PR at EOI as the denominators.

Ancillary analyses on primary endpoint FFS



Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, MIPI=MCL International Prognostic Index.

Figure 6 Forest Plot of Subgroup Analyses on FFS **(I vs. A)**; FAS, Study MCL3003

Summary of main study

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

Table 20 Summary of Efficacy for trial MCL3003

<table>
<tr><td colspan="3">Title: Phase 3 Study - Autologous transplantation after a rituximab/ibrutinib/ara-c containing induction in generalized mantle cell lymphoma –a randomized European MCL network trial</td></tr>
<tr><td>Study identifier</td><td colspan="2">54179060MCL3003 MCL3003 - TRIANGLE

Eudra-CT-Number: 2014-001363-12

ClinicalTrials.gov ID NCT02858258</td></tr>
<tr><td>Design</td><td colspan="2">Randomized, 3-arm, parallel-group, open-label, international multicenter Phase 3 study conducted by the Klinikum der Universität München, Germany, on behalf of the European MCL Network at multiple sites in Europe and in Israel in participants with previously untreated MCL eligible for ASCT to compare 3 alternating courses of R-CHOP/R-DHAP followed by ASCT (control Arm A) versus the combination of R-CHOP+ibrutinib/R-DHAP followed by ASCT and ibrutinib maintenance (experimental Arm A+I) or R-CHOP+ibrutinib/R-DHAP followed by ibrutinib maintenance without ASCT (experimental Arm I).

The planned total sample size was up to 870 participants allocated to 1 of 3 treatment arms at a 1:1:1 ratio with randomization stratified by study group and MIPI risk group at study entry.

As evidence supporting rituximab maintenance treatment was not yet established at the start of the study, rituximab maintenance was not considered a study treatment in Study MCL3003. However, upon its implementation in national treatment guidelines, rituximab maintenance therapy was to be administered to participants as per the recommendations of the site’s study group as the decision on rituximab maintenance had to be identical for all 3 study arms to avoid treatment-related bias.</td></tr>
<tr><td></td><td>Duration of main phase:

Duration of Run-in phase:

Duration of Extension phase:</td><td>18 weeks induction therapy, +/- 6 weeks ASCT, +/- 2 years ibrutinib-maintenance

N.A.

N.A.</td></tr>
<tr><td>Hypothesis</td><td colspan="2"><table>
<tr><th>FFS comparison</th><th>Null Hypothesis</th><th>Alternative Hypothesis</th></tr>
<tr><td>A versus I</td><td>A is not superior to I</td><td>A is superior to I</td></tr>
<tr><td>A+I versus A</td><td>A+I is not superior to A</td><td>A+I is superior to A</td></tr>
<tr><td>A+I versus I</td><td>A+I is not superior to I</td><td>A+I is superior to I</td></tr>
</table></td></tr>
</table>

Treatments groups	Arm A+I (Experimental)		Ibrutinib 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT followed by 2 years Ibrutinib 560 mg daily (n=292 randomized patients).
	Arm I (Experimental)		Ibrutinib 560 mg daily (Days 1-19) in combination with R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by 2 years Ibrutinib 560 mg daily without ASCT (n=290 randomized patients).
	Arm A (Control)		R-CHOP for three 21-day cycles (Cycles 1, 3, 5) alternating with three 21-day cycles of R-DHAP (Cycles 2, 4, 6) as induction therapy followed by high-dose chemotherapy and ASCT (n=288 randomized patients).
Endpoints and definitions	Primary endpoint	Failure Free Survival (FFS)	Time from randomization to stable disease at EoI, progressive disease, or death from any cause, whichever comes first.
	Major Secondary endpoint	Overall Survival (OS)	Time from randomization to death.
	Major Secondary endpoint	Progression Free Survival (PFS)	Time to progression or death from any cause. PFS from randomization was considered as the primary PFS endpoint.
	Major Secondary endpoint	Overall Response Rate (ORR)	The proportion of participants with a best overall response of CR or PR during the study.
	Major Secondary endpoint	Complete Response (CR) Rate	The proportion of participants with a best overall response of CR during the study.
Database lock	CCO date of 09 May 2024		
Results and Analysis			

Analysis description	**Primary Analysis - FFS**			
Analysis population and time point description	Patients with previously untreated MCL who are eligible for ASCT (n=870 randomized patients). Due to European GDPR, the efficacy analyses were conducted based on 809 patients (272 patients in Arm A+I, 268 patients in Arm I and 269 patients in Arm A) in the full analysis set (FAS)/modified intention-to-treat (mITT) population. Efficacy results are based on a median follow-up time on study of 54.9 months.			
Descriptive statistics and estimate variability	**Treatment group**	**Arm A+I**	**Arm I**	**Arm A**
	Number of subject	N=272	N=268	N=269
	FFS Number of Events (%)	61 (22.4%)	61 (22.8%)	87 (32.3%)
	Stable Disease at the end of induction	1 (0.4%)	1 (0.4%)	5 (1.9%)
	Disease progression	40 (14.7%)	49 (18.3%)	60 (22.3%)
	Death events	20 (7.4%)	11 (4.1%)	22 (8.2%)
Effect estimate per comparison	**Primary endpoint FFS***	**Arm I vs Arm A**		**IMBRUVICA vs ASCT Arms**
		HR (98.33% CI)		0.639 (0.428, 0.953)
		P-value		0.0068
		Arm A+I vs Arm A		**IMBRUVICA + ASCT vs ASCT Arms**
		HR (98.33% CI)		0.633 (0.425, 0.945)
		P-value		0.0058
		Arm A+I vs Arm I		**IMBRUVICA + ASCT vs IMBRUVICA Arms**
		HR (98.33% CI)		0.983 (0.637, 1.516)
		P-value		0.9224

Notes	*Based on Cox Regression Model			
Analysis description	**Major Secondary Analysis - OS**			
Descriptive statistics and estimate variability	**Treatment group**	**Arm A+I**	**Arm I**	**Arm A**
	Number of subject	N=272	N=268	N=269
	OS Number of deaths (%)	34 (12.5%)	33 (12.3%)	60 (22.3%)
Effect estimate per comparison	**Major Secondary endpoint - OS**	**Arm I vs Arm A**	**IMBRUVICA vs ASCT Arms**	
		HR (95% CI)	0.522 (0.341, 0.799)	
		P-value	0.0023	
		Arm A+I vs Arm A	**IMBRUVICA + ASCT vs ASCT Arms**	
		HR (95% CI)	0.542 (0.356, 0.826)	
		P-value	0.0038	
		Arm A+I vs Arm I	**IMBRUVICA + ASCT vs IMBRUVICA Arms**	
		HR (95% CI)	1.040 (0.644, 1.679)	
		P-value	0.8721	
Notes				
Analysis description	**Major Secondary Analysis - PFS**			
Descriptive statistics and estimate variability	**Treatment group**	**Arm A+I**	**Arm I**	**Arm A**
	Number of subject	N=272	N=268	N=269
	Number of Events (%)	62 (22.8%)	60 (22.4%)	87 (32.3%)
	Disease progression	42 (15.4%)	49 (18.3%)	63 (23.4%)
	Death events	20 (7.4%)	11 (4.1%)	24 (8.9%)

Effect estimate per comparison	**Major Secondary endpoint -PFS***	**Arm I vs Arm A**		**IMBRUVICA vs ASCT Arms**
		HR (98.33% CI)		0.633 (0.424, 0.946)
		P-value		0.0060
		Arm A+I vs Arm A		**IMBRUVICA + ASCT vs ASCT Arms**
		HR (98.33% CI)		0.651 (0.437, 0.969)
		P-value		0.0093
		Arm A+I vs Arm I		**IMBRUVICA + ASCT vs IMBRUVICA Arms**
		HR (98.33% CI)		1.021 (0.662, 1.574)
		P-value		0.9102
Notes	*Based on Cox Regression Model			
Analysis description	**Major Secondary Analysis – Overall Response Rate**			
Descriptive statistics and estimate variability	**Treatment group**	**Arm A+I**	**Arm I**	**Arm A**
	Number of subject	N=272	N=268	N=269
	ORR	260 (95.6%)	258 (96.3%)	248 (92.2%)
Effect estimate per comparison	**Major Secondary endpoint -ORR**	**Arm I vs Arm A**		**IMBRUVICA vs ASCT Arms**
		Relative risk (2-sided 95% CI)		1.044 (1.001, 1.089)
		P-value		0.0627
		Arm A+I vs Arm A		**IMBRUVICA + ASCT vs ASCT Arms**
		Relative risk (2-sided 95% CI)		1.037 (0.993, 1.083)
		P-value		0.1085

		Arm A+I vs Arm I		**IMBRUVICA Arms vs IMBRUVICA + ASCT**
		Relative risk (2-sided 95% CI)		0.993 (0.959, 1.028)
		P-value		0.8284
Notes				
Analysis description	**Major Secondary Analysis – Complete Response Rate**			
Descriptive statistics and estimate variability	**Treatment group**	**Arm A+I**	**Arm I**	**Arm A**
	Number of subject	N=272	N=268	N=269
	CR rate	196 (72.1%)	180 (67.2%)	174 (64.7%)
Effect estimate per comparison	**Major Secondary endpoint – CR rate**	**Arm I vs Arm A**		**IMBRUVICA vs ASCT Arms**
		Relative risk (2-sided 95% CI)		1.038 (0.919, 1.173)
		P-value		0.5851
		Arm A+I vs Arm A		**IMBRUVICA + ASCT vs ASCT Arms**
		Relative risk (2-sided 95% CI)		1.114 (0.993, 1.250)
		P-value		0.0788
		Arm A+I vs Arm I		**IMBRUVICA + ASCT vs IMBRUVICA Arms**
		Relative risk (2-sided 95% CI)		1.073 (0.959, 1.200)
		P-value		0.2250
Notes				

2.4.3. Discussion on clinical efficacy

Study MCL3003 (TRIANGLE) is a randomised, 3-arm, open-label, multicenter Phase 3 study.

Transplant-eligible patients ≤ 65 years with newly diagnosed MCL Stage II-IV were stratified according to MIPI risk groups and Study groups, and randomised to:

- Alternating 3 cycles R-CHOP (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction followed by ASCT (Arm A)
- Alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by ASCT, and 2 years ibrutinib maintenance (Arm A+I)
- Alternating 3 cycles R-CHOP+ibrutinib (Cycles 1, 3, and 5)/3 cycles R-DHAP (Cycles 2, 4, and 6) induction, followed by 2 years ibrutinib maintenance (Arm I)

Since the final results from the LyMa trial (Le Gouill 2017) demonstrated prolonged OS for the rituximab maintenance group after ASCT in patients with previously untreated MCL, this approach was added to all 3 treatment arms depending on implementation in the national treatment guidelines for each study site during the study.

Endpoints

The primary endpoint FFS was defined as the time from randomisation to SD at the end of induction immunochemotherapy (EoI), PD, or death from any cause, whichever comes first. Not achieving PR or better at EoI was considered treatment failure and an FFS event. FFS, as defined above, is considered an appropriate primary endpoint based on the treatment paradigm for transplant-eligible MCL patients at the time of the study initiation. Response assessment was performed based on CT scans and bone marrow examinations using of the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

The primary endpoint was FFS assessed by central medical European MCL Network case evaluation of investigator assessment per protocol criteria.

The secondary efficacy endpoints (OS, PFS, CRR, ORR, and PR to CR conversion rate) were analysed in a descriptive way without correction for multiple testing.

Sample size

Overall, the sample size calculations seem to have been well thought out.

Randomisation and blinding

The randomisation process seems to have been adequately planned. Randomization was performed via EDC system and done in accordance with pre-specified distribution in the number of subjects in each treatment group and pre-specified ratio. The study was not blinded.

Analysis sets

Initially, analysis of the primary objective was planned to be performed according to the ITT. However, the initial ICF did not explicitly request permission for participants data to be included in a dossier for global HA submissions as per the subsequently applicable GDPR.

Study participants were therefore required to re-consent to provide this permission during study conduct. It is understood that the applicant and sponsor did not systematically select which subjects would re-consent. All efforts were made to re-consent all subjects. It is deemed unlikely that selection bias occurred in regard to the re-consenting process. The exception to this is for patients that died and therefore reconsent did not apply, they were differentially selected dependent on outcome. It is deemed unlikely that these patients could have had an impact on the overall conclusion. The resulting population is termed the FAS.

The applicant did not manage to re-consent 61 of the 870 randomized participants (ITT). Data for these 61 participants are therefore not included in the analyses nor presented in the CSR. As a result, the analysis population (FAS) prepared by the Applicant is limited to the 809 participants (93% of ITT) who either provided explicit consent for their data to be included in a dossier for global HA submissions or were deceased.

Reasons for why re-consent could not be obtained include 'withdrawal of consent prior HA submission', 'lost to follow-up', 'refusal of consent' as well as 'other' reasons, including the inability to contact or reach participants.

Primary efficacy endpoint

In the pre-specified analyses section of the protocol, the sponsor chose to perform three pairwise statistical tests *one-sided at 5% significance level*, because only differences observed in the direction indicated by the respective alternative hypothesis would result in consequences for the decision in

favour of a treatment arm. Thus, the following pairwise one-sided tests were planned by the sponsor: A+I superior to A; A superior to I; A+I superior to I

Considering the hypothesis testing of e.g A vs I was one-sided to detect superiority of A vs. I, superiority of I vs A couldn't be concluded.

Consequently, the MAH prepared a separate SAP (version 5 dated 5 September 2024) with post-hoc analyses to supplement the original pre-specified analyses and thereby provide a comprehensive evaluation of the study data in support of the regulatory submission. First version of the SAP is dated 16 sept 2022.

The CSR therefore includes not only the results of original pre-specified (one-sided tests at 0.05/3 significance level for each test), but also post-hoc analyses based on 2-sided alpha at 5% significance level (i.e., two-sided test at 1.667% significance level for each pairwise test) and one-sided post-hoc analyses based on 2.5% significance level (i.e., one-sided test at 0.83% significance level for each pairwise test).

Timing of analysis

Sequential statistical design was applied in this study. Pre-planned interim analyses were performed during the study on the ITT population, as specified in the original protocol from the academic sponsor, in approximately half-yearly intervals for each pairwise comparison (1-sided overall 5% significance level) to allow early stopping for efficacy or futility using the truncated sequential probability ratio test (tSPRT) boundary-based approach. Cut-offs for superiority and futility were based on Z values and not p-values. The crossing boundaries were calculated at each interim analysis, for each pairwise comparison. Statistical monitoring would continue until next interim analysis if crossing boundary had not been reached.

To address the advice given by the MPA in 2024, the MAH was asked to re-run the interim analyses retrospectively based on the FAS population, to conclude a read-out that was based on the re-consented subjects (i.e. FAS population) with not only the pre-specified 1-sided overall 5% significance level, but also applying a two-sided 5% significance level. Results from the retrospective interim analyses on the FAS population, at the 1-sided overall 5% significance level as pre-specified in the original protocol, were aligned with the conclusions drawn by the sponsor based on the ITT analysis set (Dreyling 2024), albeit at different interim analyses for A+I vs A and A+I vs I, which happened at IA7 (dated 24 oct 2021) and IA11 (dated 09 May 2024) respectively. When a more stringent two-sided overall 5% significance level was applied, superiority boundary was crossed at IA8 (dated 22 May 2022) for comparison I vs A and futility stop at IA9 (dated 01 May 2023) for comparison A+I vs I.

As for comparison of A+I vs A, - which was part of the original scope - neither superiority nor futility could be concluded at the time of the CCO for primary analysis (IA11 dated 09 May 2024), meaning that the study should have continued to be followed up for this comparison. However, the final indication claim does not include the A+I combination regimen therefore this issue is not further pursued.

Furthermore, the applicant provided, the number of FFS events when boundaries were crossed for each hypothesis test. For the 2-sided tests at a 1.67% significance level, boundaries were crossed at IA8 for I vs. A, with a total of 106 events (69 events in Arm A and 37 events in Arm I). Based on the truncated sequential probability ratio test, it was estimated that a maximum of 230 events would be needed for the comparison A vs. I. Corresponding fixed-sample test (without interim analyses) would

require 218 events. It is noted that the actual number of events did not exceed estimated maximum number of events, which is acceptable.

Analysis methods for primary efficacy endpoint

The statistical method section is overall sparce in the initial protocol. The protocol states: *for p-values and hazard ratios for the primary analysis, the treatment effects would be calculated correcting for the sequential design*. Statistical monitoring of log-rank test for FFS is mentioned, but no details on whether this test would be unstratified or stratified by variables used during randomisation or any other stratification strata of interest.

Post-hoc SAP version 5 however, details the derivation of the primary endpoint FFS as well as the statistical methods that were planned to be used as primary estimator. One-sided unstratified log-rank test with alpha at 1,67% as well as supplementary analyses based on two-sided log-rank test with alpha at 0,83% at each tail were stated as a primary estimator. Median unbiased estimator (MUE) of hazard ratio with one-sided CI at 98,33% as well as unstratified Cox's regression model with study treatment as the sole explanatory to provide hazard ratio with one-sided 98,33% CI were also specified as primary estimator.

Analyses presented in the CSR seem to have been done in accordance with post-hoc SAP version 5. Hazards ratio from unstratified Cox-regression model and two-sided p-values from unstratified log-rank test based on 5% significance level (divided equally between each hypothesis) are presented. For the primary efficacy analysis, the FFS results were derived from both the tSPRT method and the Cox proportional hazard model. The overall conclusion between tSPRT method reflect the overall conclusion from the Cox proportional hazard model for comparison I vs. A, which is acceptable.

Stratification factors (MIPI risk group and Rituximab maintenance status) have been included in separate models respectively, however, there does not seem to be any analysis that include both stratification factors in one model. Nevertheless, a comparison between models without stratification factors [HR 0.639 CI 0.428 - 0.953] and model with stratification factors MIPI [HR 0.627 CI 0.420 - 0.936] and Rituximab Maintenance Status [HR 0.587 CI 0.393 - 0.878] for Arm I vs. A show similar results in the HR. It can be concluded that a model that includes both stratification factors Rituximab maintenance status and MIPI risk group would yield similar results and was therefore not requested.

Multiplicity

Multiplicity was planned to be controlled at 5% significant level for the whole study. It is questionable whether the type-1 error was maintained at 5% in this study. There are several points that may have contributed to the loss of type-I error i.e one-sided hypotheses that were pre-specified in the initial version of the protocol, the main analysis model that were not clearly defined in the protocol as well as the multiple interim analyses.

The protocol mentions that the tSPRT method and the Christmas tree adjustment were applied. The truncated sequential probability ratio test (tSPRT) was used for adjustment for the repeated (interim) analyses within each treatment comparison and Bonferroni approach was used for multiplicity adjustment for the three pairwise treatment comparisons. The applicant further details that the tSPRT framework is specifically designed to handle the analysis of data collected at varied intervals while effectively controlling the error rate by employing a well-defined boundary-based approach for multiple

analyses. The applicant has provided more details regarding the tSPRT method and references to a well-known published book (Whitehead, 1997), which is acknowledged.

All secondary objectives were planned to be analysed in a descriptive way without correction for multiple testing.

Intercurrent events

It is understood that treatment policy was the primary strategy for handling of intercurrent events and hypothetical strategy was used as supportive, which is acceptable. Results applying hypothetical strategy to handling of use of subsequent anticancer therapies are presented.

Sensitivity analyses

Sensitivity analyses were performed as specified in the post-hoc SAP. A stratified Cox regression model defined as sensitivity estimator 2 seem to have taken stratification variables used during randomization into account, though stratification factor Study group was substituted by Rituximab maintenance status due to the large number of categories in variable Study group. The sample CRF indicates that an external code list was made for Study group stratification factor.

Study conduct

The MAH has submitted 8 protocol versions. None of the presented substantial amendments are considered to have a major impact on the overall efficacy conclusions.

Out of 809 participants in the FAS, 62 (7.7%) had major protocol deviations. It is noted that 5 patients (1.9%) in Arm I received disallowed concomitant treatment. This is not considered to have a major impact on the overall efficacy conclusions.

Efficacy data and additional analyses

The median time on study was 54.9 months (range: 0-91). In the FAS, 82.2% participants remained ongoing in the study at the time of CCO.

Median study treatment duration was 29.21 months (range: 0-39.3) for Arm A+I and 28.45 months (range: 0.2-35.5) for Arm I versus 5.16 months (range: 0.2-12.7) for Arm A.

All participants had either discontinued (32.4%) or completed (67.5%) study treatment at CCO.

Baseline characteristics of the FAS are considered reflective of the target population and were overall balanced across the treatment arms. Median age was 57.0 years (range: 27 to 68 years) and 76.8% of the participants were male which is consistent with the described sex-distribution pattern for MCL. Most participants had an ECOG score of 0 (71.7%) or 1 (27.0%).

The distribution of poor prognostic factors such as blastoid/pleomorphic histology, increased p53 expression, and elevated Ki-67 proliferation index was similar across the treatment arms.

The proportion of participants receiving rituximab maintenance treatment was balanced across the 3 treatment arms: 59.9% in Arm A+I, 59.7% in Arm I, and 62.5% in Arm A.

A comparison of the baseline demographic and disease characteristics of the FAS (n=809) and ITT populations (n=870, Dreyling et al 2024) demonstrated consistency between the 2 populations. As a comparable and relatively large number of participants were included in the FAS across all treatment

arms (overall 809/870; 93%), the use of the FAS is not considered to have introduced a significant bias. Thus, the conclusions of the study results based on FAS are considered to adequately reflect those of the ITT population.

Pre-planned and additional analyses of primary endpoint FFS in the primary analysis

At the CCO date, 61 FFS events (22.4%) in Arm A+I, 61 FFS events (22.8%) in Arm I, and 87 FFS events (32.3%) in Arm A) were reported. Although the FFS data is not fully mature, the rather extensive duration of follow-up substitutes for this (median 54.9 months).

The proportion of censored patients in the FFS analysis at CCO date was 77.6% in Arm A+I, 77.2% in Arm I, and 67.7% in Arm A. There is no concern that informative censoring could have had major impact on the FFS analysis. EMA censoring rules were applied in study MCL3003.

Of note, FFS analyses were performed on the FAS using both:

1. One-sided test with a significance level of 1.67% (5%/3) for each of the 3 hypotheses to maintain an overall one-sided 5% significance level, as pre-specified in the original study protocol by the academic sponsor, with Bonferroni-correction for multiple testing.

- *Arm A+I vs Arm A:* Improvement in FFS was demonstrated for participants in Arm A+I vs Arm A, HR unstratified Cox regression (1-sided 98.33% CI) 0.633 (0, 0.904), p-value (1-sided) 0.0029.

- *Arm A vs Arm I*: Arm A failed to show superiority in FFS compared with Arm I, HR unstratified Cox regression (1-sided 98.33% CI) 1.565 (0, 2.233), p-value (1-sided) 0.9966.

- *Arm A+I vs Arm I*: No meaningful differences in FFS were observed for participants in Arm A+I vs Arm I, HR unstratified Cox regression (1-sided 98.33% CI) 0.983 (0, 1.445), p-value (1-sided) 0.4612.

MUE HR estimates (with adjustment for interim analyses) were numerically similar to the corresponding Cox estimates across all three analyses.

2. Additional post-hoc analyses using two-sided 5% significance level (ie, a 2-sided 1.67% level for each of the 3 tests).

- An improvement in FFS was observed for participants in *Arm A+I vs Arm A*, HR unstratified Cox regression (2-sided 98.33% CI) of 0.633 (0.425, 0.945), 2-sided p-value: 0.0058, which is in line with the results from the originally pre-specified 1-sided test of Arm A+I vs Arm A. However, as outlined above, the retrospective interim analyses on the FAS (using two-sided overall 5% significance level) showed that neither the superiority boundary nor the futility boundary for Arm A+I vs Arm A was crossed at the time of the CCO for primary analysis.

- An improvement in FFS was observed for participants in *Arm I vs Arm A*, HR unstratified Cox regression (2-sided 98.33% CI) of 0.639 (0.428, 0.953), 2-sided p-value: 0.0068. Of note, this two-sided test provides results for superiority testing of Arm I vs Arm A, as compared to results provided for the one-sided comparison of Arm A vs Arm I as pre-specified in the

original protocol, which only tested one-sided for the opposite direction, i.e., superiority of A vs I.

- No difference was observed in FFS for participants in *Arm A+I vs Arm I*, HR unstratified Cox regression (2-sided 98.33% CI) of 0.983 (0.637, 1.516), 2-sided p-value: 0.9224, which is in line with the results from the originally pre-specified 1-sided test of Arm A+I vs Arm I.

MUE HR estimates (with adjustment for interim analyses) were numerically similar to the corresponding Cox estimates across all three analyses.

The presented FFS sensitivity analyses, i.e., FFS stratified by MIPI, Rituximab status, and Investigator assessment were overall consistent with primary FFS results.

In addition, FFS supplementary analysis, censoring participants who started a subsequent anticancer therapy prior to SD at EoI or PD (1, 3, and 2 participants in Arm A+I, Arm I and Arm A, respectively), were consistent with the primary FFS results.

Moreover, to assess a potential impact of the ITT data that were not included in the FAS, FFS results for the FAS (based on the primary analysis CCO date of 09 May 2024, median follow-up 54.9 months) were compared with FFS results from the ITT population (based on a CCO date of 22 May 2022, median follow-up 31 months, as published by the sponsor, Dreyling 2024). This comparative review of the FFS results for the FAS and ITT population indicates that the efficacy results obtained with the FAS are overall consistent with the results obtained with the ITT population.

The FFS results were generally consistent across relevant subgroups. Notably, subgroup analyses are hampered by exploratory nature and small sample size.

Regarding rituximab maintenance, this approach was similarly implemented in each study arm and therefore does not incur bias with respect to the efficacy demonstration. With regards to potential heterogeneity of between-arm treatment effects depending on whether rituximab was given, subgroup analyses show overlapping confidence limits and no indication of substantially different effect sizes.

In SmPC section 5.1, a footnote was added under the Efficacy results table to specify that "*The FFS results are not controlled for type 1 error, as these analyses are derived from post-hoc analyses conducted for registrational purposes*".

Secondary endpoints

OS results were consistent with the observed results for the primary endpoint FFS. There was no indication of a detrimental effect when substituting ibrutinib for ASCT, or when adding ibrutinib to ASCT. At the time of CCO, 60 participants (22.3%) in Arm A had died, vs 34 participants (12.5%) in Arm A+I and 33 participants (12.3%) in Arm I.

Similar to the FFS results, the Kaplan Meier curves for OS showed a separation between the 2 ibrutinib containing arms and the control arm. Improvement in OS was observed for participants in Arm A+I vs Arm A (Cox regression HR [95% CI] of 0.542 [0.356, 0.826] 2-sided nominal p-value=0.0038) as well as for participants in Arm I vs Arm A (Cox regression HR [95% CI] of 0.522 [0.341, 0.799]; 2-sided

nominal p value=0.0023). As for FFS, no difference in survival was demonstrated for the comparison of Arm A+I and Arm I (HR [95% CI]: 1.040 [0.644, 1.679], 2-sided nominal p value: 0.8721).

The early increase in fatal events observed in Arm A and Arm A+I in comparison to Arm I, and the corresponding initial decline in the Kaplan-Meier OS curve for the two ASCT-containing treatment arms, were to a large extent attributed to the toxicity associated with high-dose therapy.

No increase in OS events, including relapse-related events, was observed after the completion of the maintenance period in Arm I compared to Arm A and Arm A+I.

As could be expected, subsequent anticancer therapy differed between Arm A and the ibrutinib-containing treatment arms. In Arm A, most participants received subsequent anticancer therapy at disease progression with a BTK inhibitor (i.e., 49/59 receiving subsequent anticancer therapy), while most participants in Arm A+I and Arm I received different combination regimens of antineoplastic agents following progression after ibrutinib-based treatments.

PFS results were consistent with the observed results for the primary endpoint FFS, which is expected since the only difference between these 2 endpoints is that not achieving at least PR, but instead only stable disease at EoI is considered as treatment failure and an event for FFS, whereas it is not considered an event for PFS.

Overall response rates were similar across the 3 treatment arms: 95.6% for Arm A+I, 96.3% for Arm I, and 92.2% for Arm A. The CR rate was 72.1% for Arm A+I, 67.2% for Arm I, and 64.7%, for Arm A. The ORR and CR rates are of interest for prescribers and these data are presented in SmPC section 5.1.

The published results from study MCL3003 (Dreyling, Lancet 2024) have led to the adoption of the treatment strategy in MCL3003 as alternative treatment approaches for newly diagnosed young MCL patients < 66 years, in the NCCN GL 2025. In addition, the treatment strategy of Arm I is presented as the new standard of care in younger MCL patients, based on results from study MCL3003 (Dreyling, ASH December 2024). Thus, the published results from study MCL3003 appear to have triggered practice changing initiatives in the lymphoma community. European MCL Network recently presented an abstract in which they propose the

Additional expert consultation

NA

Assessment of paediatric data on clinical efficacy

NA

2.4.4. Conclusions on the clinical efficacy

Data demonstrate a clinically meaningful improvement of efficacy in the ibrutinib-containing treatment arms, compared to the standard ASCT regimen without ibrutinib. There was no demonstrable added benefit of including ASCT in the ibrutinib-containing regimen.

Thus, data support an extension of indication as: *"IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with a R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be*

eligible for autologous stem cell transplantation (ASCT).”

2.5. Clinical safety

Introduction

Ibrutinib has been authorised for use in the EU since 2014 and approved in several indications. The safety profile previously established include diarrhoea, neutropenia, musculoskeletal pain, haemorrhage (e.g., bruising), rash, nausea, thrombocytopenia, arthralgia, and upper respiratory tract infection. Neutropenia, lymphocytosis, thrombocytopenia, hypertension, and pneumonia constitute the most common grade 3/4 adverse reactions (≥5%).

The safety specification according to the latest approved RMP version 22.1, include `Haemorrhage´, `Hepatotoxicity (including hepatic failure)´, `Atrial fibrillation´, `Ventricular tachyarrhythmias´, `Hypertension´, `Ischemic stroke´, `Cardiac failure´, and `Infections (including viral reactivation)´ as important identified risks and `PML´, `Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)´, and `Other malignancies (excluding non-melanoma skin cancer)´ as important potential risks.

The key safety data in support of this application derive from the primary analysis of Study MCL3003 (TRIANGLE) with a data cutoff date of 09 May 2024.

Patient exposure

The dose of ibrutinib used in the study was 560 mg daily which is the approved dose as single agent for the treatment of patients with relapsed/refractory MCL. Standard doses and schedules were administered for R-CHOP/R-DHAP. Rituximab maintenance was not considered a study treatment in the TRIANGLE study as evidence supporting rituximab maintenance treatment (Le Gouill 2017) was not yet established at the start of the study. However, upon its implementation in the national guidelines for a participating country, rituximab maintenance was to be administered to participants, as per the recommendation of the site´s study group.

Table 21 Duration of Study Treatment; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I	A
Analysis set: Safety	275	265	268
Total treatment duration (maximum number of months)			
N	275	265	268
Mean (SD)	22.44 (10.753)	24.42 (8.688)	5.22 (1.546)
Median	29.21	28.45	5.16
Q1, Q3	12.91, 30.85	23.62, 29.34	4.75, 5.78
Range	(0.0; 39.3)	(0.2; 35.5)	(0.2; 12.7)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, SD=standard deviation, Q1=first quartile, Q3=third quartile.
Note: Duration from the first dose of any study treatment to the last dose of any study treatment, where study treatment refers to Ibrutinib, R-CHOP, R-DHAP, BEAM, TEAM, THAM or PBSCT.

Table 22 Extent of Exposure for Ibrutinib during Induction Therapy; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I
Analysis set: Safety	275	265
Total number of cycles		
N	273	265
1 cycle	7 (2.6%)	7 (2.6%)
2 cycles	12 (4.4%)	5 (1.9%)
>=3 cycles	254 (93.0%)	253 (95.5%)
Mean (SD)	2.9 (0.41)	2.9 (0.35)
Median	3.0	3.0
Q1, Q3	3.0, 3.0	3.0, 3.0
Range	(1; 5)	(1; 4)
Total dose administered (mg)		
N	273	265
Mean (SD)	29880.0 (6120.86)	30392.2 (5297.81)
Median	31920.0	31920.0
Q1, Q3	29680, 31920	30800, 31920
Range	(560; 76720)	(2800; 48720)
Dose intensity per protocol (mg/day)[b]		
N	273	265
Mean (SD)	524.2 (107.38)	533.2 (92.94)
Median	560.0	560.0
Q1, Q3	520.7, 560.0	540.4, 560.0
Range	(10; 1346)	(49; 855)
Relative dose intensity per protocol (%)[c]		
N	273	265
Mean (SD)	93.6 (19.18)	95.2 (16.60)
Median	100.0	100.0
Q1, Q3	93.0, 100.0	96.5, 100.0
Range	(2; 240)	(9; 153)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, SD=standard deviation, Q1=first quartile, Q3=third quartile.
[a] Treatment duration is calculated as (date of last dose of Ibrutinib - date of first dose of Ibrutinib +1)/30.4375.
[b] Dose intensity per protocol is calculated as the ratio of total dose administered and planned total treatment duration per protocol (mg/day).
[c] Relative dose intensity per protocol is calculated as the ratio of dose intensity per protocol and 560 mg.
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

Table 23 Extent of Exposure for Ibrutinib during Maintenance Period; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I
Analysis set: Safety	275	265
Total treatment duration (months)[a]		
N	230	245
Mean (SD)	18.3 (7.91)	21.3 (6.24)
Median	23.2	24.0
Q1, Q3	11.4, 24.0	22.2, 24.1
Range	(0; 29)	(0; 29)
0 - <6 months	27 (11.7%)	14 (5.7%)
6 - <12 months	33 (14.3%)	12 (4.9%)
12 - <18 months	15 (6.5%)	17 (6.9%)
>= 18 months	155 (67.4%)	202 (82.4%)
Total dose administered (mg)		
N	230	245
Mean (SD)	276316.2 (135622.74)	337144.0 (110712.67)
Median	316750.0	389200.0
Q1, Q3	179060.0, 397600.0	304920.0, 408800.0
Range	(1680; 451360)	(3360; 482720)
Dose intensity (mg/day)[b]		
N	230	245
Mean (SD)	483.9 (96.74)	520.2 (70.32)
Median	537.8	555.2
Q1, Q3	424.0, 560.0	515.5, 560.0
Range	(98; 560)	(231; 561)
Relative dose intensity (%)[c]		
N	230	245
Mean (SD)	86.4 (17.28)	92.9 (12.56)
Median	96.0	99.1
Q1, Q3	75.7, 100.0	92.1, 100.0
Range	(18; 100)	(41; 100)
Dose intensity per protocol (mg/day)[d]		
N	230	245
Mean (SD)	378.5 (185.78)	461.8 (151.66)
Median	433.9	533.2
Q1, Q3	245.3, 544.7	417.7, 560.0
Range	(2; 618)	(5; 661)

	A+I	I
Relative dose intensity per protocol (%)[e]		
N	230	245
Mean (SD)	67.6 (33.18)	82.5 (27.08)
Median	77.5	95.2
Q1, Q3	43.8, 97.3	74.6, 100.0
Range	(0; 110)	(1; 118)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, SD=standard deviation, Q1=first quartile, Q3=third quartile.
[a] Treatment duration is calculated as (date of last dose of Ibrutinib - date of first dose of Ibrutinib +1)/30.4375.
[b] Dose intensity is calculated as the ratio of total dose administered and total treatment duration (mg/day).
[c] Relative dose intensity is calculated as the ratio of dose intensity and 560 mg.
[d] Dose intensity per protocol is calculated as the ratio of total dose administered and planned total treatment duration per protocol (mg/day).
[e] Relative dose intensity per protocol is calculated as the ratio of dose intensity per protocol and 560 mg.
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

Methodology for ADR Determination

Protocol Definition of an AE

Treatment-emergent AEs were defined as AEs that started or worsened in severity after the first dose of study treatment up to 30 days following the last dose of study treatment or until the start of subsequent anti-cancer therapy, if earlier, and also included any AE that was considered study treatment related regardless of the start date of the event. The last individual study specific medication in Arm A is the ASCT, in Arm A+I and Arm I it is the last dose of Ibrutinib-Maintenance.

ADR Term Selection

The following steps were used to determine ADR terms for the labelling pool(s):

- **Step Ia**. TEAE data from Arm A+I and Arm I from the Study MCL3003 were compared to the TEAEs from Arm A. TEAE preferred terms (including grouped terms) that met the following criteria were identified:
  - TEAE reported in ≥10% of participants in Arm A+I and/or Arm I and reported at a >5% higher incidence compared to Arm A.

- **Step Ib**. Serious TEAE data from Arm A+I and Arm I from Study MCL3003 were compared to the serious TEAEs from Arm A. Serious TEAE preferred terms (including grouped terms) that met the following criteria were identified:
  - Serious TEAEs reported in ≥2% of participants in any of the two ibrutinib-containing arms, Arm A+I and Arm I and reported at a >2% higher incidence when any of the two arms, Arm A+I and Arm I is compared to Arm A.
- **Step II**. Medical review of potential ADRs identified in Steps Ia and Ib was conducted. In addition, a review of all ADRs from the current SmPC and any events from Study MCL3003 were conducted, to identify additional ADRs that are biologically plausible based on the current biological and clinical knowledge of ibrutinib therapy (e.g., mechanism of action, pharmacological profile or well-established ADR for ibrutinib from other clinical trials or post marketing spontaneous reports, consistent trending across multiple studies).
- **Step III**. A final list of ADRs as identified in Steps I and II above was compiled and applied to the safety population in Study MCL3003 to establish ADR frequency rates for proposed labelling.

Table 24 Incidence of Treatment-emergent Adverse Drug Reaction (ADR) by Toxicity Grade, System Organ Class and ADR Term (EUPI, rounded) - MCL3003; Safety Population

		A+I (N=275)			I (N=265)		
System Organ Class	Adverse Drug Reactions	Frequency (All Grades)	All Grades (%)	Grade >=3 (%)	Frequency (All Grades)	All Grades (%)	Grade >=3 (%)
Blood and lymphatic system disorders	Thrombocytopenia*	Very common	78	72	Very common	69	61
	Neutropenia*	Very common	76	75	Very common	63	60
	Febrile neutropenia	Very common	36	36	Very common	14	14
	Leukocytosis	Common	7	3	Common	3	<1
	Lymphocytosis*	Common	4	1		0	0
Cardiac disorders	Atrial fibrillation	Common	8	5	Common	10	4
	Cardiac failure*	Common	2	<1	Common	2	0
	Ventricular tachyarrhythmia*	Uncommon	<1	<1		0	0
Eye disorders	Vision blurred	Uncommon	<1	0	Uncommon	<1	0
	Eye haemorrhage		0	0	Uncommon	<1	0
Gastrointestinal disorders	Nausea	Very common	41	8	Very common	32	4
	Diarrhoea	Very common	38	7	Very common	28	5
	Vomiting	Very common	22	4	Very common	18	4
	Stomatitis*	Very common	21	10	Very common	11	2
	Constipation	Very common	21	0	Very common	17	<1
	Dyspepsia	Common	7	0	Common	8	0
General disorders and administration site conditions	Pyrexia	Very common	35	3	Very common	22	2
	Oedema peripheral	Common	5	<1	Common	5	0
Hepatobiliary disorders	Hepatic failure*	Uncommon	<1	<1		0	0
Immune system disorders	Interstitial lung disease*	Common	3	1	Common	5	<1
Infections and infestations	Pneumonia* ≠	Very common	26	15	Very common	16	9
	Skin infection*	Very common	13	2	Very common	12	3
	Upper respiratory tract infection	Very common	11	1	Common	6	<1
	Sepsis* ≠	Common	10	9	Common	2	2
	Urinary tract infection	Common	6	1	Common	6	<1
	Sinusitis*	Common	4	1	Common	6	<1
	Aspergillus infections*	Uncommon	<1	<1	Uncommon	<1	<1
	Pneumocystis infections*	Uncommon	<1	<1		0	0
Investigations	Hypokalaemia	Very common	23	9	Very common	14	6
	Blood creatinine increased	Very common	15	<1	Very common	16	1
	Hypomagnesaemia	Very common	11	2	Common	7	<1
Metabolism and nutrition disorders	Hyperuricaemia	Common	5	2	Common	8	3
	Tumour lysis syndrome*	Uncommon	<1	<1	Common	3	3

		A+I (N=275)			I (N=265)		
System Organ Class	Adverse Drug Reactions	Frequency (All Grades)	All Grades (%)	Grade >=3 (%)	Frequency (All Grades)	All Grades (%)	Grade >=3 (%)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	Very common	23	3	Very common	19	2
	Muscle spasms	Common	10	<1	Common	9	1
	Arthralgia	Common	8	0	Common	8	<1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-Melanoma skin cancer*	Common	1	0	Common	1	<1
	Basal cell carcinoma	Uncommon	<1	0	Common	1	<1
	Squamous cell carcinoma	Uncommon	<1	0		0	0
Nervous system disorders	Peripheral neuropathy*	Very common	36	4	Very common	35	3
	Headache	Very common	11	0	Very common	11	1
	Dizziness	Common	5	0	Common	6	<1
	Transient ischaemic attack		0	0	Uncommon	<1	0
Renal and urinary disorders	Acute kidney injury	Very common	11	4	Very common	11	5
Skin and subcutaneous tissue disorders	Rash*	Very common	33	4	Very common	23	2
	Erythema	Common	4	<1	Common	5	0
	Onychoclasis	Common	1	0	Common	2	0
	Urticaria	Common	1	<1	Uncommon	<1	0
	Neutrophilic Dermatoses*	Uncommon	<1	0		0	0
	Angioedema		0	0	Uncommon	<1	0
	Cutaneous vasculitis		0	0	Uncommon	<1	0
	Panniculitis*		0	0	Uncommon	<1	0
Vascular disorders	Haemorrhage*	Very common	13	<1	Very common	14	2
	Bruising*	Common	4	0	Common	8	<1
	Epistaxis	Common	8	<1	Common	6	1
	Petechiae	Common	2	<1	Common	3	0
	Hypertension*	Common	10	4	Very common	14	5

* Terms required grouping
# Includes events with fatal outcome.
Frequencies are defined as: very common (>=1/10), common (>=1/100 to <1/10), uncommon (>=1/1000 to <1/100), rare (>=1/10000 to <1/1000), very rare (<1/10000).
MedDRA is in version 26.1
Use EU ADR strategy.

Adverse events

Overall summary of TEAEs

Table 25 Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 4179060MCL3003)

	A+I	I	A
Analysis set: Safety	275	265	268
Subjects with 1 or more:			
Treatment-emergent adverse events	273 (99.3%)	263 (99.2%)	267 (99.6%)
Grade >= 3	268 (97.5%)	247 (93.2%)	250 (93.3%)
Ibrutinib-related [a]	233 (84.7%)	212 (80.0%)	NA
Treatment-emergent serious adverse events	186 (67.6%)	171 (64.5%)	123 (45.9%)
Grade >= 3	158 (57.5%)	146 (55.1%)	105 (39.2%)
Ibrutinib-related [a]	69 (25.1%)	50 (18.9%)	NA
Treatment-emergent adverse events leading to death [b]	15 (5.5%)	6 (2.3%)	11 (4.1%)
Treatment-emergent adverse events leading to death within 30 days of last dose of study treatment	6 (2.2%)	4 (1.5%)	5 (1.9%)
Treatment-emergent adverse events leading to Ibrutinib discontinuation	105 (38.2%)	61 (23.0%)	NA
Treatment-emergent adverse events leading to Ibrutinib dose reduction	54 (19.6%)	43 (16.2%)	NA
COVID-19 Treatment-emergent adverse events	49 (17.8%)	52 (19.6%)	5 (1.9%)
COVID-19 Treatment-emergent serious adverse events	21 (7.6%)	23 (8.7%)	4 (1.5%)
COVID-19 Treatment-emergent adverse events with outcome of death	5 (1.8%)	4 (1.5%)	2 (0.7%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, COVID-19=Coronavirus Disease 2019, TEAE=treatment-emergent adverse event, EOT=end of treatment, SMQ=Standardized MedDRA Queries.
[a] Relatedness is based on investigator assessment. The causal relationship of an adverse event to study treatment is only collected for Ibrutinib.
[b] Adverse events leading to death are based on AE outcome of Fatal. This includes patients with fatal TEAEs and date of death >30 days after EOT if the respective TEAE started within 30 days after EOT.
Note: There was no Grade 1/2 reporting required after the safety run-in phase.
Note: COVID-19 TEAEs include all TEAEs with preferred terms having SMQ 'COVID-19 (SMQ)' and scope 'NARROW'.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Table 26 Overall Summary of Treatment-emergent Adverse Events - MCL3003 Induction; Safety Population

Analysis set: Safety Population	A+I 275	I 265	A 268
Subjects with 1 or more:			
Treatment-emergent adverse events	272 (98.9%)	259 (97.7%)	262 (97.8%)
Grade >= 3	241 (87.6%)	228 (86.0%)	220 (82.1%)
Ibrutinib-related [a]	150 (54.5%)	148 (55.8%)	NA
Treatment-emergent serious adverse events	118 (42.9%)	119 (44.9%)	110 (41.0%)
Grade >= 3	92 (33.5%)	90 (34.0%)	89 (33.2%)
Ibrutinib-related [a]	28 (10.2%)	22 (8.3%)	NA
Treatment-emergent adverse events leading to death [b]	2 (0.7%)	1 (0.4%)	3 (1.1%)
Treatment-emergent adverse events leading to death within 30 days of last dose of study treatment	1 (0.4%)	1 (0.4%)	0
Treatment-emergent adverse events leading to Ibrutinib discontinuation	18 (6.5%)	13 (4.9%)	NA
Treatment-emergent adverse events leading to Ibrutinib dose reduction	4 (1.5%)	10 (3.8%)	NA
COVID-19 Treatment-emergent adverse events	5 (1.8%)	3 (1.1%)	3 (1.1%)
COVID-19 Treatment-emergent serious adverse events	4 (1.5%)	2 (0.8%)	2 (0.7%)
COVID-19 Treatment-emergent adverse events with outcome of death	1 (0.4%)	1 (0.4%)	1 (0.4%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, COVID-19=Coronavirus Disease 2019, TEAE=treatment-emergent adverse event, EOT=end of treatment, SMQ=Standardized MedDRA Queries.
[a] Relatedness is based on investigator assessment. The causal relationship of an adverse event to study treatment is only collected for Ibrutinib.
[b] Adverse events leading to death are based on AE outcome of Fatal. This includes patients with fatal TEAEs and date of death >30 days after EOT if the respective TEAE started within 30 days after EOT.
Note: There was no Grade 1/2 reporting required after the safety run-in phase.
Note: COVID-19 TEAEs include all TEAEs with preferred terms having SMQ 'COVID-19 (SMQ)' and scope 'NARROW'.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

[tsfae01ind.rtf] [PROD/jnj-54179060/triangle/dbr_csr/re_csr/tsfae01ind.sas] 25OCT2024, 13:40

Common TEAEs

Table 27 Incidence of TEAEs Occurring in 10% or More Subjects in Any Treatment Group by System Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
Analysis set: Safety	All Grades 275	Grade 3/4	Grade 5	All Grades 265	Grade 3/4	Grade 5	All Grades 268	Grade 3/4	Grade 5
Subjects with any TEAE	273 (99.3%)	253 (92.0%)	15 (5.5%)	263 (99.2%)	241 (90.9%)	6 (2.3%)	267 (99.6%)	239 (89.2%)	11 (4.1%)
System organ class Preferred term									
Blood and lymphatic system disorders	240 (87.3%)	226 (82.2%)	0	199 (75.1%)	172 (64.9%)	0	221 (82.5%)	201 (75.0%)	0
Anaemia	162 (58.9%)	121 (44.0%)	0	119 (44.9%)	57 (21.5%)	0	155 (57.8%)	92 (34.3%)	0
Neutropenia	141 (51.3%)	136 (49.5%)	0	112 (42.3%)	104 (39.2%)	0	110 (41.0%)	104 (38.8%)	0
Thrombocytopenia	124 (45.1%)	109 (39.6%)	0	105 (39.6%)	92 (34.7%)	0	121 (45.1%)	114 (42.5%)	0
Febrile neutropenia	98 (35.6%)	98 (35.6%)	0	37 (14.0%)	37 (14.0%)	0	71 (26.5%)	71 (26.5%)	0
Leukopenia	38 (13.8%)	34 (12.4%)	0	33 (12.5%)	25 (9.4%)	0	37 (13.8%)	30 (11.2%)	0
Infections and infestations	223 (81.1%)	106 (38.5%)	10 (3.6%)	186 (70.2%)	72 (27.2%)	4 (1.5%)	137 (51.1%)	56 (20.9%)	6 (2.2%)
Pneumonia	56 (20.4%)	28 (10.2%)	2 (0.7%)	27 (10.2%)	14 (5.3%)	0	14 (5.2%)	10 (3.7%)	1 (0.4%)
COVID-19	41 (14.9%)	7 (2.5%)	4 (1.5%)	37 (14.0%)	10 (3.8%)	2 (0.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Herpes zoster	29 (10.5%)	9 (3.3%)	0	6 (2.3%)	1 (0.4%)	0	1 (0.4%)	0	0
Upper respiratory tract infection	29 (10.5%)	4 (1.5%)	0	17 (6.4%)	1 (0.4%)	0	10 (3.7%)	1 (0.4%)	0
Gastrointestinal disorders	216 (78.5%)	84 (30.5%)	1 (0.4%)	169 (63.8%)	39 (14.7%)	0	190 (70.9%)	69 (25.7%)	4 (1.5%)
Nausea	112 (40.7%)	23 (8.4%)	0	84 (31.7%)	11 (4.2%)	0	105 (39.2%)	21 (7.8%)	0
Diarrhoea	105 (38.2%)	20 (7.3%)	0	75 (28.3%)	14 (5.3%)	0	78 (29.1%)	16 (6.0%)	0
Vomiting	61 (22.2%)	11 (4.0%)	0	49 (18.5%)	11 (4.2%)	0	47 (17.5%)	10 (3.7%)	0
Constipation	57 (20.7%)	0	0	44 (16.6%)	1 (0.4%)	0	49 (18.3%)	3 (1.1%)	0
Stomatitis	51 (18.5%)	27 (9.8%)	0	24 (9.1%)	4 (1.5%)	0	42 (15.7%)	21 (7.8%)	0
Abdominal pain	28 (10.2%)	3 (1.1%)	0	13 (4.9%)	0	0	22 (8.2%)	4 (1.5%)	0
General disorders and administration site conditions	191 (69.5%)	60 (21.8%)	0	144 (54.3%)	27 (10.2%)	0	175 (65.3%)	50 (18.7%)	1 (0.4%)
Pyrexia	96 (34.9%)	8 (2.9%)	0	57 (21.5%)	5 (1.9%)	0	89 (33.2%)	12 (4.5%)	0
Mucosal inflammation	86 (31.3%)	43 (15.6%)	0	22 (8.3%)	5 (1.9%)	0	74 (27.6%)	35 (13.1%)	0
Fatigue	65 (23.6%)	6 (2.2%)	0	46 (17.4%)	6 (2.3%)	0	31 (11.6%)	4 (1.5%)	0
Asthenia	32 (11.6%)	3 (1.1%)	0	24 (9.1%)	3 (1.1%)	0	26 (9.7%)	3 (1.1%)	0
Investigations	182 (66.2%)	136 (49.5%)	0	153 (57.7%)	115 (43.4%)	0	155 (57.8%)	113 (42.2%)	0
Platelet count decreased	100 (36.4%)	98 (35.6%)	0	87 (32.8%)	78 (29.4%)	0	91 (34.0%)	89 (33.2%)	0
Neutrophil count decreased	89 (32.4%)	86 (31.3%)	0	68 (25.7%)	64 (24.2%)	0	65 (24.3%)	62 (23.1%)	0
White blood cell count decreased	45 (16.4%)	38 (13.8%)	0	24 (9.1%)	17 (6.4%)	0	38 (14.2%)	36 (13.4%)	0
Blood creatinine increased	40 (14.5%)	2 (0.7%)	0	42 (15.8%)	3 (1.1%)	0	32 (11.9%)	2 (0.7%)	0
Gamma-glutamyltransferase increased	28 (10.2%)	15 (5.5%)	0	12 (4.5%)	6 (2.3%)	0	18 (6.7%)	11 (4.1%)	0
Nervous system disorders	138 (50.2%)	19 (6.9%)	0	135 (50.9%)	25 (9.4%)	0	104 (38.8%)	14 (5.2%)	0
Polyneuropathy	35 (12.7%)	5 (1.8%)	0	21 (7.9%)	2 (0.8%)	0	10 (3.7%)	0	0
Headache	31 (11.3%)	0	0	29 (10.9%)	3 (1.1%)	0	28 (10.4%)	2 (0.7%)	0
Peripheral sensory neuropathy	22 (8.0%)	1 (0.4%)	0	28 (10.6%)	3 (1.1%)	0	14 (5.2%)	0	0
Paraesthesia	20 (7.3%)	1 (0.4%)	0	28 (10.6%)	2 (0.8%)	0	14 (5.2%)	0	0
Skin and subcutaneous tissue disorders	124 (45.1%)	17 (6.2%)	0	91 (34.3%)	4 (1.5%)	0	51 (19.0%)	2 (0.7%)	0
Rash	49 (17.8%)	7 (2.5%)	0	36 (13.6%)	3 (1.1%)	0	15 (5.6%)	1 (0.4%)	0
Respiratory, thoracic and mediastinal disorders	119 (43.3%)	25 (9.1%)	1 (0.4%)	83 (31.3%)	10 (3.8%)	0	63 (23.5%)	17 (6.3%)	2 (0.7%)
Cough	43 (15.6%)	2 (0.7%)	0	33 (12.5%)	0	0	12 (4.5%)	0	0
Metabolism and nutrition disorders	113 (41.1%)	48 (17.5%)	0	89 (33.6%)	43 (16.2%)	0	96 (35.8%)	40 (14.9%)	0
Hypokalaemia	64 (23.3%)	25 (9.1%)	0	37 (14.0%)	17 (6.4%)	0	43 (16.0%)	12 (4.5%)	0
Hypomagnesaemia	30 (10.9%)	5 (1.8%)	0	18 (6.8%)	1 (0.4%)	0	14 (5.2%)	2 (0.7%)	0
Musculoskeletal and connective tissue disorders	99 (36.0%)	10 (3.6%)	0	85 (32.1%)	12 (4.5%)	0	57 (21.3%)	6 (2.2%)	0
Vascular disorders	73 (26.5%)	21 (7.6%)	0	65 (24.5%)	21 (7.9%)	0	60 (22.4%)	16 (6.0%)	0
Hypertension	23 (8.4%)	10 (3.6%)	0	33 (12.5%)	11 (4.2%)	0	21 (7.8%)	12 (4.5%)	0
Renal and urinary disorders	71 (25.8%)	16 (5.8%)	0	68 (25.7%)	21 (7.9%)	0	56 (20.9%)	15 (5.6%)	1 (0.4%)
Acute kidney injury	31 (11.3%)	11 (4.0%)	0	29 (10.9%)	12 (4.5%)	0	31 (11.6%)	7 (2.6%)	1 (0.4%)
Cardiac disorders	53 (19.3%)	23 (8.4%)	0	54 (20.4%)	13 (4.9%)	1 (0.4%)	22 (8.2%)	9 (3.4%)	0
Injury, poisoning and procedural complications	36 (13.1%)	9 (3.3%)	0	55 (20.8%)	12 (4.5%)	0	32 (11.9%)	5 (1.9%)	0
Psychiatric disorders	31 (11.3%)	1 (0.4%)	1 (0.4%)	23 (8.7%)	2 (0.8%)	0	20 (7.5%)	1 (0.4%)	0
Ear and labyrinth disorders	28 (10.2%)	2 (0.7%)	0	39 (14.7%)	7 (2.6%)	0	27 (10.1%)	2 (0.7%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Induction Phase

Table 28 Incidence of Treatment-emergent Adverse Events Occurring in 10% or More Subjects by Toxicity Grade, System Organ Class and Preferred Term - MCL3003 Induction; Safety Population

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety Population	275			265			268		
Subjects with any TEAE	272 (98.9%)	239 (86.9%)	2 (0.7%)	259 (97.7%)	227 (85.7%)	1 (0.4%)	262 (97.8%)	217 (81.0%)	3 (1.1%)
System organ class Preferred term									
Blood and lymphatic system disorders	198 (72.0%)	172 (62.5%)	0	190 (71.7%)	162 (61.1%)	0	185 (69.0%)	156 (58.2%)	0
Anaemia	118 (42.9%)	80 (29.1%)	0	114 (43.0%)	54 (20.4%)	0	123 (45.9%)	59 (22.0%)	0
Thrombocytopenia	106 (38.5%)	93 (33.8%)	0	101 (38.1%)	89 (33.6%)	0	105 (39.2%)	98 (36.6%)	0
Neutropenia	95 (34.5%)	88 (32.0%)	0	91 (34.3%)	83 (31.3%)	0	94 (35.1%)	85 (31.7%)	0
Febrile neutropenia	33 (12.0%)	33 (12.0%)	0	33 (12.5%)	33 (12.5%)	0	26 (9.7%)	26 (9.7%)	0
Leukopenia	29 (10.5%)	25 (9.1%)	0	30 (11.3%)	23 (8.7%)	0	29 (10.8%)	22 (8.2%)	0
Gastrointestinal disorders	166 (60.4%)	30 (10.9%)	0	156 (58.9%)	31 (11.7%)	0	145 (54.1%)	30 (11.2%)	1 (0.4%)
Nausea	91 (33.1%)	6 (2.2%)	0	79 (29.8%)	11 (4.2%)	0	85 (31.7%)	10 (3.7%)	0
Vomiting	48 (17.5%)	8 (2.9%)	0	46 (17.4%)	9 (3.4%)	0	35 (13.1%)	9 (3.4%)	0
Constipation	46 (16.7%)	0	0	41 (15.5%)	1 (0.4%)	0	44 (16.4%)	3 (1.1%)	0
Diarrhoea	38 (13.8%)	9 (3.3%)	0	58 (21.9%)	11 (4.2%)	0	34 (12.7%)	6 (2.2%)	0
Investigations	160 (58.2%)	113 (41.1%)	0	145 (54.7%)	108 (40.8%)	0	139 (51.9%)	96 (35.8%)	0
Platelet count decreased	89 (32.4%)	82 (29.8%)	0	83 (31.3%)	75 (28.3%)	0	82 (30.6%)	76 (28.4%)	0
Neutrophil count decreased	62 (22.5%)	59 (21.5%)	0	58 (21.9%)	55 (20.8%)	0	56 (20.9%)	51 (19.0%)	0
Blood creatinine increased	35 (12.7%)	2 (0.7%)	0	41 (15.5%)	3 (1.1%)	0	32 (11.9%)	2 (0.7%)	0
White blood cell count decreased	32 (11.6%)	25 (9.1%)	0	22 (8.3%)	16 (6.0%)	0	26 (9.7%)	24 (9.0%)	0
General disorders and administration site conditions	128 (46.5%)	14 (5.1%)	0	120 (45.3%)	20 (7.5%)	0	104 (38.8%)	16 (6.0%)	0
Pyrexia	44 (16.0%)	3 (1.1%)	0	41 (15.5%)	3 (1.1%)	0	40 (14.9%)	5 (1.9%)	0
Fatigue	42 (15.3%)	4 (1.5%)	0	37 (14.0%)	6 (2.3%)	0	22 (8.2%)	3 (1.1%)	0
Infections and infestations	109 (39.6%)	32 (11.6%)	1 (0.4%)	100 (37.7%)	32 (12.1%)	1 (0.4%)	79 (29.5%)	23 (8.6%)	1 (0.4%)
Nervous system disorders	99 (36.0%)	8 (2.9%)	0	108 (40.8%)	16 (6.0%)	0	87 (32.5%)	8 (3.0%)	0
Metabolism and nutrition disorders	75 (27.3%)	30 (10.9%)	0	81 (30.6%)	38 (14.3%)	0	66 (24.6%)	19 (7.1%)	0
Hypokalaemia	40 (14.5%)	16 (5.8%)	0	35 (13.2%)	16 (6.0%)	0	26 (9.7%)	4 (1.5%)	0
Respiratory, thoracic and mediastinal disorders	63 (22.9%)	8 (2.9%)	0	53 (20.0%)	6 (2.3%)	0	38 (14.2%)	9 (3.4%)	0
Renal and urinary disorders	59 (21.5%)	14 (5.1%)	0	54 (20.4%)	17 (6.4%)	0	52 (19.4%)	12 (4.5%)	0
Acute kidney injury	29 (10.5%)	11 (4.0%)	0	28 (10.6%)	11 (4.2%)	0	29 (10.8%)	7 (2.6%)	0
Musculoskeletal and connective tissue disorders	53 (19.3%)	4 (1.5%)	0	46 (17.4%)	3 (1.1%)	0	46 (17.2%)	4 (1.5%)	0
Skin and subcutaneous tissue disorders	47 (17.1%)	2 (0.7%)	0	48 (18.1%)	3 (1.1%)	0	20 (7.5%)	0	0
Vascular disorders	36 (13.1%)	12 (4.4%)	0	40 (15.1%)	14 (5.3%)	0	46 (17.2%)	12 (4.5%)	0
Cardiac disorders	25 (9.1%)	12 (4.4%)	0	31 (11.7%)	5 (1.9%)	0	9 (3.4%)	4 (1.5%)	0
Ear and labyrinth disorders	23 (8.4%)	1 (0.4%)	0	29 (10.9%)	3 (1.1%)	0	22 (8.2%)	2 (0.7%)	0
Injury, poisoning and procedural complications	21 (7.6%)	2 (0.7%)	0	39 (14.7%)	5 (1.9%)	0	28 (10.4%)	4 (1.5%)	0

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the Arm A+I group; those with the same total frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 26.1.

TEAEs by severity

Table 29 Incidence of Grade 3 or Higher TEAEs Occurring in 2% or More Subjects in Any Treatment Group by System Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
Analysis set: Safety	Grade 3 - 5 275	Grade 3/4	Grade 5	Grade 3 - 5 265	Grade 3/4	Grade 5	Grade 3 - 5 268	Grade 3/4	Grade 5
Subjects with any Grade 3 or higher TEAE	268 (97.5%)	253 (92.0%)	15 (5.5%)	247 (93.2%)	241 (90.9%)	6 (2.3%)	250 (93.3%)	239 (89.2%)	11 (4.1%)
System organ class Preferred term									
Blood and lymphatic system disorders	226 (82.2%)	226 (82.2%)	0	172 (64.9%)	172 (64.9%)	0	201 (75.0%)	201 (75.0%)	0
Neutropenia	136 (49.5%)	136 (49.5%)	0	104 (39.2%)	104 (39.2%)	0	104 (38.8%)	104 (38.8%)	0
Anaemia	121 (44.0%)	121 (44.0%)	0	57 (21.5%)	57 (21.5%)	0	92 (34.3%)	92 (34.3%)	0
Thrombocytopenia	109 (39.6%)	109 (39.6%)	0	92 (34.7%)	92 (34.7%)	0	114 (42.5%)	114 (42.5%)	0
Febrile neutropenia	98 (35.6%)	98 (35.6%)	0	37 (14.0%)	37 (14.0%)	0	71 (26.5%)	71 (26.5%)	0
Leukopenia	34 (12.4%)	34 (12.4%)	0	25 (9.4%)	25 (9.4%)	0	30 (11.2%)	30 (11.2%)	0
Leukocytosis	9 (3.3%)	9 (3.3%)	0	2 (0.8%)	2 (0.8%)	0	2 (0.7%)	2 (0.7%)	0
Lymphopenia	3 (1.1%)	3 (1.1%)	0	5 (1.9%)	5 (1.9%)	0	8 (3.0%)	8 (3.0%)	0
Investigations	136 (49.5%)	136 (49.5%)	0	115 (43.4%)	115 (43.4%)	0	113 (42.2%)	113 (42.2%)	0
Platelet count decreased	98 (35.6%)	98 (35.6%)	0	78 (29.4%)	78 (29.4%)	0	89 (33.2%)	89 (33.2%)	0
Neutrophil count decreased	86 (31.3%)	86 (31.3%)	0	64 (24.2%)	64 (24.2%)	0	62 (23.1%)	62 (23.1%)	0
White blood cell count decreased	38 (13.8%)	38 (13.8%)	0	17 (6.4%)	17 (6.4%)	0	36 (13.4%)	36 (13.4%)	0
Lymphocyte count decreased	21 (7.6%)	21 (7.6%)	0	12 (4.5%)	12 (4.5%)	0	15 (5.6%)	15 (5.6%)	0
Gamma-glutamyltransferase increased	15 (5.5%)	15 (5.5%)	0	6 (2.3%)	6 (2.3%)	0	11 (4.1%)	11 (4.1%)	0
Alanine aminotransferase increased	8 (2.9%)	8 (2.9%)	0	3 (1.1%)	3 (1.1%)	0	6 (2.2%)	6 (2.2%)	0
Infections and infestations	116 (42.2%)	106 (38.5%)	10 (3.6%)	76 (28.7%)	72 (27.2%)	4 (1.5%)	62 (23.1%)	56 (20.9%)	6 (2.2%)
Pneumonia	30 (10.9%)	28 (10.2%)	2 (0.7%)	14 (5.3%)	14 (5.3%)	0	11 (4.1%)	10 (3.7%)	1 (0.4%)
Sepsis	14 (5.1%)	13 (4.7%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	0	7 (2.6%)	4 (1.5%)	3 (1.1%)
Device related infection	12 (4.4%)	12 (4.4%)	0	2 (0.8%)	2 (0.8%)	0	7 (2.6%)	7 (2.6%)	0
COVID-19	11 (4.0%)	7 (2.5%)	4 (1.5%)	12 (4.5%)	10 (3.8%)	2 (0.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Herpes zoster	9 (3.3%)	9 (3.3%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Infection	9 (3.3%)	9 (3.3%)	0	5 (1.9%)	5 (1.9%)	0	8 (3.0%)	8 (3.0%)	0
COVID-19 pneumonia	6 (2.2%)	5 (1.8%)	1 (0.4%)	9 (3.4%)	7 (2.6%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Gastrointestinal disorders	85 (30.9%)	84 (30.5%)	1 (0.4%)	39 (14.7%)	39 (14.7%)	0	73 (27.2%)	69 (25.7%)	4 (1.5%)
Stomatitis	27 (9.8%)	27 (9.8%)	0	4 (1.5%)	4 (1.5%)	0	21 (7.8%)	21 (7.8%)	0
Nausea	23 (8.4%)	23 (8.4%)	0	11 (4.2%)	11 (4.2%)	0	21 (7.8%)	21 (7.8%)	0
Diarrhoea	20 (7.3%)	20 (7.3%)	0	14 (5.3%)	14 (5.3%)	0	16 (6.0%)	16 (6.0%)	0
Vomiting	11 (4.0%)	11 (4.0%)	0	11 (4.2%)	11 (4.2%)	0	10 (3.7%)	10 (3.7%)	0
General disorders and administration site conditions	60 (21.8%)	60 (21.8%)	0	27 (10.2%)	27 (10.2%)	0	51 (19.0%)	50 (18.7%)	1 (0.4%)
Mucosal inflammation	43 (15.6%)	43 (15.6%)	0	5 (1.9%)	5 (1.9%)	0	35 (13.1%)	35 (13.1%)	0
Pyrexia	8 (2.9%)	8 (2.9%)	0	5 (1.9%)	5 (1.9%)	0	12 (4.5%)	12 (4.5%)	0
Fatigue	6 (2.2%)	6 (2.2%)	0	6 (2.3%)	6 (2.3%)	0	4 (1.5%)	4 (1.5%)	0
Metabolism and nutrition disorders	48 (17.5%)	48 (17.5%)	0	43 (16.2%)	43 (16.2%)	0	40 (14.9%)	40 (14.9%)	0
Hypokalaemia	25 (9.1%)	25 (9.1%)	0	17 (6.4%)	17 (6.4%)	0	12 (4.5%)	12 (4.5%)	0
Decreased appetite	6 (2.2%)	6 (2.2%)	0	3 (1.1%)	3 (1.1%)	0	11 (4.1%)	11 (4.1%)	0
Hyperglycaemia	6 (2.2%)	6 (2.2%)	0	8 (3.0%)	8 (3.0%)	0	4 (1.5%)	4 (1.5%)	0
Hyperuricaemia	6 (2.2%)	6 (2.2%)	0	8 (3.0%)	8 (3.0%)	0	1 (0.4%)	1 (0.4%)	0
Tumour lysis syndrome	1 (0.4%)	1 (0.4%)	0	7 (2.6%)	7 (2.6%)	0	3 (1.1%)	3 (1.1%)	0
Respiratory, thoracic and mediastinal disorders	26 (9.5%)	25 (9.1%)	1 (0.4%)	10 (3.8%)	10 (3.8%)	0	19 (7.1%)	17 (6.3%)	2 (0.7%)
Cardiac disorders	23 (8.4%)	23 (8.4%)	0	14 (5.3%)	13 (4.9%)	1 (0.4%)	9 (3.4%)	9 (3.4%)	0
Atrial fibrillation	13 (4.7%)	13 (4.7%)	0	10 (3.8%)	10 (3.8%)	0	5 (1.9%)	5 (1.9%)	0
Vascular disorders	21 (7.6%)	21 (7.6%)	0	21 (7.9%)	21 (7.9%)	0	16 (6.0%)	16 (6.0%)	0
Hypertension	10 (3.6%)	10 (3.6%)	0	11 (4.2%)	11 (4.2%)	0	12 (4.5%)	12 (4.5%)	0
Nervous system disorders	19 (6.9%)	19 (6.9%)	0	25 (9.4%)	25 (9.4%)	0	14 (5.2%)	14 (5.2%)	0
Syncope	7 (2.5%)	7 (2.5%)	0	6 (2.3%)	6 (2.3%)	0	5 (1.9%)	5 (1.9%)	0
Skin and subcutaneous tissue disorders	17 (6.2%)	17 (6.2%)	0	4 (1.5%)	4 (1.5%)	0	2 (0.7%)	2 (0.7%)	0
Rash	7 (2.5%)	7 (2.5%)	0	3 (1.1%)	3 (1.1%)	0	1 (0.4%)	1 (0.4%)	0
Renal and urinary disorders	16 (5.8%)	16 (5.8%)	0	21 (7.9%)	21 (7.9%)	0	16 (6.0%)	15 (5.6%)	1 (0.4%)
Acute kidney injury	11 (4.0%)	11 (4.0%)	0	12 (4.5%)	12 (4.5%)	0	8 (3.0%)	7 (2.6%)	1 (0.4%)
Musculoskeletal and connective tissue disorders	10 (3.6%)	10 (3.6%)	0	12 (4.5%)	12 (4.5%)	0	6 (2.2%)	6 (2.2%)	0
Injury, poisoning and procedural complications	9 (3.3%)	9 (3.3%)	0	12 (4.5%)	12 (4.5%)	0	5 (1.9%)	5 (1.9%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2.5%)	5 (1.8%)	2 (0.7%)	6 (2.3%)	5 (1.9%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Immune system disorders	6 (2.2%)	6 (2.2%)	0	3 (1.1%)	3 (1.1%)	0	5 (1.9%)	5 (1.9%)	0
Ear and labyrinth disorders	2 (0.7%)	2 (0.7%)	0	7 (2.6%)	7 (2.6%)	0	2 (0.7%)	2 (0.7%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

TEAEs related to ibrutinib

Table 30 Incidence of Treatment-emergent Adverse Events Related to Ibrutinib Occurring in 5% or More Subjects in Any Treatment Group by System Organ Class and Preferred Term; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I	A
Analysis set: Safety	275	265	268
Subjects with any Ibrutinib-related TEAE	233 (84.7%)	212 (80.0%)	0
System organ class			
Preferred term			
Blood and lymphatic system disorders	132 (48.0%)	103 (38.9%)	0
Neutropenia	84 (30.5%)	61 (23.0%)	0
Thrombocytopenia	31 (11.3%)	29 (10.9%)	0
Anaemia	24 (8.7%)	40 (15.1%)	0
Febrile neutropenia	19 (6.9%)	8 (3.0%)	0
Infections and infestations	95 (34.5%)	65 (24.5%)	0
Pneumonia	24 (8.7%)	13 (4.9%)	0
Herpes zoster	16 (5.8%)	5 (1.9%)	0
Investigations	79 (28.7%)	66 (24.9%)	0
Neutrophil count decreased	39 (14.2%)	30 (11.3%)	0
Platelet count decreased	23 (8.4%)	20 (7.5%)	0
White blood cell count decreased	79 (28.7%)	57 (21.5%)	0
Gastrointestinal disorders	46 (16.7%)	35 (13.2%)	0
Diarrhoea	30 (10.9%)	24 (9.1%)	0
Nausea	12 (4.4%)	14 (5.3%)	0
Skin and subcutaneous tissue disorders	50 (18.2%)	49 (18.5%)	0
Rash	19 (6.9%)	19 (7.2%)	0
General disorders and administration site conditions	45 (16.4%)	37 (14.0%)	0
Musculoskeletal and connective tissue disorders	42 (15.3%)	42 (15.8%)	0
Muscle spasms	22 (8.0%)	17 (6.4%)	0
Nervous system disorders	40 (14.5%)	36 (13.6%)	0
Respiratory, thoracic and mediastinal disorders	20 (7.3%)	25 (9.4%)	0
Cardiac disorders	16 (5.8%)	27 (10.2%)	0
Atrial fibrillation	11 (4.0%)	19 (7.2%)	0
Vascular disorders	14 (5.1%)	24 (9.1%)	0
Hypertension	2 (0.7%)	14 (5.3%)	0
Metabolism and nutrition disorders	11 (4.0%)	14 (5.3%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.
Note: The causal relationship of an adverse event to study treatment is only collected for Ibrutinib.

Table 31 Incidence of Grade 3 or Higher Treatment-emergent Adverse Events Related to Ibrutinib Occurring in 2% or More Subjects in Any Treatment Group by System Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	Grade 3 - 5	Grade 3/4	Grade 5	Grade 3 - 5	Grade 3/4	Grade 5	Grade 3 - 5	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any Grade 3 or higher Ibrutinib-related TEAE	186 (67.6%)	184 (66.9%)	2 (0.7%)	143 (54.0%)	143 (54.0%)	0	0	0	0
System organ class Preferred term									
Blood and lymphatic system disorders	118 (42.9%)	118 (42.9%)	0	84 (31.7%)	84 (31.7%)	0	0	0	0
Neutropenia	80 (29.1%)	80 (29.1%)	0	56 (21.1%)	56 (21.1%)	0	0	0	0
Febrile neutropenia	19 (6.9%)	19 (6.9%)	0	8 (3.0%)	8 (3.0%)	0	0	0	0
Thrombocytopenia	17 (6.2%)	17 (6.2%)	0	21 (7.9%)	21 (7.9%)	0	0	0	0
Anaemia	11 (4.0%)	11 (4.0%)	0	17 (6.4%)	17 (6.4%)	0	0	0	0
Leukocytosis	8 (2.9%)	8 (2.9%)	0	5 (1.9%)	5 (1.9%)	0	0	0	0
Leukopenia	7 (2.5%)	7 (2.5%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Investigations	59 (21.5%)	59 (21.5%)	0	40 (15.1%)	40 (15.1%)	0	0	0	0
Neutrophil count decreased	44 (16.0%)	44 (16.0%)	0	31 (11.7%)	31 (11.7%)	0	0	0	0
Platelet count decreased	24 (8.7%)	24 (8.7%)	0	18 (6.8%)	18 (6.8%)	0	0	0	0
White blood cell count decreased	8 (2.9%)	8 (2.9%)	0	9 (3.4%)	9 (3.4%)	0	0	0	0
Infections and infestations	36 (13.1%)	35 (12.7%)	1 (0.4%)	25 (9.4%)	25 (9.4%)	0	0	0	0
Pneumonia	15 (5.5%)	15 (5.5%)	0	7 (2.6%)	7 (2.6%)	0	0	0	0
Herpes zoster	7 (2.5%)	7 (2.5%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Gastrointestinal disorders	15 (5.5%)	15 (5.5%)	0	11 (4.2%)	11 (4.2%)	0	0	0	0
Diarrhoea	9 (3.3%)	9 (3.3%)	0	7 (2.6%)	7 (2.6%)	0	0	0	0
Cardiac disorders	10 (3.6%)	10 (3.6%)	0	8 (3.0%)	8 (3.0%)	0	0	0	0
Atrial fibrillation	6 (2.2%)	6 (2.2%)	0	8 (3.0%)	8 (3.0%)	0	0	0	0
Nervous system disorders	5 (1.8%)	5 (1.8%)	0	6 (2.3%)	6 (2.3%)	0	0	0	0
Vascular disorders	4 (1.5%)	4 (1.5%)	0	6 (2.3%)	6 (2.3%)	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (1.1%)	3 (1.1%)	0	7 (2.6%)	7 (2.6%)	0	0	0	0
Metabolism and nutrition disorders	2 (0.7%)	2 (0.7%)	0	7 (2.6%)	7 (2.6%)	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.
Note: The causal relationship of an adverse event to study drug is only collected for Ibrutinib.

Serious adverse event and deaths

Deaths

Table 32 Summary of Deaths During Study; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I	A	Total
Analysis set: Safety	275	265	268	808
Total number of subjects who died during the study	34 (12.4%)	33 (12.5%)	60 (22.4%)	127 (15.7%)
Primary cause of death				
Adverse event [a]	15 (5.5%)	6 (2.3%)	11 (4.1%)	32 (4.0%)
COVID-19 Related [b]	5 (1.8%)	4 (1.5%)	2 (0.7%)	11 (1.4%)
Progressive disease	9 (3.3%)	14 (5.3%)	30 (11.2%)	53 (6.6%)
Other [c]	9 (3.3%)	13 (4.9%)	17 (6.3%)	39 (4.8%)
Unknown	1 (0.4%)	0	2 (0.7%)	3 (0.4%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, COVID-19=Coronavirus Disease 2019, TEAE=treatment-emergent adverse event, EOT=end of treatment, SMQ=Standardized MedDRA Queries.
[a] Includes patients with fatal TEAEs and date of death >30 days after EOT if the respective TEAE started within 30 days after EOT.
[b] COVID-19 TEAEs include all TEAEs with preferred terms COVID-19, COVID-19 pneumonia and Coronavirus infection.
[c] Other includes non-treatment-emergent concomitant disease and malignancies, and therapy.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominators.

Table 33 Incidence of Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I	A
Analysis set: Safety	275	265	268
Subjects with any TEAE leading to death	15 (5.5%)	6 (2.3%)	11 (4.1%)
System organ class Preferred term			
Infections and infestations	10 (3.6%)	4 (1.5%)	6 (2.2%)
COVID-19	4 (1.5%)	2 (0.8%)	1 (0.4%)
Pneumonia	2 (0.7%)	0	1 (0.4%)
COVID-19 pneumonia	1 (0.4%)	2 (0.8%)	1 (0.4%)
Influenza	1 (0.4%)	0	0
Pneumonia viral	1 (0.4%)	0	0
Sepsis	1 (0.4%)	0	3 (1.1%)
Septic shock	1 (0.4%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7%)	1 (0.4%)	1 (0.4%)
Malignant melanoma	1 (0.4%)	0	0
Malignant neoplasm of thymus	1 (0.4%)	0	0
Oesophageal adenocarcinoma	0	1 (0.4%)	0
Rectal adenocarcinoma	0	0	1 (0.4%)
Gastrointestinal disorders	1 (0.4%)	0	4 (1.5%)
Gastric haemorrhage	1 (0.4%)	0	1 (0.4%)
Enterocolitis	0	0	1 (0.4%)
Ileus paralytic	0	0	1 (0.4%)
Intestinal perforation	0	0	1 (0.4%)
Psychiatric disorders	1 (0.4%)	0	0
Completed suicide	1 (0.4%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	0	2 (0.7%)
Acute respiratory distress syndrome	1 (0.4%)	0	1 (0.4%)
Respiratory failure	0	0	1 (0.4%)
Cardiac disorders	0	1 (0.4%)	0
Acute myocardial infarction	0	1 (0.4%)	0
General disorders and administration site conditions	0	0	1 (0.4%)
Sudden death	0	0	1 (0.4%)
Renal and urinary disorders	0	0	1 (0.4%)
Acute kidney injury	0	0	1 (0.4%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Serious Adverse Events

Table 34 Incidence of Treatment-emergent Serious Adverse Events Occurring in 2% or More Subjects in Any Treatment Group by System Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TESAE	186 (67.6%)	143 (52.0%)	15 (5.5%)	171 (64.5%)	140 (52.8%)	6 (2.3%)	123 (45.9%)	94 (35.1%)	11 (4.1%)
System organ class									
Preferred term									
Infections and infestations	103 (37.5%)	77 (28.0%)	10 (3.6%)	72 (27.2%)	56 (21.1%)	4 (1.5%)	36 (13.4%)	27 (10.1%)	6 (2.2%)
Pneumonia	26 (9.5%)	20 (7.3%)	2 (0.7%)	11 (4.2%)	9 (3.4%)	0	8 (3.0%)	7 (2.6%)	1 (0.4%)
COVID-19	12 (4.4%)	4 (1.5%)	4 (1.5%)	12 (4.5%)	9 (3.4%)	2 (0.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Sepsis	9 (3.3%)	8 (2.9%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	3 (1.1%)	3 (1.1%)
COVID-19 pneumonia	8 (2.9%)	5 (1.8%)	1 (0.4%)	10 (3.8%)	7 (2.6%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Device related infection	7 (2.5%)	6 (2.2%)	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Herpes zoster	6 (2.2%)	6 (2.2%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Blood and lymphatic system disorders	53 (19.3%)	53 (19.3%)	0	33 (12.5%)	33 (12.5%)	0	30 (11.2%)	30 (11.2%)	0
Febrile neutropenia	39 (14.2%)	39 (14.2%)	0	28 (10.6%)	28 (10.6%)	0	19 (7.1%)	19 (7.1%)	0
Thrombocytopenia	5 (1.8%)	5 (1.8%)	0	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	6 (2.2%)	0
Gastrointestinal disorders	32 (11.6%)	26 (9.5%)	1 (0.4%)	21 (7.9%)	17 (6.4%)	0	23 (8.6%)	16 (6.0%)	4 (1.5%)
Diarrhoea	7 (2.5%)	7 (2.5%)	0	2 (0.8%)	2 (0.8%)	0	3 (1.1%)	2 (0.7%)	0
Vomiting	5 (1.8%)	4 (1.5%)	0	9 (3.4%)	7 (2.6%)	0	4 (1.5%)	3 (1.1%)	0
Renal and urinary disorders	26 (9.5%)	14 (5.1%)	0	25 (9.4%)	13 (4.9%)	0	20 (7.5%)	7 (2.6%)	1 (0.4%)
Acute kidney injury	15 (5.5%)	10 (3.6%)	0	18 (6.8%)	10 (3.8%)	0	14 (5.2%)	4 (1.5%)	1 (0.4%)
Renal failure	8 (2.9%)	4 (1.5%)	0	5 (1.9%)	2 (0.8%)	0	4 (1.5%)	2 (0.7%)	0
General disorders and administration site conditions	19 (6.9%)	7 (2.5%)	0	18 (6.8%)	8 (3.0%)	0	13 (4.9%)	7 (2.6%)	1 (0.4%)
Pyrexia	12 (4.4%)	3 (1.1%)	0	8 (3.0%)	2 (0.8%)	0	8 (3.0%)	4 (1.5%)	0
Cardiac disorders	16 (5.8%)	15 (5.5%)	0	19 (7.2%)	11 (4.2%)	1 (0.4%)	4 (1.5%)	3 (1.1%)	0
Atrial fibrillation	8 (2.9%)	7 (2.5%)	0	12 (4.5%)	8 (3.0%)	0	1 (0.4%)	1 (0.4%)	0
Investigations	12 (4.4%)	6 (2.2%)	0	11 (4.2%)	5 (1.9%)	0	11 (4.1%)	7 (2.6%)	0
Blood creatinine increased	6 (2.2%)	1 (0.4%)	0	5 (1.9%)	0	0	4 (1.5%)	0	0
Platelet count decreased	5 (1.8%)	5 (1.8%)	0	0	0	0	6 (2.2%)	6 (2.2%)	0
Respiratory, thoracic and mediastinal disorders	8 (2.9%)	6 (2.2%)	1 (0.4%)	3 (1.1%)	2 (0.8%)	0	7 (2.6%)	5 (1.9%)	2 (0.7%)
Injury, poisoning and procedural complications	7 (2.5%)	6 (2.2%)	0	7 (2.6%)	6 (2.3%)	0	4 (1.5%)	3 (1.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (2.5%)	4 (1.5%)	2 (0.7%)	5 (1.9%)	4 (1.5%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Nervous system disorders	7 (2.5%)	5 (1.8%)	0	14 (5.3%)	11 (4.2%)	0	7 (2.6%)	5 (1.9%)	0
Metabolism and nutrition disorders	6 (2.2%)	4 (1.5%)	0	11 (4.2%)	11 (4.2%)	0	11 (4.1%)	11 (4.1%)	0
Vascular disorders	6 (2.2%)	5 (1.8%)	0	5 (1.9%)	4 (1.5%)	0	5 (1.9%)	1 (0.4%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TESAE=treatment-emergent serious adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Other significant events

Treatment-emergent Adverse Events of Clinical Interest: Major Haemorrhage

Table 35 Incidence of Treatment-emergent Major Hemorrhage Events; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TE Major Hemorrhage Events	11 (4.0%)	8 (2.9%)	1 (0.4%)	10 (3.8%)	8 (3.0%)	0	9 (3.4%)	8 (3.0%)	1 (0.4%)
Preferred Term									
Gastrointestinal haemorrhage	2 (0.7%)	2 (0.7%)	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Post procedural haemorrhage	2 (0.7%)	2 (0.7%)	0	0	0	0	0	0	0
Catheter site haemorrhage	1 (0.4%)	0	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Diverticulum intestinal haemorrhagic	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Epistaxis	1 (0.4%)	1 (0.4%)	0	3 (1.1%)	3 (1.1%)	0	3 (1.1%)	3 (1.1%)	0
Gastric haemorrhage	1 (0.4%)	0	1 (0.4%)	0	0	0	1 (0.4%)	0	1 (0.4%)
Haematuria	1 (0.4%)	0	0	0	0	0	0	0	0
Petechiae	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Retroperitoneal haemorrhage	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Anal haemorrhage	0	0	0	1 (0.4%)	0	0	0	0	0
Blood loss anaemia	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Haematoma	0	0	0	3 (1.1%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Haemorrhage intracranial	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Intestinal haemorrhage	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Rectal haemorrhage	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Subarachnoid haemorrhage	0	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TE=treatment-emergent.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Other Safety Observations:

Atrial Fibrillation

The incidence of any grade atrial fibrillation was higher in both ibrutinib-containing arms: Arms A+I (23 [8.4%]) and Arm I (26 [9.8%]) compared with participants in Arm A (6 [2.2%]). Grade 3 and 4 events were reported in 13 (4.7%) and 10 (3.8%) participants in Arm A+I and Arm I, respectively, compared to 5 (1.9%) participants in Arm A. Serious atrial fibrillation was reported in 8 (2.9%) and 12 (4.5%) participants in Arm A+I and Arm I compared to 1 (0.4%) participant in Arm A. There were no fatal events of atrial fibrillation. Atrial fibrillation resulted in ibrutinib discontinuation in 6 (2.2%) and 5 (1.9%) participants in Arm A+I and Arm I, respectively . In 5 (1.9%) participants, atrial fibrillation led to an ibrutinib dose reduction in Arm I, no ibrutinib dose reduction occurred in Arm A+I due to atrial fibrillation.

Induction Period

The number of participants with atrial fibrillation during induction period was higher in Arm A+I (14 [5.1%]) and Arm I (14 [5.3%] participants), as compared to participants receiving induction immunochemotherapy without ibrutinib in Arm A (3 [1.1%] participants). Serious TEAEs of atrial fibrillation were reported in 4 (1.5%) and 6 (2.3%) participants in Arm A+I and Arm I, and in 1 (0.4%) participant from Arm A. In Arm A+I and Arm I, 4 (1.5%) and 1 (0.4%) participant(s) respectively, had a TEAE of atrial fibrillation that led to ibrutinib treatment discontinuation, and 2 participants in Arm I had a TEAE of atrial fibrillation that resulted in ibrutinib dose reduction.

Ventricular Tachyarrhythmias

Table 36 Incidence of Treatment-emergent Ventricular Tachyarrhythmia by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TE Ventricular Tachyarrhythmia	2 (0.7%)	1 (0.4%)	0	0	0	0	0	0	0
Preferred Term									
Ventricular arrhythmia	1 (0.4%)	0	0	0	0	0	0	0	0
Ventricular fibrillation	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TE=treatment-emergent.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Other Cardiac Arrhythmias (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmia)

Table 37 Incidence of Treatment-emergent Cardiac Arrhythmias (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmia) Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - MCL3003; Safety Population

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety Population	275			265			268		
Subjects with any TEAE	34 (12.4%)	10 (3.6%)	0	34 (12.8%)	7 (2.6%)	0	24 (9.0%)	7 (2.6%)	1 (0.4%)
System organ class									
Preferred term									
Cardiac disorders	24 (8.7%)	3 (1.1%)	0	27 (10.2%)	1 (0.4%)	0	14 (5.2%)	3 (1.1%)	0
Tachycardia	7 (2.5%)	1 (0.4%)	0	7 (2.6%)	0	0	6 (2.2%)	1 (0.4%)	0
Sinus tachycardia	5 (1.8%)	0	0	5 (1.9%)	0	0	3 (1.1%)	1 (0.4%)	0
Palpitations	4 (1.5%)	1 (0.4%)	0	7 (2.6%)	0	0	1 (0.4%)	0	0
Supraventricular tachycardia	4 (1.5%)	0	0	0	0	0	0	0	0
Atrial flutter	3 (1.1%)	1 (0.4%)	0	2 (0.8%)	0	0	0	0	0
Atrial tachycardia	1 (0.4%)	0	0	0	0	0	0	0	0
Bradycardia	1 (0.4%)	0	0	3 (1.1%)	0	0	4 (1.5%)	1 (0.4%)	0
Bundle branch block right	1 (0.4%)	0	0	0	0	0	0	0	0
Sinoatrial block	1 (0.4%)	0	0	0	0	0	0	0	0
Supraventricular extrasystoles	1 (0.4%)	0	0	0	0	0	0	0	0
Arrhythmia	0	0	0	1 (0.4%)	0	0	0	0	0
Atrioventricular block	0	0	0	1 (0.4%)	0	0	0	0	0
Atrioventricular block first degree	0	0	0	1 (0.4%)	0	0	0	0	0
Extrasystoles	0	0	0	1 (0.4%)	0	0	0	0	0
Paroxysmal arrhythmia	0	0	0	1 (0.4%)	0	0	0	0	0
Sinus bradycardia	0	0	0	1 (0.4%)	0	0	0	0	0
Sinus node dysfunction	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Nervous system disorders	10 (3.6%)	7 (2.5%)	0	12 (4.5%)	6 (2.3%)	0	10 (3.7%)	5 (1.9%)	0
Syncope	10 (3.6%)	7 (2.5%)	0	12 (4.5%)	6 (2.3%)	0	10 (3.7%)	5 (1.9%)	0
Investigations	3 (1.1%)	0	0	0	0	0	0	0	0
Electrocardiogram QT prolonged	1 (0.4%)	0	0	0	0	0	0	0	0
Heart rate increased	1 (0.4%)	0	0	0	0	0	0	0	0
Heart rate irregular	1 (0.4%)	0	0	0	0	0	0	0	0
General disorders and administration site conditions	0	0	0	0	0	0	1 (0.4%)	0	1 (0.4%)
Sudden death	0	0	0	0	0	0	1 (0.4%)	0	1 (0.4%)

Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the Arm A+I group; those with the same total frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 26.1.

Cardiac Failure

Table 38 Incidence of Treatment-emergent Cardiac Failure Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - MCL3003; Safety Population

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety Population	275			265			268		
Subjects with any TEAE	5 (1.8%)	2 (0.7%)	0	5 (1.9%)	0	0	3 (1.1%)	1 (0.4%)	0
System organ class Preferred term									
Cardiac disorders	4 (1.5%)	2 (0.7%)	0	3 (1.1%)	0	0	0	0	0
Cardiac failure	4 (1.5%)	2 (0.7%)	0	1 (0.4%)	0	0	0	0	0
Cardiac failure chronic	0	0	0	2 (0.8%)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.4%)	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Pulmonary oedema	1 (0.4%)	0	0	0	0	0	1 (0.4%)	1 (0.4%)	0
Investigations	0	0	0	2 (0.8%)	0	0	2 (0.7%)	0	0
Ejection fraction decreased	0	0	0	2 (0.8%)	0	0	2 (0.7%)	0	0

Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the Arm A+I group; those with the same total frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 26.1.

Hypertension

Table 39 Incidence of Treatment-emergent Hypertension by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TE Hypertension	27 (9.8%)	12 (4.4%)	0	36 (13.6%)	14 (5.3%)	0	24 (9.0%)	12 (4.5%)	0
Preferred Term									
Hypertension	23 (8.4%)	10 (3.6%)	0	33 (12.5%)	11 (4.2%)	0	21 (7.8%)	12 (4.5%)	0
Hypertensive crisis	4 (1.5%)	2 (0.7%)	0	2 (0.8%)	2 (0.8%)	0	2 (0.7%)	0	0
Blood pressure increased	2 (0.7%)	1 (0.4%)	0	0	0	0	0	0	0
Blood pressure systolic increased	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Metabolic syndrome	0	0	0	0	0	0	1 (0.4%)	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TE=treatment-emergent.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Ischemic Stroke

Table 40 Incidence of Treatment-emergent Ischaemic Stroke by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TE Ischaemic Stroke	0	0	0	2 (0.8%)	0	0	2 (0.7%)	0	0
Preferred Term									
Amaurosis fugax	0	0	0	0	0	0	1 (0.4%)	0	0
Cerebral infarction	0	0	0	0	0	0	1 (0.4%)	0	0
Transient ischaemic attack	0	0	0	2 (0.8%)	0	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TE=treatment-emergent.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Infections (Including Viral Reactivation)

A higher proportion of participants in Arm A+I (81.1%) compared to Arm I (70.2%) and Arm A (51.1%) had TEAEs within the SOC of Infections and Infestations. Treatment-emergent infections reported in ≥10% of participants in any study arm included **pneumonia** (20.4% participants in Arm A+I, 10.2% in Arm I, and 5.2% in Arm A), **COVID-19** (14.9% in Arm A+I, 14.0% in Arm I, and 1.1% in Arm A), **herpes zoster** (10.5% in Arm A+I, 2.3% in Arm I, and 0.4% in Arm A), and **upper respiratory tract infection** (10.5% in Arm A+I, 6.4% in Arm I, and 3.7% in Arm A).

The proportion of participants with Grade 3 or 4 TEAEs was higher in participants in Arm A+I (38.5%) compared to Arm I (27.2%) and Arm A (20.9%). The most frequently reported Grade 3 or 4 infection was **pneumonia** which was reported in a higher proportion of participants in Arm A+I (10.2%) compared to Arm I (5.3%) and Arm A (3.7%).

Treatment-emergent SAEs of any grade were reported at a higher incidence in Arm A+I (37.5%) compared to Arm I (27.2%) and Arm A (13.4%). **Pneumonia**, the most commonly reported serious infection of any grade and at Grade 3 or 4 was numerically higher in Arm A+I (9.5% and 7.3%) but similar in Arm I (4.2% and 3.4%) and Arm A (3.0% and 2.6%). Ten participants (3.6%) in Arm A+I, 4 (1.5%) participants in Arm I and 6 (2.2%) participants in Arm A were reported with a fatal infection. Infections and infestations leading to ibrutinib dose reduction or treatment discontinuation were reported for 1.8% and 13.1% participants in Arm A+I and 2.6% and 7.2% participants in Arm I.

Induction Phase

The incidence of treatment-emergent infections of any grade was higher in participants receiving induction therapy in combination with ibrutinib (Arm A+I 39.6% and Arm I 37.7%) compared to participants in Arm A (29.5%). The rate of Grade 3 or 4 events was comparable across the treatment arms (11.6% in Arm A+I, 12.1% in Arm I and 8.6% in Arm A). Fatal TEAEs were reported in one participant (0.4%) of each arm during the induction period. As for the entire treatment-emergent period, the most frequently reported infectious event during induction was **pneumonia** with similar incidences of any grade and Grade 3 or 4 across treatment arms (3.3% and 1.5% in Arm A+I, 1.5% and 1.1% in Arm I and 3.0% and 1.9% in Arm A). Whilst 0.7% and 1.5% had infections resulting in ibrutinib discontinuation, no ibrutinib dose reductions were reported for infectious events in either arm.

Second Primary Malignancies

Table 41 Incidence of Second Primary Malignancies During the Entire Study Period by Preferred Term; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I	A
Analysis set: Safety	275	265	268
Subjects with any second primary malignancies	21 (7.6%)	20 (7.5%)	11 (4.1%)
Non-Melanoma Skin Cancer	7 (2.5%)	3 (1.1%)	1 (0.4%)
Basal cell carcinoma	3 (1.1%)	3 (1.1%)	1 (0.4%)
Squamous cell carcinoma	2 (0.7%)	0	0
Neoplasm skin	1 (0.4%)	0	0
Squamous cell carcinoma of skin	1 (0.4%)	0	0
Non-Skin cancer (malignant)	14 (5.1%)	16 (6.0%)	10 (3.7%)
Angiosarcoma	1 (0.4%)	0	0
Bladder cancer	1 (0.4%)	0	0
Breast cancer	1 (0.4%)	1 (0.4%)	0
Colon cancer	1 (0.4%)	0	0
Invasive ductal breast carcinoma	1 (0.4%)	0	0
Leiomyosarcoma	1 (0.4%)	0	0
Lung adenocarcinoma	1 (0.4%)	1 (0.4%)	0
Lung neoplasm malignant	1 (0.4%)	0	0
Malignant neoplasm of thymus	1 (0.4%)	0	0
Metastases to meninges	1 (0.4%)	0	0
Myelodysplastic syndrome	1 (0.4%)	0	1 (0.4%)
Neoplasm malignant	1 (0.4%)	1 (0.4%)	0
Neuroendocrine tumour	1 (0.4%)	0	0
Prostate cancer	1 (0.4%)	6 (2.3%)	1 (0.4%)
Renal cell carcinoma	1 (0.4%)	0	0
Renal neoplasm	1 (0.4%)	1 (0.4%)	0
Acute myeloid leukaemia	0	0	2 (0.7%)
Adenosquamous cell lung cancer	0	1 (0.4%)	0
B-cell lymphoma	0	0	1 (0.4%)
Bladder cancer recurrent	0	1 (0.4%)	0
Bladder transitional cell carcinoma	0	0	1 (0.4%)
Follicular thyroid cancer	0	1 (0.4%)	0
Metastases to central nervous system	0	1 (0.4%)	0
Oesophageal adenocarcinoma	0	1 (0.4%)	0
Pancreatic carcinoma	0	0	1 (0.4%)
Plasma cell myeloma	0	1 (0.4%)	0
Rectal adenocarcinoma	0	0	1 (0.4%)
Renal cancer	0	0	1 (0.4%)
Small cell lung cancer	0	1 (0.4%)	0
Transitional cell carcinoma	0	0	1 (0.4%)
Transitional cell carcinoma recurrent	0	0	1 (0.4%)
	A+I	I	A
Melanoma Skin Cancer	1 (0.4%)	1 (0.4%)	0
Malignant melanoma	1 (0.4%)	1 (0.4%)	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Interstitial Lung Disease (ILD)

Table 42 Incidence of Treatment-emergent Interstitial Lung Disease (ILD) by Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TE Interstitial Lung Disease (ILD)	7 (2.5%)	4 (1.5%)	0	12 (4.5%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Preferred Term									
Pneumonitis	4 (1.5%)	2 (0.7%)	0	7 (2.6%)	0	0	1 (0.4%)	1 (0.4%)	0
Interstitial lung disease	2 (0.7%)	2 (0.7%)	0	3 (1.1%)	1 (0.4%)	0	0	0	0
Alveolitis	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Lung infiltration	1 (0.4%)	0	0	0	0	0	0	0	0
Pulmonary fibrosis	0	0	0	1 (0.4%)	0	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TE=treatment-emergent.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Cytopenic Adverse Events

Table 43 Incidence of Treatment-emergent Cytopenia Adverse Events by Toxicity Grade, Grouped Term and Preferred Term - MCL3003; Safety Population

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis Set: Safety Population	275			265			268		
Subjects with any Cytopenic TEAE	251 (91.3%)	245 (89.1%)	0	224 (84.5%)	209 (78.9%)	0	233 (86.9%)	225 (84.0%)	0
Grouped Term Preferred Term									
Anaemia*	162 (58.9%)	121 (44.0%)	0	122 (46.0%)	58 (21.9%)	0	157 (58.6%)	93 (34.7%)	0
Anaemia	162 (58.9%)	121 (44.0%)	0	119 (44.9%)	57 (21.5%)	0	155 (57.8%)	92 (34.3%)	0
Haemoglobin decreased	1 (0.4%)	0	0	3 (1.1%)	1 (0.4%)	0	2 (0.7%)	1 (0.4%)	0
Febrile neutropenia	98 (35.6%)	98 (35.6%)	0	37 (14.0%)	37 (14.0%)	0	71 (26.5%)	71 (26.5%)	0
Neutropenia*	210 (76.4%)	205 (74.5%)	0	167 (63.0%)	158 (59.6%)	0	171 (63.8%)	163 (60.8%)	0
Neutropenia	141 (51.3%)	136 (49.5%)	0	112 (42.3%)	104 (39.2%)	0	110 (41.0%)	104 (38.8%)	0
Neutrophil count decreased	89 (32.4%)	86 (31.3%)	0	68 (25.7%)	64 (24.2%)	0	65 (24.3%)	62 (23.1%)	0
Thrombocytopenia*	214 (77.8%)	197 (71.6%)	0	182 (68.7%)	162 (61.1%)	0	202 (75.4%)	193 (72.0%)	0
Thrombocytopenia	124 (45.1%)	109 (39.6%)	0	105 (39.6%)	92 (34.7%)	0	121 (45.1%)	114 (42.5%)	0
Platelet count decreased	100 (36.4%)	98 (35.6%)	0	87 (32.8%)	78 (29.4%)	0	91 (34.0%)	89 (33.2%)	0

Key: TEAE = Treatment-emergent adverse event. * Grouped term.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are coded using MedDRA Version 26.1.

Hepatic Toxicity Including Hepatic Failure

Table 44 Incidence of Treatment-emergent Hepatotoxicity Adverse Events by Toxicity Grade, System Organ Class and Preferred Term - MCL3003; Safety Population

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety Population	275			265			268		
Subjects with any TEAE	4 (1.5%)	2 (0.7%)	0	5 (1.9%)	0	0	2 (0.7%)	0	0
System organ class Preferred term									
Hepatobiliary disorders	4 (1.5%)	2 (0.7%)	0	5 (1.9%)	0	0	2 (0.7%)	0	0
Hepatotoxicity	2 (0.7%)	1 (0.4%)	0	4 (1.5%)	0	0	0	0	0
Hepatic failure	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Hepatitis	1 (0.4%)	0	0	0	0	0	0	0	0
Hepatic steatosis	0	0	0	1 (0.4%)	0	0	0	0	0
Liver disorder	0	0	0	0	0	0	2 (0.7%)	0	0

Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the Arm A+I group; those with the same total frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 26.1.

Laboratory findings

Hematologic Abnormalities

Table 45 Haematology: Incidence of Treatment-Emergent Worst Toxicity Grade During Treatment - MCL3003; Safety Population

	A+I			I			A		
	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4
Analysis set: Safety	275			265			268		
Hemoglobin (Decrease)	254 (92.4%)	127 (46.2%)	127 (46.2%)	210 (79.2%)	156 (58.9%)	54 (20.4%)	238 (88.8%)	142 (53.0%)	96 (35.8%)
Platelets (Decrease)	271 (98.5%)	11 (4.0%)	260 (94.5%)	253 (95.5%)	65 (24.5%)	188 (70.9%)	262 (97.8%)	11 (4.1%)	251 (93.7%)
ANC (Decrease)	266 (96.7%)	15 (5.5%)	251 (91.3%)	239 (90.2%)	46 (17.4%)	193 (72.8%)	245 (91.4%)	14 (5.2%)	231 (86.2%)

Key: ANC = Absolute neutrophils counts.
Note: Only subjects whose grade worsened from baseline were counted in numerator. Percentages are calculated with the number of subjects in safety population as the denominators.
Note: Baseline results include values collected outside of the 28-day screening window.

Clinical Chemistry

Table 46 Chemistry: Incidence of Treatment-Emergent Worst Toxicity Grade During Treatment - MCL3003; Safety Population

	A+I			I			A		
	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4	Any Grade	Grade 1/2	Grade 3/4
Analysis set: Safety	275			265			268		
Total Bilirubin (Increase)	75 (27.3%)	68 (24.7%)	7 (2.5%)	77 (29.1%)	74 (27.9%)	3 (1.1%)	50 (18.7%)	43 (16.0%)	7 (2.6%)
Creatinine clearance (Decrease)	0	0	0	0	0	0	0	0	0
Creatinine (Increase)	243 (88.4%)	221 (80.4%)	22 (8.0%)	242 (91.3%)	226 (85.3%)	16 (6.0%)	226 (84.3%)	214 (79.9%)	12 (4.5%)
ALT (Increase)	149 (54.2%)	135 (49.1%)	14 (5.1%)	130 (49.1%)	119 (44.9%)	11 (4.2%)	143 (53.4%)	132 (49.3%)	11 (4.1%)
AST (Increase)	122 (44.4%)	117 (42.5%)	5 (1.8%)	101 (38.1%)	99 (37.4%)	2 (0.8%)	122 (45.5%)	117 (43.7%)	5 (1.9%)
ALP (Increase)	133 (48.4%)	133 (48.4%)	0	99 (37.4%)	97 (36.6%)	2 (0.8%)	113 (42.2%)	109 (40.7%)	4 (1.5%)

Key: ALT = Alanine Aminotransferase. AST = Aspartate Aminotransferase. ALP = Alkaline Phosphatase.
Note: Only subjects whose grade worsened from baseline were counted in numerator. Percentages are calculated with the number of subjects in safety population as the denominators.
Note: Baseline results include values collected outside of the 28-day screening window.
Only subjects with both baseline and post-baseline are included.

Discontinuation due to adverse events

Table 47 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Ibrutinib by System Organ Class, Preferred Term and Toxicity Grade; Safety Analysis Set (Study 54179060MCL3003)

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TEAE leading to treatment discontinuation	105 (38.2%)	64 (23.3%)	12 (4.4%)	61 (23.0%)	34 (12.8%)	5 (1.9%)	0	0	0
System organ class Preferred term									
Infections and infestations	36 (13.1%)	12 (4.4%)	9 (3.3%)	19 (7.2%)	11 (4.2%)	4 (1.5%)	0	0	0
COVID-19	8 (2.9%)	2 (0.7%)	4 (1.5%)	4 (1.5%)	2 (0.8%)	2 (0.8%)	0	0	0
Pneumonia	7 (2.5%)	3 (1.1%)	2 (0.7%)	2 (0.8%)	1 (0.4%)	0	0	0	0
Hepatitis E	2 (0.7%)	1 (0.4%)	0	0	0	0	0	0	0
Herpes zoster	2 (0.7%)	0	0	0	0	0	0	0	0
Pneumonia fungal	2 (0.7%)	0	0	1 (0.4%)	0	0	0	0	0
Sepsis	2 (0.7%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0
Septic shock	2 (0.7%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0
Bronchitis	1 (0.4%)	0	0	0	0	0	0	0	0
COVID-19 pneumonia	1 (0.4%)	0	0	6 (2.3%)	3 (1.1%)	2 (0.8%)	0	0	0
Campylobacter gastroenteritis	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Campylobacter infection	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Coronavirus infection	1 (0.4%)	0	0	0	0	0	0	0	0
Impetigo	1 (0.4%)	0	0	0	0	0	0	0	0
Influenza	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Meningitis bacterial	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Paronychia	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Pneumonia viral	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Sinusitis	1 (0.4%)	0	0	0	0	0	0	0	0
Tooth infection	1 (0.4%)	0	0	0	0	0	0	0	0
Cerebral fungal infection	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Enterovirus infection	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Erysipelas	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Fungal infection	0	0	0	1 (0.4%)	0	0	0	0	0
Infection	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Intervertebral discitis	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Soft tissue infection	0	0	0	1 (0.4%)	0	0	0	0	0
Urosepsis	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Blood and lymphatic system disorders	20 (7.3%)	18 (6.5%)	0	4 (1.5%)	3 (1.1%)	0	0	0	0
Neutropenia	14 (5.1%)	13 (4.7%)	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Thrombocytopenia	3 (1.1%)	2 (0.7%)	0	1 (0.4%)	0	0	0	0	0
Anaemia	2 (0.7%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Febrile neutropenia	2 (0.7%)	2 (0.7%)	0	0	0	0	0	0	0
Leukocytosis	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0
Pancytopenia	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Investigations	18 (6.5%)	15 (5.5%)	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Neutrophil count decreased	11 (4.0%)	10 (3.6%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Platelet count decreased	5 (1.8%)	4 (1.5%)	0	0	0	0	0	0	0
C-reactive protein increased	1 (0.4%)	0	0	0	0	0	0	0	0
Gamma-glutamyltransferase increased	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Weight decreased	1 (0.4%)	0	0	0	0	0	0	0	0
White blood cell count decreased	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Cardiac disorders	12 (4.4%)	10 (3.6%)	0	9 (3.4%)	4 (1.5%)	1 (0.4%)	0	0	0
Atrial fibrillation	6 (2.2%)	5 (1.8%)	0	5 (1.9%)	4 (1.5%)	0	0	0	0
Atrial flutter	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0
Cardiac disorder	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Cardiac failure	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Myocardial infarction	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Sinoatrial block	1 (0.4%)	0	0	0	0	0	0	0	0
Ventricular fibrillation	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Acute myocardial infarction	0	0	0	1 (0.4%)	0	1 (0.4%)	0	0	0
Cardiac failure chronic	0	0	0	1 (0.4%)	0	0	0	0	0
Tachycardia	0	0	0	1 (0.4%)	0	0	0	0	0
Tachycardia induced cardiomyopathy	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Gastrointestinal disorders	8 (2.9%)	4 (1.5%)	1 (0.4%)	4 (1.5%)	3 (1.1%)	0	0	0	0
Diarrhoea	5 (1.8%)	3 (1.1%)	0	2 (0.8%)	1 (0.4%)	0	0	0	0
Abdominal pain upper	1 (0.4%)	0	0	0	0	0	0	0	0
Chronic gastritis	1 (0.4%)	0	0	0	0	0	0	0	0
Gastric haemorrhage	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Nausea	1 (0.4%)	0	0	0	0	0	0	0	0
Retroperitoneal haemorrhage	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Vomiting	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Intestinal perforation	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
General disorders and administration site conditions	6 (2.2%)	0	0	3 (1.1%)	1 (0.4%)	0	0	0	0
Pyrexia	2 (0.7%)	0	0	0	0	0	0	0	0
Asthenia	1 (0.4%)	0	0	0	0	0	0	0	0
Fatigue	1 (0.4%)	0	0	1 (0.4%)	0	0	0	0	0
Localised oedema	1 (0.4%)	0	0	0	0	0	0	0	0
Mucosal inflammation	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Malaise	0	0	0	1 (0.4%)	0	0	0	0	0
Nervous system disorders	5 (1.8%)	1 (0.4%)	0	6 (2.3%)	5 (1.9%)	0	0	0	0
Neuropathy peripheral	2 (0.7%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Peripheral sensory neuropathy	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Polyneuropathy	1 (0.4%)	0	0	0	0	0	0	0	0
Tremor	1 (0.4%)	0	0	0	0	0	0	0	0
Encephalitis autoimmune	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Haemorrhage intracranial	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Headache	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Radiculopathy	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Transient ischaemic attack	0	0	0	1 (0.4%)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	5 (1.8%)	1 (0.4%)	0	6 (2.3%)	1 (0.4%)	0	0	0	0
Cough	2 (0.7%)	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease	1 (0.4%)	0	0	0	0	0	0	0	0
Dyspnoea exertional	1 (0.4%)	0	0	0	0	0	0	0	0
Pneumonitis	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	0	0	0	0	0
Interstitial lung disease	0	0	0	2 (0.8%)	1 (0.4%)	0	0	0	0
Nocturnal dyspnoea	0	0	0	1 (0.4%)	0	0	0	0	0
Organising pneumonia	0	0	0	1 (0.4%)	0	0	0	0	0
Skin and subcutaneous tissue disorders	5 (1.8%)	0	0	3 (1.1%)	2 (0.8%)	0	0	0	0
Rash	2 (0.7%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Acute febrile neutrophilic dermatosis	1 (0.4%)	0	0	0	0	0	0	0	0
Neurodermatitis	1 (0.4%)	0	0	0	0	0	0	0	0
Skin lesion	1 (0.4%)	0	0	0	0	0	0	0	0
Drug eruption	0	0	0	1 (0.4%)	0	0	0	0	0
Toxic skin eruption	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Musculoskeletal and connective tissue disorders	4 (1.5%)	3 (1.1%)	0	5 (1.9%)	1 (0.4%)	0	0	0	0
Muscle spasms	2 (0.7%)	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0
Arthritis	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Myalgia	1 (0.4%)	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0
Arthralgia	0	0	0	1 (0.4%)	0	0	0	0	0
Muscular weakness	0	0	0	1 (0.4%)	0	0	0	0	0
Myositis	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.5%)	3 (1.1%)	1 (0.4%)	0	0	0	0	0	0
Lung adenocarcinoma	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Lung neoplasm malignant	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Malignant neoplasm of thymus	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Metastases to meninges	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Ear and labyrinth disorders	2 (0.7%)	0	0	0	0	0	0	0	0
Tinnitus	1 (0.4%)	0	0	0	0	0	0	0	0
Vestibular disorder	1 (0.4%)	0	0	0	0	0	0	0	0
Hepatobiliary disorders	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Hepatic failure	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Dehydration	1 (0.4%)	0	0	0	0	0	0	0	0
Decreased appetite	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Psychiatric disorders	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Completed suicide	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0
Renal and urinary disorders	1 (0.4%)	0	0	3 (1.1%)	3 (1.1%)	0	0	0	0
Renal failure	1 (0.4%)	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Acute kidney injury	0	0	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Vascular disorders	1 (0.4%)	0	0	0	0	0	0	0	0
Haematoma	1 (0.4%)	0	0	0	0	0	0	0	0
Reproductive system and breast disorders	0	0	0	1 (0.4%)	0	0	0	0	0
Erectile dysfunction	0	0	0	1 (0.4%)	0	0	0	0	0

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib, TEAE=treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the All Grades column for that adverse event.
Note: Adverse events are presented by decreasing frequency of system organ class and preferred term within A+I column; those with the same frequency are presented alphabetically.
Note: Percentages are calculated with the number of subjects in safety analysis set as denominator.
Adverse events are coded using MedDRA Version 26.1.

Table 48 Incidence of Treatment-emergent Adverse Events Leading to Dose Reduction by Toxicity Grade, System Organ Class and

	A+I			I			A		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Analysis set: Safety	275			265			268		
Subjects with any TEAE leading to dose reduction	4 (1.5%)	4 (1.5%)	0	10 (3.8%)	9 (3.4%)	0	0	0	0
System organ class Preferred term									
Blood and lymphatic system disorders	4 (1.5%)	4 (1.5%)	0	5 (1.9%)	5 (1.9%)	0	0	0	0
Neutropenia	2 (0.7%)	2 (0.7%)	0	4 (1.5%)	4 (1.5%)	0	0	0	0
Leukocytosis	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0
Thrombocytopenia	1 (0.4%)	1 (0.4%)	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Cardiac disorders	0	0	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Atrial fibrillation	0	0	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Gastrointestinal disorders	0	0	0	2 (0.8%)	2 (0.8%)	0	0	0	0
Diarrhoea	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Gastritis	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Nausea	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Vomiting	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
General disorders and administration site conditions	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Mucosal inflammation	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Investigations	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Platelet count decreased	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Rash	0	0	0	1 (0.4%)	1 (0.4%)	0	0	0	0
Vascular disorders	0	0	0	1 (0.4%)	0	0	0	0	0
Hypertension	0	0	0	1 (0.4%)	0	0	0	0	0

Key: TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Adverse events are presented by descending total frequency of SOC and PT within SOC in the Arm A+I group; those with the same total frequency are presented alphabetically.
Adverse events are coded using MedDRA Version 26.1.

Table 49 Dose Reduction of Ibrutinib during Induction Therapy; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I
Analysis set: Safety	275	265
Number of dose reductions[a]		
0	268 (97.5%)	251 (94.7%)
1	5 (1.8%)	10 (3.8%)
2	0	3 (1.1%)
3	0	1 (0.4%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
[a] Refers to number of reductions in dose level. The maximum dose reduction is considered for each subject.
Note: Percentages are calculated with the number of subjects in the safety analysis set in each treatment group as the denominators.

Table 50 Dose Reduction of Ibrutinib during Maintenance Period; Safety Analysis Set (Study 54179060MCL3003)

	A+I	I
Analysis set: Safety	275	265
Subjects that received at least one dose of Ibrutinib	230	245
Number of dose reductions[a]		
0	152 (66.1%)	191 (78.0%)
1	36 (15.7%)	28 (11.4%)
2	35 (15.2%)	20 (8.2%)
3	7 (3.0%)	6 (2.4%)

Key: ASCT=autologous stem cell transplant, A=ASCT, A+I=ASCT+Ibrutinib, I=Ibrutinib.
[a] Refers to number of reductions in dose level. The maximum dose reduction is considered for each subject.
Note: Percentages are calculated with the number of subjects in the safety analysis set that received at least one dose of Ibrutinib during Maintenance in each treatment group as the denominators.

Post marketing experience

2.5.1. Discussion on clinical safety

The key safety data in support of this application derive from the primary analysis of Study MCL3003 (TRIANGLE) with a data cutoff date of 09 May 2024.

The safety data base is considered of an acceptable magnitude for detecting any changes to the already known safety profile of ibrutinib and/or identifying new safety concerns including those related to this new treatment combination and patient population.

The median treatment duration was approx. 29 months (range 0 to 39.3) for Arm A+I, 28 months (range 0.2 to 35.5) for Arm I and 5 months (range 0.2 to 12.7) for Arm A.

As judged by the data on the extent of exposure during the induction phase, ibrutinib appears well tolerated in both the A+I and the I arm (dose intensity median 560 mg/day and relative dose intensity median 100 for both arms).

Not unexpectedly (especially with reference to the A+I arm which included high-dose chemotherapy and ASCT), this changed during the maintenance phase where a tendency to less tolerability for ibrutinib was noted.

It is also notable that due to the definition of TEAE's (AEs that started or worsened in severity after the first dose of study treatment up to 30 days following the last dose of study treatment or until the start of subsequent anti-cancer therapy) observation-time is substantially longer in the ibrutinib-containing arms. Thus, time-unadjusted incidence rates are biased in favour of the reference arm (arm A).

Common TEAEs

The only PT occurring at a ≥10% higher frequency in Arm I as compared with Arm A was **COVID-19** (Arm A+I: 14.9%; Arm I:14.0%; Arm A: 1.1%).

Most common TEAEs by PT occurring at a ≥10% higher frequency in Arm A or Arm A+I as compared with Arm I were: **Anaemia** (Arm A+I: 58.9%, Arm I: 44.9%; Arm A: 57.8%); **Febrile neutropenia** (Arm A+I: 35.6%; Arm I: 14.0%; Arm A: 26.5%); **Pneumonia** (Arm A+I: 20.4%; Arm I: 10.2%; Arm A: 5.2%; **Pyrexia** (Arm A+I: 34.9%; Arm I: 21.5%; Arm A: 33.2%); **Mucosal inflammation** (Arm A+I: 31.3%; Arm I: 8.3%; Arm A: 27.6%).

Induction Phase

TEAEs that were reported with an incidence of ≥5% difference between participants receiving ibrutinib during the induction period (Arm A+I or Arm I) compared to participants who did not receive ibrutinib as part of the induction regimen (Arm A) were **Leukocytosis** (Arm A+I: 7.3%, Arm I: 1.9%, Arm A: 1.5%); **Diarrhoea** (Arm A+I: 13.8%, Arm I: 21.9%, Arm A: 12.7%); **Fatigue**: (Arm A+I: 15.3%, Arm I: 14.0%, Arm A: 8.2%) and **Rash**: (Arm A+I: 5.1%, Arm I: 7.2%, Arm A: 0.7%). Table 28

TEAEs by Grade

The proportion of participants with Grade 3 or 4 TEAEs was similar for Arm A+I, Arm I, and Arm A (92.0%, 90.9% and 89.2%, respectively).

The only Grade 3 or 4 TEAE occurring at a≥10% higher frequency in Arm A+I as compared with Arm A was **neutropenia** (Arm A+I: 49.5%; Arm I: 39.2%; Arm A: 38.8%).

Grade 3 or 4 TEAEs occurring at a≥10% higher frequency in Arm A+I or Arm A as compared with Arm I were **Anaemia** (Arm A+I: 44.0%; Arm I: 21.5%; Arm A: 34.3%), **Neutropenia** (Arm A+I: 49.5%; Arm I: 39.2%; Arm A: 38.8%), **Febrile neutropenia** (Arm A+I: 35.6%; Arm I: 14.0%; Arm A: 26.5%), **Mucosal inflammation** (Arm A+I: 15.6%; Arm I: 1.9%; Arm A: 13.1%).

Induction Phase

The only Grade 3 or 4 TEAE reported with a ≥5% difference between participants in any of the treatment arms was **anaemia** (Arm A+I: 29.1%; Arm I: 20.4%; Arm A: 22.0%).

Ibrutinib-related TEAEs

The most frequently reported TEAEs related to ibrutinib (≥5%) by SOC and PT are provided in Table 30. The proportion of any Grade TEAEs related to ibrutinib was 84.7% in Arm A+I and 80.0% in Arm I. The proportion of Grade 3 or 4 TEAEs related to ibrutinib was higher in participants in Arm A+I (66.9%) compared with Arm I (54.0%). There were two Grade 5 ibrutinib-related events reported in Arm A+I which included **septic shock** and **malignant melanoma**.

Induction Phase

All-grade ibrutinib-related TEAEs were reported for similar proportions of participants in the ibrutinib-containing arms during the Induction Phase: 54.5% in Arm A+I and 55.8% in Arm I. Grade 3/4 ibrutinib-related TEAEs were reported in 36.4% in Arm A+I and 33.6% in Arm I. There were no Grade 5 TEAE reported in either arm.

Deaths

At the time of the CCO, there were in total 127 deaths (15.7%) with 22.4% occurring in Arm A compared with Arm I (12.5%), and Arm A+I (12.4%). A total of 53 deaths (6.6%) were caused by progressive disease (3.3% in Arm A+I, 5.3% in Arm I, and 11.2% in Arm A).

A total of 32 deaths were attributed to AEs. Fewer fatal AEs were observed for participants in Arm I (2.3%) compared with both ASCT-containing arms (5.5% and 4.1% events in Arm A+I and Arm A, respectively).

Induction Phase

Treatment-emergent SAEs during the induction period were reported in 42.9% of the participants in Arm A+I and in 44.9% participants in Arm I compared with 41.0% participants in Arm A. The most frequently reported (≥5% in any treatment arm) treatment-emergent SAEs by PT were **febrile neutropenia** (Arm A+I: 9.8%, Arm I: 9.8%, Arm A: 6.7%) and **acute kidney injury** (Arm A+I: 5.5%, Arm I: 6.8%, Arm A: 4.9%).

Adverse Events Leading to Ibrutinib Treatment Discontinuation

The incidence of TEAEs leading to ibrutinib discontinuation was higher in participants in Arm A+I (38.2%) compared with participants in Arm I (23.0%).

In regard to the induction phase, the proportion of ibrutinib discontinuation due to AEs is considered low and comparable between the ibrutinib-containing arms: Arm A+I (6.5%) and Arm I (4.9%). However, as may be expected, the majority of TEAEs leading to ibrutinib discontinuation occurred during the maintenance period, with a higher incidence in Arm A+I compared with Arm I with a majority of TEAEs leading to ibrutinib discontinuation in the SOCs of Infections and infestations and Blood and lymphatic system disorders.

The most frequent (≥5% in either ibrutinib-containing arm) TEAEs leading to ibrutinib discontinuation were within the SOCs of **Infections and infestations** (13.1% and 7.2% in Arm A+I and Arm I, respectively), **Blood and lymphatic system disorders** (7.3% and 1.5% in Arm A+I and Arm I, respectively), and **Investigations** (6.5% and 0.8% in Arm A+I and Arm I, respectively).

Adverse Events Leading to Ibrutinib Dose Reduction

TEAEs leading to ibrutinib dose reduction were reported for comparable proportions of participants in Arm A+I (19.6%) and in Arm I (16.2%). At the SOC level, TEAEs leading to ibrutinib dose reduction were most commonly (≥5% in either arm) classified as Blood and lymphatic system disorders (10.5% of Arm A+I and 4.9% of Arm I participants).

Whilst the proportions of TEAEs leading to ibrutinib dose reduction during the Induction Phase were reported at a low level (98% and 95% with no dose reductions in the A+I and I arm, respectively (Table 49), this changed during the maintenance phase thus indicating a lesser tolerability for ibrutinib (66% and 78% with no dose reductions in the A+I and I arms, respectively).

Other Safety Observations

For Major haemorrhage, Cardiac failure and Cytopenic Adverse Events, there were similar rates reported between the three arms. In terms of Other Cardiac Arrhythmias, Hypertension, ILD and Atrial fibrillation, the rates of reports were higher in the I arm compared to the other two arms. Ventricular Tachyarrhythmias were only reported for the A+I arm. Reports of Ischemic stroke were similar in the I and A arm (about 1%). Rates of reports for Second Primary Malignancies and Hepatic Toxicity Including Hepatic Failure were similar in the A+I and I arm.

During the induction phase, the ibrutinib + R-CHOP combination appears well-tolerated as judged by a high extent of exposure, low proportions of ibrutinib discontinuations due to AEs and low proportions of dose reductions. That changes during the maintenance phase however, where the extent of ibrutinib exposure decreases which is most obvious in the A+I arm with high-dose chemotherapy and ASCT preceding the ibrutinib maintenance treatment.

When comparing the overall toxicity profile of Arm I to that of arm A, the former appears overall more tolerable in comparison with the exception of a slightly higher rate of reports for SAEs (including grade ≥3). Notably, the proportion of deaths due to AEs (including deaths within 30 days of last dose of study treatment) is lower in arm I compared to arm A (in total 2.3% and 4.1%, respectively). There is no indication of a detrimental effect on overall survival when substituting ibrutinib for ASCT.

At PT level, certain differences in the safety profiles were observed between Arm A and Arm I. Whilst the rate of reports of neutropenia were similar between the arms, reports of febrile neutropenia was almost twice as high in Arm A compared to Arm I.

In comparison with arm A and arm I, the A+I arm, appears overall less tolerable with higher rates of reports for TEAEs Grade ≥3, SAEs, SAEs grade ≥3, deaths due to AEs (including deaths within 30 days of last dose of study treatment), ibrutinib discontinuations and reductions.

2.5.2. Conclusions on clinical safety

Based on the data from the TRIANGLE study no new safety concerns have been identified. The safety profile is mainly in line with what has previously been established for ibrutinib. The safety profile of ibrutinib is considered acceptable for the proposed use.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 23.1. is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

No update of the safety concerns is required by this procedure.

Table 51 Summary of Safety Concerns

Important identified risks	Hemorrhage
	Hepatotoxicity (including hepatic failure)
	Atrial fibrillation
	Ventricular tachyarrhythmias
	Hypertension
	Ischemic stroke
	Cardiac failure
	Infections (including viral reactivation)
Important potential risks	Progressive multifocal leukoencephalopathy (PML)
	Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)
	Other malignancies (excluding non-melanoma skin cancer)
Missing information	Use in patients with severe cardiac disease

Pharmacovigilance plan

No update of the pharmacovigilance plan is required

Table 52: Ongoing and Planned Additional Pharmacovigilance Activities

Study & Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

Risk minimisation measures

No additional risk minimisation measures are required.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2. of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Cyprus and Greece.

2.7.1. User consultation

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

Full user testing in compliance with the above-mentioned legislative requirements was performed (n= 20 participants) on the package leaflet in the initial Marketing Authorisation Application and subsequently on the combined package leaflet for IMBRUVICA 140 mg, 280 mg, 420 mg, 560 mg film-coated tablets, in a tablet line extension application.

Based on the above, with the currently proposed Type II variation to extend the existing IMBRUVICA indication in MCL, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet. The use of lay language for the additional indication and side effects aligns with the currently approved leaflet.

However, as MAH has proposed major changes to section 4, a focus test for section 4 is requested.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final approved indication is:

IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT)"

3.1.2. Available therapies and unmet medical need

Newly diagnosed patients with MCL have so far typically been categorized into 2 subpopulations defined by their suitability and eligibility for intensive treatment including autologous stem cell transplant (ASCT).

For the younger (< 65 years) and transplant-eligible patients, an intensive treatment approach including induction therapy followed by ASCT with rituximab maintenance therapy has represented the present standard of care treatment (ESMO GL 2017). Alternating R-CHOP with cytarabine-containing regimens are among the most commonly used combinations for induction therapy.

Despite an intensive approach with ASCT, no curative treatment is available for MCL. Hence, there is an unmet medical need for more effective treatments.

3.1.3. Main clinical studies

Study MCL3003 (TRIANGLE) which is a randomized, 3-arm, open-label, multicenter Phase 3 study, compared three alternating courses of R-CHOP/R-DHAP followed by ASCT (control Arm A), versus the combination with ibrutinib in induction and maintenance (experimental Arm A+I), and the experimental arm without ASCT (experimental Arm I) in patients ≤ 65 years with previously untreated MCL who were eligible for ASCT. Due to the implementation of rituximab maintenance in national treatment guidelines during the study, this approach was introduced to all 3 treatment arms throughout the study.

The primary endpoint failure-free survival (FFS) was defined as the time from randomization to stable disease at the end of induction immunochemotherapy, progressive disease, or death from any cause, whichever comes first.

3.2. Favourable effects

An improvement in FFS was seen for Arm I compared with Arm A, HR of 0.639 (0.428, 0.953), p-value: 0.0068 (post-hoc analysis performed for registrational purposes).

Improvement in **OS** was observed for participants in in Arm I vs Arm A (Cox regression HR [95% CI] of 0.522 [0.341, 0.799]; 2-sided nominal p value=0.0023)..

3.3. Uncertainties and limitations about favourable effects

The impact of rituximab maintenance given with ibrutinib monotherapy during the maintenance phase was not investigated and therefore remains unclear.

3.4. Unfavourable effects

Based on the data from the TRIANGLE study no new safety concerns have been identified. The safety profile is mainly in line with what has previously been established for ibrutinib.

The overall incidence of TEAEs (any grade) was similar in Arm I (99.2%), and Arm A (99.6%). The proportion of participants with Grade 3 or 4 TEAEs was also similar for Arm I, and Arm A (90.9% and 89.2%, respectively).

The most frequently reported (≥10%) Grade 3 or 4 TEAEs in either treatment arm by PT were e.g. Neutropenia (39.2% in Arm I, and 38.8% in Arm A); Anaemia (21.5% in Arm I, and 34.3% in Arm A), Thrombocytopenia (34.7% in Arm I, and 42.5% in Arm A); Febrile neutropenia (14% in Arm I, and 26.5% in Arm A); Leukopenia (9.4% in Arm I, and 11.2% in Arm A), Pneumonia (5.3% in Arm I, and 3.7% in Arm A); Mucosal inflammation (1.9% in Arm I, and 13.1% in Arm A).

Deaths

At the time of the CCO, there were in total 127 deaths (15.7%) with 22.4% occurring in Arm A compared with Arm I (12.5%). A total of 32 deaths were attributed to AEs.

Fewer fatal AEs were observed for participants in Arm I (2.3%) compared with ASCT (4.1% events).

3.5. Uncertainties and limitations about unfavourable effects

No uncertainties are identified.

3.6. Effects Table

Table 1. Effects Table for Study MCL3003 (TRIANGLE), data cut-off: 09 May 2024

Effect	Short description	Unit	Treatment	Treatment	Control	Uncertainties / Strength of evidence	References
	Favourable Effects						
Treatment arms	**Full analysis set (FAS) n=809**			**ibrutinib**	**ASCT**		
FFS (primary endpoint)	Time from randomization to stable disease at end of induction, progressive disease, or death from any cause, whichever comes first	Median, months (95%CI)		NE (NE, NE)	NE (NE, NE)	HR unstratified Cox regression (2-sided 98.33% CI), two-sided p-value from unstratified log-rank test: Arm I vs A, HR of 0.639 (0.428, 0.953), p-value: 0.0068. Median time on study 54.9 months with 61 FFS events (22.8%) in Arm I, and 87 FFS	MCL3003

Effect	Short description	Unit	Treatment	Treatment	Control	Uncertainties / Strength of evidence	References
						events (32.3%) in Arm A Unc: Post-hoc, no type-I error control, FAS population	
	Unfavourable Effects						
Treatment arms	**Safety analysis set**			**Arm I** **N=265**	**Arm A** **N=268**		
TEAEs any grade	Incidence of TEAEs Occurring in ≥10%	%		99.2	99.6		
Grade ≥3		%		93.2	93.3		
Grade 3/4		%		90.9	89.2		
Anaemia				21.5	34.3		
Neutropenia				39.2	38.8		
Pneumonia				5.3	3.7		
Diarrhoea				5.3	6.0		
Deaths due to AEs		%		2.3	4.1		
Discontinuation of ibrutinib due to AEs		%		23.0	N/A		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FFS analyses of study MCL3003 demonstrate a clinically meaningful improvement of FFS in Arm I vs Arm A, together with a different safety profile when ASCT is substituted by the use of ibrutinib in induction and maintenance phase. This finding is supported by descriptive OS data indicating a potential benefit. Importantly, there is no indication of a detrimental OS effect when substituting ibrutinib for ASCT.

In summary, there is a nominally large improvement in FFS (further supported by encouraging OS data) when substituting ibrutinib for ASCT, in combination with a different, and arguably more favorable, safety profile. Given that this is a substitution, in principle similar efficacy could be acceptable. Thus, despite the uncertainty introduced by the lack of proper type 1 error control, efficacy as well as positive B/R is inferred for this treatment modality.

The results from MCL3003 did not demonstrate any additional benefits of combining ibrutinib with ASCT and provided no clear indications of such benefits in any specific subgroup. Moreover, ASCT is associated with substantial toxicity, including treatment-related deaths. Thus, data support an

extension of indication to substitute ibrutinib for ASCT, but the support for their combined use was not compelling and during the procedure, the MAH dropped their claim for use in combination with ASCT

3.7.2. Balance of benefits and risks

The benefit-risk balance of IMBRUVICA in the proposed patient population is positive, since the demonstrated benefits of IMBRUVICA in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP without IMBRUVICA, followed by IMBRUVICA monotherapy for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplant (ASCT) are considered to outweigh the toxicity of this treatment regimen, which is considered generally acceptable and manageable in the current clinical setting.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Imbruvica as proposed for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT) is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include Imbruvica in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) alternating with R-DHAP without IMBRUVICA, followed by Imbruvica monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).

Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated

in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Version 23.1 of the RMP has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

4.1. Conclusions

The overall B/R of Imbruvica in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) alternating with R-DHAP (or R-DHAOx) without IMBRUVICA, followed by IMBRUVICA monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT)is positive

Similarity with authorised orphan medicinal products

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'