

Single Technology Appraisal

**Ibrutinib with R-CHOP for untreated
mantle cell lymphoma when a stem cell
transplant is suitable [ID6596]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when a stem cell transplant is suitable [ID6596]

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

1. **Company submission from Johnson & Johnson Innovative Medicine:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
2. **Clarification questions and company responses**
 - a. Response
 - b. Response to B15 and B16
3. **Patient group, professional group, and NHS organisation submissions** from:
 - a. Lymphoma Action
4. **Expert personal perspectives** from:
 - a. Dr David Lewis – clinical expert, nominated by Johnson & Johnson Innovative Medicine UK
 - b. Dr Rory McCulloch - clinical expert, nominated by NICE
 - c. Patient expert, nominated by Lymphoma Action
5. **External Assessment Report** prepared by Kleijnen Systematic Reviews
6. **External Assessment Report – factual accuracy check**
7. **Managed Access Feasibility Assessment**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Company evidence submission

January 2026

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Abbreviations

Abbreviation	Definition
1L	First-Line
2L	Second-Line
3L	Third-Line
AEs	Adverse Events
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criteria
AMR	Annual Mortality Rate
ASCT	Autologous Stem Cell Transplantation
BCR	B-Cell Receptor

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BEAC	Carmustine, Etoposide, Cytarabine and Cyclophosphamide
BEAM	Carmustine, Etoposide, Cytarabine and Melphalan
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
BR	Bendamustine and Rituximab
BSA	Body Surface Area
BSC	Best Supportive Care
BSH	British Society of Haematology
BTK	Bruton's Tyrosine Kinase
CCO	Clinical Cut-Off
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukaemia
CNS	Central Nervous System
CR	Complete Response
CRR	Complete Response Rate
CSR	Clinical Study Report
CT	Computed Tomography
DCO	Data Cut-Off
DSA	Deterministic Sensitivity Analyses
EAG	Evidence Assessment Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-3D-3L	EuroQol Three Dimensions Three Level
EQ-5D	EuroQol Five Dimensions
EQ-5D-5L	EuroQol Five Dimensions Five Level
ESMO	European Society for Medical Oncology
EU	Europe
FAS	Full Analysis Set
FF 1L	Failure-Free on First-Line Treatment
FFS	Failure-Free Survival
GDPR	General Data Protection Regulation
GI	Gastrointestinal
HDT	High-Dose Chemotherapy
HMRN	Haematological Malignancy Research Network
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSCT	Haematopoietic Stem Cell Transplantation
HSUV	Health State Utility Values
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICF	Informed Consent Form
ICU	Intensive-Care Unit

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INHB	Incremental Net Health Benefit
IPCW	Inverse Probability of Censoring Weighting
IPD	Individual Patient-Level Data
ISMCL	In Situ Mantle Cell Neoplasia
ITC	Indirect Treatment Comparisons
ITT	Intention-To-Treat
IV	Intravenous
KM	Kaplan-Meier
LYG	Life Years Gained
LYs	Life Years
MCL	Mantle Cell Lymphoma
MHRA	Medicines and Healthcare Products Regulatory Agency
MIPI	MCL International Prognostic Index
MMRM	Mixed-Model Repeated Measures
N/A	Not Applicable
NF-κB	Nuclear Factor Kappa-Light Chain-Enhancer of Activated B Cells
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressed Disease
PET	Positron Emission Tomography
PF 2L	Progression-Free On Second-Line Treatment
PFS	Progression-Free Survival
PH	Proportional Hazards
PICO	Patient Intervention Comparator Outcome
PPS	Post-Progression Survival
PR	Partial Response
PRISMA	Preferred Reporting Items For Systematic Literature Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
R-BAC	Rituximab, Bendamustine and Cytarabine
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone
R-DHAOx	Rituximab, Dexamethasone, High-Dose Cytarabine and Oxaliplatin
R-DHAP	Rituximab, Dexamethasone, High-Dose Cytarabine and Cisplatin
R-HDAC	Rituximab, High-Dose Cytosine Arabinoside
RCT	Randomised Controlled Trials

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ROBINS-I	Risk of Bias In Non-Randomised Studies of Interventions
RoB	Risk of Bias
s-MIPI	Simplified Score-Based MCL International Prognostic Index
SAEs	Serious Adverse Event
SAP	Statistical Analysis Plan
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
TEAEs	Treatment-Emergent Adverse Events
TESAEs	Treatment-Emergent Serious Adverse Events
THAM	Fractionated Total Body Irradiation, Cytarabine and Melphalan
TSD	Technical Support Document
TTF	Time-To-Failure
TTP	Time-To-Progression
UK	United Kingdom
US	United States
WHO	World Health Organisation
WTP	Willingness-To-Pay
vs	Versus

1 Decision problem, description of the technology and clinical care pathway

1.1 *Decision problem*

This submission covers the full marketing authorisation for ibrutinib in the indication under consideration: ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) alternating with rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin [R-DHAox]) without ibrutinib, followed by ibrutinib monotherapy for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).¹ In line with the Summary of Product Characteristics (SmPC) for ibrutinib in this indication, rituximab may be added to ibrutinib maintenance treatment as per national treatment guidelines.¹ This regimen is henceforth referred to as the ibrutinib regimen.

The decision problem addressed within this submission is consistent with the National Institute of Health and Care Excellence (NICE) final scope for this appraisal.² Additionally, the economic analysis follows the NICE reference case thereby ensuring alignment with the NICE decision problem. Any minor differences between the decision problem addressed within this submission and the NICE final scope are outlined in Table 1 below.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated MCL when an ASCT is suitable.	Adults with untreated MCL when an ASCT is suitable.	N/A
Intervention	Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, followed by ibrutinib monotherapy.	Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, followed by ibrutinib monotherapy. ^a	N/A
Comparator(s)	Induction phase: - Alternating R-CHOP and R-DHAP or R-DHAOx - Acalabrutinib with bendamustine and rituximab (subject to NICE evaluation) Consolidation phase: - ASCT Maintenance phase: - Rituximab	Induction phase: - Alternating R-CHOP and R-DHAP or R-DHAOx Consolidation phase: - ASCT Maintenance phase: - Rituximab	At the time of this submission, acalabrutinib with bendamustine and rituximab has not undergone NICE evaluation. ³ Furthermore, acalabrutinib with bendamustine and rituximab is only licensed as an induction regimen for patients who are not eligible for ASCT. This positioning was clarified by the manufacturer in ID6155 and is in accordance with the most recent European Society for Medical Oncology (ESMO) and British Society of Haematology (BSH) guidelines. ³⁻⁵ Acalabrutinib with bendamustine and rituximab would therefore not represent a relevant comparator to the ibrutinib regimen, even if it was recommended by NICE.
Outcomes	- Overall survival (OS) - Failure-free survival (FFS) - Progression-free survival (PFS) - Response rates - Adverse effects (AEs) of treatment - Health-related quality-of-life (HRQoL)	- OS - FFS - PFS - Response rates: - Complete response rate (CRR) - Overall response rate (ORR) - Conversion rate of partial response (PR) to complete response (CR)	In line with the NICE scope, all requested outcomes (key survival, response, safety and HRQoL data) are presented within this submission. Of note, TRIANGLE was an investigator-initiated trial and as such, J&J IM did not have any input into the trial design or endpoints selected. HRQoL data were not collected as part of the TRIANGLE trial; utility values informing the cost-effectiveness model were therefore informed by values from alternative sources. Further information on the utility data informing the model is provided in Section 3.4.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		during-follow up after end of induction therapy • AEs and serious AEs • HRQoL	
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • Costs will be considered from an NHS and Personal Social Services (PSS) perspective • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	• The economic analysis has been conducted as per the final scope and in line with the NICE reference case	N/A

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability and cost of biosimilar and generic products should be taken into account		
Subgroups to be considered	If evidence allows, subgroups based on baseline clinical disease characteristics, cytology of mantle cell lymphoma, p53 expression and receipt of rituximab maintenance may be considered.	Subgroup analyses for the clinical endpoint of FFS, based on baseline clinical disease characteristics, cytology of MCL, p53 expression and receipt of rituximab maintenance are presented.	Subgroup data for the primary endpoint of TRIANGLE (FFS) are presented in this submission (see Section 2.8). However, subgroups are not considered in the cost-effectiveness analysis (see Section 3) given that they are not anticipated to be important for decision-making in UK clinical practice. ⁶
Special considerations including issues related to equity or equality	None specified.	No special considerations including issues related to equity or equality are relevant to this submission.	N/A

^a Rituximab may be added to ibrutinib maintenance treatment. The addition of rituximab to ibrutinib maintenance treatment is in line with the UK license for ibrutinib in this indication, which notes that “rituximab may be added [to ibrutinib maintenance treatment] as per national treatment guidelines”.¹

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; CHOP: cyclophosphamide, doxorubicin; CR: complete response; DHAox: dexamethasone, high-dose cytarabine and oxaliplatin; DHAP: dexamethasone, high-dose cytarabine, platinum; FFS: failure-free survival; HRQoL: health-related quality-of-life; MCL: mantle cell lymphoma; N/A: not applicable; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; OS: overall survival; PFS: progression-free survival; PR: partial response; PSS: Personal Social Services; R-: rituximab.

Source: NICE TA11802 Final Scope (2025).²

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1.2 Description of the technology being evaluated

A description of the mechanism of action, marketing authorisation status, costs and administration requirements associated with the ibrutinib regimen for the treatment of untreated MCL is provided in Table 2. The SmPC is presented in Appendix A.

Table 2: Technology being evaluated

UK approved name and brand name	Ibrutinib (IMBRUVICA®)
Mechanism of action	Ibrutinib is a potent, small-molecule inhibitor of Bruton's tyrosine kinase (BTK) that forms a covalent bond with a cysteine residue (specifically, cysteine-481) in the BTK active site, leading to sustained inhibition of BTK.¹ Inhibition of BTK disrupts B cell receptor (BCR) signalling and thereby reduces malignant B cell proliferation and survival, cell migration and substrate adhesion, as shown in Figure 1.¹ Figure 1: Mechanism of action of ibrutinib Abbreviations: BCR: B cell antigen receptor; BTK: Bruton's tyrosine kinase; Cys: cysteine; Syk: spleen tyrosine kinase. Source: Ayyildiz (2014).⁷ Aberrant BCR signalling contributes significantly to the proliferation and survival of malignant B cells in MCL. BTK's role in signalling through the BCR activates pathways crucial for B-cell trafficking, chemotaxis, and adhesion. Ibrutinib's inhibition of BTK therefore blocks BCR signalling, induces apoptosis, and blocks B-cell migration and adhesion. Ibrutinib therefore impacts several key pathways and functions within B cells, thereby preventing the proliferation and survival of malignant B cells in MCL.¹ Further information on the mechanism of action of ibrutinib can be found in Section 1.3.6.
Marketing authorisation/CE mark status	Ibrutinib in combination R-CHOP alternating with R-DHAP (or R-DHAox) without ibrutinib, followed by ibrutinib monotherapy ^a received a positive opinion from the CHMP on 19 th June 2025. ⁸ The marketing authorisation was subsequently granted by the Medicines and Healthcare products Regulatory Agency (MHRA) on 8 th August 2025 via the International Recognition Procedure. ^{1, 9}

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Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The marketing authorisation in the UK of relevance to this submission for ibrutinib (IMBRUVICA®) in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy^a is:¹ - For the treatment of adult patients with previously untreated MCL who would be eligible for ASCT. Ibrutinib currently has a marketing authorisation from the MHRA in the following therapeutic indications related to MCL, chronic lymphocytic leukaemia (CLL) and Waldenström's macroglobulinaemia (WM):¹ MCL: - Ibrutinib as a single agent is indicated for the treatment of adult patients with relapsed or refractory MCL. CLL: - Ibrutinib as a single agent or in combination with rituximab or obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL. - Ibrutinib as a single agent or in combination with BR is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. WM: - Ibrutinib as a single agent is indicated for the treatment of adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy - Ibrutinib in combination with rituximab is indicated for the treatment of adult patients with WM. Further details on the indications and any restrictions associated with ibrutinib are provided within the SmPC,¹ which is provided within the reference pack accompanying this submission.
Method of administration and dosage	Oral; 560 mg once daily.¹ The ibrutinib regimen is a fixed duration regimen, as follows: Induction: - Ibrutinib in combination with R-CHOP on Days 1–19 of Cycles 1, 3 and 5 (each cycle is 21 days) - R-DHAP or R-DHAOx without ibrutinib on Cycles 2, 4, 6 (each cycle is 21 days) Maintenance: - Ibrutinib daily for 24 months. Rituximab may be added as per national treatment guidelines.
Additional tests or investigations	N/A.
List price and average cost of a course of treatment	The list price of ibrutinib is £5,723.20 per 28 pack of 560 mg tablets.¹⁰
Patient access scheme (if applicable)	A simple patient access scheme (PAS) discount of ■% is in place for all ibrutinib indications funded via baseline commissioning.¹¹⁻¹³ The with-PAS price of ibrutinib is ■■■■■ per 28 pack of 560 mg tablets.

^a Treatment should start after recovery of peripheral blood counts. Rituximab may be added as per national treatment guidelines.

Abbreviations: ASCT: autologous stem cell transplant; BCR: B cell receptor; BTK: of Bruton's tyrosine kinase; CHMP: The Committee for Medicinal Products for Human Use; CHOP: cyclophosphamide, doxorubicin; CLL: chronic lymphocytic leukaemia; DHAOx: dexamethasone, high-dose cytarabine and oxaliplatin; DHAP: dexamethasone, high-dose cytarabine, platinum; MCL: mantle cell lymphoma; MHRA: Medicines and Healthcare products Regulatory Agency; N/A: not applicable; NICE: National Institute for Health and Care Excellence; PAS: patient access scheme; R-: rituximab; SmPC: summary of product characteristics; WM: Waldenström's macroglobulinaemia.

Source: MHRA Ibrutinib SmPC (2025).¹

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1.3 *Health condition and position of the technology in the treatment pathway*

MCL is a rare, high-grade and aggressive subtype of non-Hodgkin's lymphoma (NHL) with a complex aetiology that presents with an extensive range of symptoms

- MCL is characterised by the excessive proliferation of malignant B-cells in the mantle zone as a result of cyclin D1 overexpression.^{4, 14, 15}
- Each year in the UK, approximately 600 people are diagnosed with MCL;¹⁶ the majority of patients with MCL (up to 58%) are diagnosed over the age of 70.¹⁷ Owing to the non-specific symptoms and the disease's aggressive nature, MCL is often widespread at diagnosis; the majority (95%) of patients with MCL are diagnosed at an advanced stage of disease, indicating multiple nodal and/or extra nodal sites of involvement.^{4, 18}
- Patients with MCL present with a wide variety of symptoms, including fever, night sweats, swelling of the lymph nodes, low blood cell count and enlargement of the liver and/or spleen. This range of symptoms often arises from sites of extra nodal involvement such as the kidneys, gastrointestinal (GI) tract and nervous system.^{4, 14}

MCL is an incurable disease with the poorest prognosis of all types of NHL, highlighting the need for efficacious first-line treatments

- MCL is a heterogeneous disease with a variable clinical course, and as such, prognosis varies depending on a number of factors, largely the pattern of genetic and epigenetic alterations.^{14, 17} The advanced stage at which MCL is typically diagnosed negatively impacts survival.^{4, 17, 19}
- Whilst transplant-eligible patients tend to be younger and fitter than their ineligible counterparts, and as such are associated with better outcomes, many patients still experience disease relapse with the current SoC and eventually die.²⁰
- Survival rates in patients with relapsed or refractory (r/r) MCL decline following each subsequent line of treatment. Prognosis is particularly poor for patients who experience disease progression following first-line treatment highlighting the need for efficacious options at first line.^{21, 22}

MCL is associated with a significant clinical, psychological and economic burden

- In addition to the poor prognosis, MCL imposes a significant clinical disease burden in patients due its wide range of presenting symptoms.^{4, 14} These symptoms severely impair patients' quality of life (QoL), affecting physical, emotional, and psychological well-being, with delays in diagnosis further prolonging suffering.²³
- Caregivers face emotional stress, logistical challenges, and disruption to their daily lives due to patient care needs, including transportation, hospital visits, and supporting loved ones during and after intensive treatments.

The SoC for patients with previously untreated MCL who are fit enough to receive it is ASCT. ASCT is associated with substantial toxicity which exacerbates the existing disease burden to MCL patients. Furthermore, ASCT is associated with substantial costs to the National Health Service (NHS)

- The most relevant guidelines for the management of untreated MCL in the UK include the BSH guidelines and the NICE guidelines for the diagnosis and management of NHL (NG52).^{4, 24}
- Choice of first-line treatment for patients with MCL is dependent on an individual's eligibility for ASCT, based on patient fitness.

- The recommend therapy for ASCT-eligible patients is rituximab-based immunochemotherapy induction and HDT-ASCT consolidation treatment, followed by rituximab maintenance therapy; hereafter referred to as the ASCT regimen.^{4, 24}
- The ASCT regimen prolongs survival but does not prevent disease relapse.⁵ Among untreated MCL patients under the age of 66 years receiving the ASCT regimen, median progression-free survival (PFS) is 8.5 years.²⁰ Notably, patients experience significantly worse outcomes with each subsequent line of therapy, with the greatest decline in prognosis occurring after the failure of first-line therapy.²⁵
- Furthermore, current SoC with the ASCT regimen for untreated patients with MCL is associated with both short and long-term toxicities (adverse events [AEs] including anaemia, thrombocytopenia, serious infections, organ toxicity, haemorrhage, second malignancies) and prolonged immunosuppression which can lead to social isolation due to patients' susceptibility to infection.^{26, 27}
- The emotional and psychological impact of the ASCT regimen on both patients and their caregivers is also substantial. During a patient research study conducted by the Company, patients with MCL who have undergone the ASCT regimen and the caregivers of these patients (n=10) described the ASCT regimen as "isolating", "despairing", "soul destroying, mind destroying".²⁷
- In addition, treatment with the ASCT regimen requires prolonged inpatient stays which are associated with significant cost to the NHS and further exacerbates the existing disease burden on patients.^{26, 27}

The ibrutinib regimen represents an alternative first-line treatment option that offers efficacious outcomes and a tolerable safety profile for adult patients with previously untreated MCL

- It is anticipated that if recommended, the ibrutinib regimen would be positioned in line with its full marketing authorisation within in the MCL pathway as an alternative first-line treatment to the ASCT regimen in ASCT-eligible adult patients with previously untreated MCL.

The introduction of the ibrutinib regimen into the UK clinical pathway would address the significant unmet need among untreated MCL patients by providing patients and their clinicians with an effective treatment option which can delay or prevent disease progression, prolong survival, and offer an improved safety profile compared with the current SoC ASCT regimen.

- Crucially, the ibrutinib regimen removes the need for ASCT, and thus the requirement for overnight stays and extensive follow up post-ASCT procedure, which in turn, would minimise disruptions to both patients' and caregivers' lives allowing them to work, spend time with friends and maintain their way of life for longer, whilst also helping to free up valuable NHS resources.

1.3.1 *Disease overview*

Presentation

Non-Hodgkin's lymphoma (NHL) refers to a diverse spectrum of cancers that impact the lymphatic system. The lymphatic system plays a crucial role in supporting the immune system, and comprises the lymph vessels, lymph nodes, and other lymphatic organs, including the bone marrow, spleen, and thymus gland.²⁸ NHLs are categorised as low or high grade depending on how likely they are to grow and spread; that is, how aggressive the cancer is. MCL is a rare and usually aggressive type of NHL.²⁸ MCL is therefore typically classed as a high-grade lymphoma that is fast growing.²⁸ MCL is characterised by the excessive proliferation of malignant B-cells which arise from the mantle zone within the lymph node.^{4, 14, 15} These cells overexpress cyclin D1, a cell cycle gene, which contributes to the abnormal proliferation of malignant B-cells.¹⁴ Due to the aggressive nature of the cancer, it is often widespread at diagnosis.¹⁶

Disease presentation and clinical symptoms of MCL vary based on the site of involvement and as such patients with MCL present with heterogeneous symptoms. The most common signs and symptoms of MCL are swelling of the lymph nodes, enlargement of the spleen, which can lead to abdominal pain and fullness, low blood cell count (including red blood cells, white blood cells and platelets caused by bone marrow infiltration) and leukemic involvement (infiltration of cancer cells throughout various organs beyond the site of origin [bone marrow]).^{4, 14} In addition, around 40% of patients with MCL will present with 'B symptoms' including fever, night sweats, and unexplained weight loss.²⁹

Diagnosis

Diagnosis of MCL is a complex process which involves histopathological assessment, clinical assessment, frailty assessment and disease staging, which assess the extent of disease spread within the body.

In the first instance, tumour biopsies are collected from the lymph nodes and bone marrow and undergo a series of test to determine the molecular profile of the tumour.⁴ These tests include identifying the appearance and structure of the tumour (histo-morphology), the markers present on the surface or inside the tumour (immuno-phenotypic) and any key genetic mutations. In parallel, patients undergo clinical assessment of symptoms, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and fitness for immunochemotherapy treatment.⁴ Finally, disease staging is determined by tumour involvement across organs, including lymph nodes, spleen, bone marrow, and the gastrointestinal (GI) tract to classify the extent of disease spread.⁴ The Ann Arbor staging system is commonly used to classify disease stage at diagnosis, taking into account the number of lymph nodes and extra nodal sites affected.¹⁸ The Ann Arbor staging system was used to assess disease stage of patients in the TRIANGLE trial, the principal trial informing the clinical evidence for the ibrutinib regimen in this indication (see Section 2).³⁰ The four Ann Arbor stages are summarised in Table 3 below.

Table 3: Ann Arbor Staging for NHL

Stage	Definition
I	Involvement of one node or a group of adjacent nodes
II	Involvement of two or more nodal groups on the same side of the diaphragm
III	Involvement of nodes on both sides of the diaphragm OR Involvement of nodes above the diaphragm and involvement of the spleen
IV	Widespread involvement of nodes, bone marrow and organ involvement including liver or lungs

Abbreviations: NHL: Non-Hodgkin's Lymphoma.

Source: Leukemia & Lymphoma Society.¹⁸

MCL classification

MCL is primarily classified into three main subtypes depending on the locations of lymph node and extra nodal involvement. Globally, the most common subtype is classical MCL (80–90% of cases), which usually presents primarily as nodal disease with an aggressive disease progression.³¹ The second category is leukemic non-nodal MCL, which follows a more indolent disease course and reflects 10–20% of MCL cases.^{15, 31} Finally, in situ mantle cell neoplasia (ISMCL) is a rare form of MCL often discovered incidentally and frequently found alongside other lymphomas. ISMCL generally has a low risk of progressing to more aggressive disease, and its malignant potential is typically quite limited.¹⁵

Prognosis

Owing to its aggressive nature, MCL typically progresses in line with more high-grade lymphomas. A United Kingdom (UK) Haematological Malignancy Research Network (HMRN) analysis of patients with lymphoid cancer diagnosed between 2005 and 2019 (n=22,414) determined that the 5-year OS rate for patients with MCL (n=501) was 47.3% (95% CI: 35.5–58.2).³² It should however be noted that as MCL is a heterogeneous disease, it is associated with a variable clinical course and hence prognosis varies depending on a number of factors, largely the pattern of genetic and epigenetic alterations.^{4, 14} Beyond these key factors, patient characteristics including age, ECOG PS, extent of comorbidities, extra nodal presentation, high lactate dehydrogenase levels, white blood cell count and the percentage of cells in a tumour which are Ki-67 positive (Ki-67%) all impact prognosis.^{14, 17}

The majority of patients with MCL (up to 58%) are diagnosed over the age of 70 and with advanced stage disease (Ann Arbor stage III or IV).^{4, 17, 19} Both factors negatively impact survival, with overall survival (OS) decreasing with age and disease severity.³³ A systematic literature review (SLR) of MCL across the G20 countries published in 2020 found that 3-year OS rates decreased from 76–81% in patients aged ≤65 years to 46–64% in patients aged >65 years.³³ Similarly, the study found that 3-year survival rates decreased from 73–80% in patients diagnosed with stage I MCL to 48–53% in patients diagnosed with stage IV MCL.³³

In patients with MCL, prognosis is often measured by the MCL international prognostic index (MIPI) system, which allows risk to be calculated as low, medium or high based on a computed formula or a simplified score-based index (s-MIPI).¹⁴ The 5-year OS estimates for patients with MCL treated with the ASCT regimen progressively worsen depending on the MIPI score assigned at diagnosis, with low-, intermediate-, and high-risk MIPI categories having 5-year OS rates of 84%, 58%, and 40%, respectively.³⁴ Further details on the prognosis of patients with MCL, and specifically transplant-eligible patients with MCL, are provided in Section 1.3.3.

1.3.2 *Epidemiology*

MCL is a rare subtype of NHL, accounting for around 5% of all NHL diagnoses in the UK.^{16, 19} Each year in the UK, approximately 600 people are diagnosed with MCL, resulting in an average annual incidence of 0.9 cases per 100,000 people.¹⁹ Data from the HMRN estimates that there are 2,730 patients with MCL in the UK based on diagnoses from 2010–2019.¹⁹

Regarding MCL subtypes, most patients are diagnosed with classical MCL (up to 90% of patients). Of note, owing to its aggressive nature, most patients are diagnosed once their cancer is advanced (stage IV disease; 70% of patients).^{15, 29} As noted in Section 1.3.1, diagnosis at an advanced stage significantly reduces survival outcomes for patients with MCL, with 3-year survival rates up to a third lower for patients diagnosed with stage IV MCL compared to stage I MCL.³³

Several factors are associated with an increase in the incidence of MCL, including age and gender. MCL is typically diagnosed in older patients; as noted in Section 1.3.1 above, the majority (58%) of MCL cases in the UK are diagnosed in patients ≥70 years old and the median age at diagnosis is 67 (range 35–85) years old.^{19, 29} In addition, MCL is more prevalent in men, who make up the majority (65%) of cases in the UK.¹⁹

Environmental factors have been found to increase the risk of developing MCL, including Lyme disease (cutaneous borrelia burgdorferi) and pesticide exposure.¹⁴ Genetic associations have also been found to contribute to the risk of MCL, with IL-10 gene mutations and autoimmune diseases known to increase the risk of developing MCL.¹⁴ MCL can also be familial, with variants in the DNA damage repair pathway and mismatch repair genes associated with early disease onset.^{14, 35} A 2022 study in Japan of 2,066 lymphoma patients found that 9.1% of patients with MCL presented with at least one of four pathogenic germline variants tested.³⁵ The study found that four gene variants (in *BRCA1*, *BRCA2*, *ATM* and *TP53*) were associated with a particularly high risk of developing MCL compared to other lymphoma subtypes.³⁵

1.3.3 *Burden of MCL and impact on patients (and caregivers)*

Symptom burden

MCL imposes a significant clinical burden on patients due its wide range of presenting symptoms.^{4, 14} As described in Section 1.3.1, MCL commonly manifests as swollen or painful lymph nodes.¹⁴ However, extra nodal features are often responsible for initial symptoms and contribute substantially to disease burden, with 90% of patients presenting with such manifestations.¹⁷ For example, involvement of the GI tract can cause diarrhoea, nausea, indigestion and vomiting. Additionally, bone marrow infiltration can result in increased bruising or bleeding.^{16, 17} Another commonly observed symptom is abdominal pain, and pain in the lower back and extremities due to enlargement of the spleen, which is observed in 40% of patients with MCL.^{16, 17} Additional symptoms include 'B symptoms' which can present as loss of appetite (and corresponding weight loss), night sweats, fever and fatigue.²⁹ The varied symptom manifestation and often non-specific presentation also results in increased time to diagnosis. This ultimately prolongs the length of time patients experience symptoms of MCL with no treatment, which further exacerbates the symptom burden experienced by patients.³⁶ The significant burden disease symptoms place on patients is highlighted via the fact that in prior appraisals in MCL patients specifically noted that a quick reduction in symptoms is a particularly important treatment goal.¹¹

Humanistic burden

The clinical burden of MCL highlighted above has a detrimental impact on patient quality of life (QoL) versus (vs.) the general population, this burden only worsens as patients' disease progresses. The Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

literature review of QoL assessment in patients with haematological malignancies cited above demonstrated that disease symptoms impair the QoL for many patients.²³ Specifically, patients reported that symptoms including fatigue, anaemia, insomnia and difficulties with memory and concentration had a significant detrimental impact on their QoL.¹¹ Additionally, the fact that these symptoms result in non-specific presentation and subsequent delays in diagnosis further increases the length of time during which patients experience poor QoL.

In addition to the physical burden of the disease, MCL has a detrimental impact on the mental state of patients with psychological difficulties including anxiety, depression, insomnia, intimacy and mood swings reported amongst patients.¹¹ The negative impact of the disease on patients mental health has been demonstrated by a literature review of QoL assessment conducted in patients with haematological malignancies (n=7,349). The review found that decrements in QoL were observed across most domains measured, including psychological health.²³

In addition to the burden caused by the disease, the existing standard of care (SoC) for patients with untreated MCL (who are fit enough to receive it) in the UK is ASCT (as described in Section 1.3.4), which imparts a substantial clinical burden and negatively affects patient QoL. Treatment with ASCT is associated with high rates of severe side effects, several weeks of hospitalisation and intensive post-treatment monitoring.^{26, 37} During in-depth interviews undertaken as part of a patient research study conducted by the Company, patients with MCL who have undergone ASCT and the caregivers of these patients (n=10) described the process as “isolating”, “despairing”, “soul destroying, mind destroying”.²⁷ The impact of ASCT on patients and their caregivers is discussed further in Section 1.3.5.

Prognosis

MCL is an incurable disease with the poorest prognosis of all types of NHL. Transplant-eligible patients tend to be younger and fitter than their ineligible counterparts, and thus tend to have better outcomes; however, many patients still experience disease relapse and eventually die. MCL is characterised by a continual pattern of disease relapse, including amongst patients receiving the current SoC (the ASCT regimen; see Section 1.3.4).²⁰ Among untreated MCL patients under the age of 66 years receiving the ASCT regimen, median progression-free survival (PFS) is 8.5 years which translates to a median OS of 12.7 years.²⁰

In addition to the widely used oncology endpoint of PFS, failure-free survival (FFS; defined as the time from randomisation to stable disease at end of induction, progressive disease or death from any cause) is a key endpoint in MCL and therefore is commonly used to assess the efficacy of a treatment in MCL trials.³⁸⁻⁴¹ In a Phase 2 trial evaluating intensive consolidation treatment (high-dose cytarabine followed by BEAM [carmustine, etoposide, cytarabine and melphalan]) followed by ASCT in patients with newly diagnosed MCL up to the age of 65 years who were responsive to R-CHOP, FFS at 4 years was found to be 36%.⁴⁰ The clinical importance of FFS in MCL is described in detail in Section 2.6.1.

Disease relapse is associated with increased symptom burden and reduced health-related quality of life (HRQoL).²² Furthermore, after relapse, patients experience significantly worse outcomes with each subsequent line of therapy, with the greatest decline in prognosis occurring after the failure of first-line therapy.²⁵ The availability of effective first-line treatments is therefore of crucial importance in MCL.

Effect on caregivers

Given the rare nature of MCL, there are limited publicly available data on the impact of MCL on caregivers. As care is most likely provided in the informal setting by family members or close friends of the patient, the relationship between the patient and their close ones will undoubtedly be impacted by the diagnosis. A loved one diagnosed with a fatal condition and a poor survival outlook is likely to be

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associated with increased feelings of anxiety and hopelessness. In addition, the responsibilities associated with caring for a patient with MCL can place significant strain on relationships with family and friends, which may result in patients feeling isolated. Furthermore, as noted above, the current SoC for untreated MCL is an ASCT regimen during which patients are required to remain in hospital for extended periods of time to receive consolidation treatment with high-dose chemotherapy therapy (HDT) and ASCT, and then frequent hospital visits during the lengthy recovery process.²⁶ Some patients may not be fit enough to drive to hospital or may live in areas without local access or transport to an appropriate treatment centre. In many cases, patients would need a caregiver to provide transport to the infusion unit. This leads to disruption among caregivers' daily lives.²⁷ The impact of MCL, and specifically treatment with ASCT, on caregivers is discussed further in Section 1.3.5.

Economic burden

There are limited available evidence on the economic burden of MCL, as highlighted within the economic SLR (Appendix G). However, within the context of the treatment burden described above, MCL is associated with considerable healthcare resource utilisation and costs, driven by management of the multitude of adverse events (AEs) associated with MCL and the need for ongoing management. As emphasised by UK-based clinical experts at the November 2025 advisory board the current SoC (the ASCT regimen) imparts a substantial economic burden on the NHS, given the need for prolonged inpatient admissions, intensive care unit (ICU) stays, as well as extensive follow-up visits and scans given the toxic nature of treatment.⁴² Among patients undergoing HDT and ASCT, it is reported in the literature that 1 in 20 (5.0%) patients are admitted to ICU,^{43, 44} which is associated with substantial costs. Furthermore, feedback received at the November 2025 advisory board indicated that this proportion may be closer to 10%.⁴² Indirect costs, such as loss of productivity, long-term disability and caregiver support further compound the significant economic burden posed by MCL in the UK.²⁷

1.3.4 *Clinical pathway of care*

Treatment guidelines

There is a variety of clinical guidelines available in the UK for the management of MCL including the British Society of Haematology (BSH) guidelines (2023), ESMO (2025) clinical practice guidelines and NICE guidelines for the diagnosis and management of NHL (NG52).^{4, 5, 24, 45, 46} The guidelines are broadly consistent; however, there are variations in the determination of patient fitness and the length of rituximab treatment recommended for maintenance.^{4, 5, 24, 45, 46} Feedback received from UK clinical experts in MCL indicated that the BSH guidelines are most commonly used to inform management of MCL in the UK and as such, the below pathway is primarily based on these guidelines alongside NICE technology appraisal recommendations and feedback received from UK clinical experts.^{4, 42}

Current UK clinical pathway

The overall management of MCL in the UK is summarised in Figure 2 and described in further detail below. As noted in Section 1.3.3, MCL remains an incurable disease, and thus the goal of treatment is to improve patient QoL, delay remission.²⁰

Choice of first-line treatment for patients with MCL in the UK is dependent on eligibility for ASCT, which is based on patient fitness. Assessment of a patient's fitness is carried out by the medical team responsible for the patient's treatment and is based on factors including age, weight, mobility, comorbidities, and cognitive health.^{4, 47} In clinical practice, patients with MCL who are eligible for ASCT are generally <65 years old.⁴⁵ There are no MCL-specific assessments to determine patient fitness, and therefore eligibility for treatment with ASCT. The BSH guidelines recommend options such as The Geriatric 8 screening tool, The Cumulative Illness Rating Scale for Geriatrics and the Geriatric Assessment in Haematology to assess patient frailty.⁴

This submission focuses on patients who are eligible for ASCT and as such the treatment pathway discussed below is for ASCT-eligible patients only. Current SoC for patients eligible for ASCT is rituximab-based immunochemotherapy induction treatment followed by HDT conditioning and ASCT consolidation, followed by rituximab maintenance therapy, hereafter referred to as the ASCT regimen.⁴ Further detail on each component of this regimen is provided below.

The aim of induction therapy prior to ASCT is to reduce tumour burden, achieve remission, and improve the likelihood of a successful transplant by decreasing the number of malignant cells before reinfusing the patient's own stem cells.⁴⁸ As noted above, induction therapy consists of a rituximab-based immunochemotherapy. Additionally, the BSH guidelines recommend an induction regimen which contains high-dose cytarabine.⁴ In UK clinical practice the three most commonly used induction regimens satisfying these criteria are: alternating cycles of Maxi-R-CHOP and rituximab and high-dose cytosine arabinoside (R-HDAC; commonly referred to as the 'Nordic approach'), alternating cycles of R-CHOP and R-DHAP, and four cycles of R-DHAP ($\pm$ four cycles of R-CHOP; commonly referred to as the LyMA regimen).⁴⁹ Of note, UK clinical experts at a November 2025 advisory board summarised that approximately 80% of patients with MCL receive the Nordic approach in current clinical practice, with the remaining 20% of patients receiving other induction regimens.⁴²

The BSH guidelines state that no specific induction regimen is superior over another in terms of efficacy.⁴ In fact, all three of the above induction regimens lead to overall response rates (ORRs) ~90% and computed tomography (CT)-based complete response rates (CRR) >50%.⁴ The equivalency of these regimens was further supported by feedback received from UK clinical experts who confirmed that the available induction regimens in the UK are generally accepted as clinically equivalent.⁴²

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The goal of consolidation therapy with HDT-ASCT is to restore normal blood cell production.⁵⁰ Stem cells are mobilised and collected following induction treatment but prior to HDT, then reinfused following HDT to replenish the bone marrow cells lost during HDT.⁵⁰ As part of the HDT-ASCT process, patients receive a HDT conditioning regimen to kill remaining lymphoma cells following induction: BEAM (carmustine, etoposide, cytarabine and melphalan) or BEAC (carmustine, etoposide, cytarabine and cyclophosphamide) are commonly used as conditioning regimens in UK clinical practice and require inpatient admission into hospital for six days to receive the treatment via a central line.^{4, 26} Stem cells are then infused via a central line, a process which takes approximately one hour.²⁶ The final process of HDT-ASCT is engraftment: the process by which the newly infused stem cells settle in the bone marrow and begin generating blood cells.²⁶

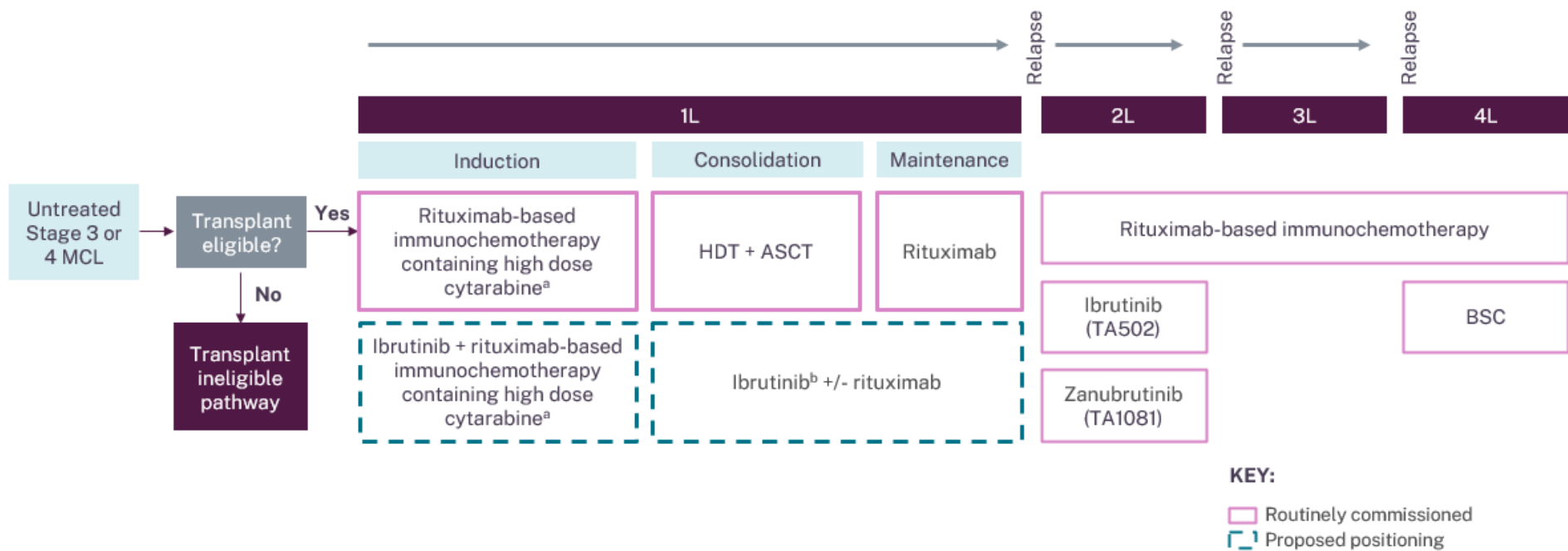
Following ASCT, the BSH recommends three years of treatment with rituximab maintenance therapy, based on the LyMA trial;^{4, 49} however, rituximab maintenance treatment is only reimbursed by NICE for two years following ASCT. As such, most regional NHS trusts recommend and prescribe rituximab maintenance for two years.^{24, 45} Feedback from UK clinical experts at the November 2025 advisory board indicated that there are discrepancies in prescribing practice across the UK, with some NHS trusts reimbursing up to three years of rituximab maintenance.⁴² Additionally, clinical experts noted that some patients may self-fund the third year of rituximab maintenance treatment.⁴²

Subsequent treatments

Unfortunately, whilst responses following treatment with the ASCT regimen are durable, ASCT is not curative for a large proportion of patients and many are likely to receive subsequent treatment. In the UK, the following treatments are reimbursed by NICE for use in patients with relapsed or refractory (r/r) MCL:⁴

- Ibrutinib [TA502] or Zanubrutinib [TA1081] for the treatment of patients relapsing after first-line immunochemotherapy^{4, 51}
- Rituximab-based immunochemotherapy (e.g. rituximab, bendamustine and cytarabine [R-BAC] and bendamustine and rituximab [BR]) for the treatment of patients relapsing after second-line therapy

Figure 2: The current MCL treatment pathway and proposed positioning of the ibrutinib regimen



^a Regimens includes the Nordic approach (Maxi-R-CHOP + R-HDAC) or R-CHOP/R-DHAP; ^b 2-year course.
Abbreviations: ASCT: autologous stem cell transplant; BSC: best supportive care; CHOP: cyclophosphamide, doxorubicin; DHAP: dexamethasone, high-dose cytarabine, platinum; HDAC: high-dose cytosine arabinoside; HDT: high-dose therapy; L: line; MCL: mantle cell lymphoma; R-: rituximab.
Source: Eyre (2023),⁴ NICE TA502,¹¹ NICE TA1081.⁵¹

1.3.5 **Unmet need**

Overview of ASCT

SoC in the UK for patients with untreated MCL who are deemed eligible is the ASCT regimen (see Section 1.3.4).⁴ However, the overall impact of ASCT on both patient and caregiver lives is widespread and significantly life-altering.²⁷

ASCT is a highly toxic treatment option which presents a considerable burden for patients, both during the induction and conditioning regimens and following completion of ASCT. Following ASCT, patients experience extreme fatigue, weakness, and prolonged inability to perform daily activities, sometimes lasting over a year.²⁷ Intense high-dose immunochemotherapy side effects, mental health impacts such as anxiety, depression, and isolation due to loss of independence and infection risk, also have a significant impact.²⁷ Patients often do not fully comprehend the intensity and complications associated with ASCT until late in the process of receiving treatment.²⁷ Beyond the physical and emotional impact of the ASCT procedure, treatment with ASCT does not guarantee long-term remission for patients with MCL. Many patients with MCL will experience refractory disease or relapse following the ASCT regimen.^{22, 52, 53} For patients with r/r MCL, the available therapeutic options are limited, and the survival outcomes decrease with each progressive line of therapy.^{33, 54}

Burden of the ASCT regimen on patients

Physical burden

Treatment with the ASCT regimen imparts a substantial physical burden on patients. As noted in Section 1.3.4, patients receiving the ASCT regimen receive conditioning treatment with HDT prior to transplant.²⁶ The side effects associated with this stage of the ASCT regimen are vast, including oral mucositis, anaemia, thrombocytopenia, nausea and vomiting.²⁶ Patients consulted as part of a patient research study conducted by the Company between July and October 2025 described the conditioning chemotherapy phase of the process as intense and overwhelming following the initial induction chemotherapy, and particularly when complications arose.²⁷ The impact of the resulting side effects from HDT treatment were also described as being much worse than anticipated.²⁷

Patients consulted as part of a patient research study conducted by the Company described the extensive **burden associated with the HDT conditioning** phase of the ASCT regimen, which follows the initial induction chemotherapy:²⁷

“They gave me the consent form. And reading through that, I was like, oh my God. It was pretty full-on, there’s a chance you can die! And I think that’s when it really, really hit me, because I understood, from what they told me, that the chemo, the first three I had, were about a four out of ten. The second lot were about a six, seven out of ten in severity... And they said the one before the stem cell transplant, which is a week’s worth, is, like, a nine and a half out of ten!” – Patient with MCL who received the ASCT regimen

“I mean, it was starting to drag you down, but each round was worse. The bounce-back time was longer. And I think, actually, in some ways you’d actually recovered from that last round, were feeling quite well, and then the thought that you’re going to go in for even stronger

chemo and feel rubbish again, it wasn't great. I think we were both like, we just want to get our lives back to normal now.” – Patient with MCL who received the ASCT regimen

“I don't think you'd probably ever realise how hard and intense that actually is. It sounds quite an easy thing, really. But it's the 6 days of chemo before [transplant] that kills you” – Patient with MCL who received the ASCT regimen

Patients additionally experience a number of side effects within the immediate recovery period following ASCT, further contributing to the physical burden of treatment. Side effects noted by patients within the immediate recovery phase of ASCT included profound fatigue and weakness, GI toxicity (which sometimes leading to dehydration, inability to eat, and re-admissions), loss of appetite, taste and weight, infections and fevers, oral mucositis and sore mouth.²⁷ Nearly half (46%) of patients undergoing ASCT will experience at least one side effect following the procedure, notably infections (bacterial [36.0%], viral [8.4%], fungal [6.6%], parasitic [0.1%] and unspecified [43.7%]), as well as GI (31.8%), neuropsychiatric (3.0%), pulmonary (2.2%) and hepatic complications (0.4%).³⁷ These treatment-associated side effects further exacerbate the existing clinical burden of MCL for patients, and contribute to the detrimental impact of MCL on patient HRQoL.

Patients and caregivers consulted as part of a patient research study conducted by the Company described the burden of **side effects during the immediate recovery period** following treatment with the ASCT regimen:²⁷

“He couldn't even walk out of his room. He was that weak and tired...” – Caregiver of a patient with MCL who received treatment with the ASCT regimen

“The night sweats are horrible. The dry mouth, that's a lot worse than ever explained to you. The lining of your mouth stops, it gets stripped out, you can peel it off. Everything tasting horrible.” – Patient with MCL who received the ASCT regimen

Psychological/QoL burden

Beyond the physical impact of treatment on patients, there is also a substantial emotional and psychological impact associated with undergoing treatment with the ASCT regimen. The side effects of the regimen can frequently lead to mood changes and depression, particularly given patients often feel a loss of independence due to side effects.²⁷ For example, severe fatigue is common and endurance can drop dramatically, leading to patients experiencing challenges with exercise and personal hobbies.²⁷ Of note, patients are also immunocompromised for several weeks following the ASCT regimen, putting them at high risk of infections; therefore, the majority of patients remain in isolation in hospital post-ASCT procedure until their blood counts have sufficiently recovered.²⁶ The risk of infections often prevents patients from socialising with friends and family, resulting in intense feelings of isolation among patients, even once discharged from the hospital.²⁷ Additionally, the anxiety associated with the vulnerability to infection negatively impacts the emotional wellbeing of both patients and their caregivers.²⁷

Patients and caregivers consulted as part of the patient research study conducted by the Company reported the detrimental impact of the ASCT regimen on their **psychological wellbeing**, including the impact of increased **vulnerability to infections**:²⁷

“I think with hindsight, I probably had a couple of panic attacks... dealing with it, not feeling well, slightly despairing ” – Patient with MCL who received the ASCT regimen

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“I was very conscious about getting another infection... that is soul destroying, mind destroying for me.” – Patient with MCL who received the ASCT regimen

“Isolation, I think, is the worst thing, Not being able to see people” – Patient with MCL who received the ASCT regimen

Long-term burden

The burden of the ASCT regimen on patients and their caregivers is persistent and long lasting; the ASCT regimen often requires major adjustments to daily lives for both patients and their caregivers. After patients are released from hospital they require intensive monitoring, with weekly follow-ups and blood transfusions.^{26, 27} During this period, it is common for patients to see an increase in symptoms, such as fatigue, and nearly half of patients (47%) experience treatment-related pain. It can take patients up to six months to recover and return to normal day to day life (such as work).^{26, 55} This long-term recovery and associated follow-up further highlights both the significant physical and psychological long-term burden existing SoC places on patients, in addition to the high cost and long-term resource use borne by the NHS.¹¹

Of note, a 2024 long-term QoL study in the United States (US) on patients with MCL who received treatment with ASCT between 2000 and 2023 (n=106; median age at ASCT of 59 years, median follow-up from treatment with the ASCT regimen of 9.3 years) identified that 18% and 16% patients reported poorer physical and cognitive function, respectively, compared with the general population.⁵⁶ These patients were also significantly less likely to be in work. Furthermore, 5–12% had more symptoms of anxiety, depression, fatigue, sleep disturbance, and pain,⁵⁶ demonstrating that the ASCT regimen continues to detrimentally impact patients wellbeing, even ~9 years post-completion of the ASCT regimen.

Burden of the ASCT regimen on caregivers

The burden of ASCT treatment and the long-term follow-up required not only impacts patients, but also significantly impacts their caregivers who, as noted in Section 1.3.3, are typically family members or close friends of the patient. The recovery period following ASCT is particularly burdensome on carers, as they are often required to provide extensive medical support during the patient's recovery. The transition from hospital to home can leave caregivers feeling solely responsible for complex aspects of the patient's ongoing care, with many patients reporting that they often feel under-prepared to manage the medical side of their loved one's recovery.²⁷ Due to patients' physical (and often mental) limitations following ASCT, caregivers frequently take on responsibilities such as medication management, monitoring symptoms, coordinating appointments and are often required to make health-related decisions and assist with daily medical tasks at home.²⁷ All of these tasks, combined with the increased stress and anxiety have a physical and psychological burden on caregivers.

Beyond the physical burden, treatment with the ASCT regimen results in increased logistical and financial burden on caregivers. This includes travel and accommodation costs associated with frequent hospital visits and unpredictable overnight stays, as well as loss of work and corresponding income. Collectively, these create significant expenses for patients and their carers.²⁷

Caregivers consulted as part of a patient research study conducted by the Company reported that the **logistical and financial burden** of treatment often fell on them.²⁷

“There's a huge financial burden having to travel and stop overnight. I mean, you're talking about thousands of pounds at a time when you really don't need the extra financial burden... I dread to think people who haven't got the means how they would cope.” – Caregiver of a patient with MCL who received treatment with the ASCT regimen

Burden of the ASCT regimen on the NHS

In addition to the substantial physical and psychological burden to patients and their caregivers, treatment with the ASCT regimen is incredibly resource intensive to the NHS. Patients must stay in hospital for up to a month during treatment and are then required to have continued follow-up for several months.²⁶ The most time intensive process of ASCT is engraftment, the process by which the newly infused stem cells settle in the bone marrow and begin generating blood cells.²⁶ This process can take 2–3 weeks or more, and during this time patients are immunosuppressed and at risk of severe infection.²⁶ Therefore, the majority of patients remain in isolation in hospital until their blood count has sufficiently recovered.²⁶ This long-term stay in hospital comes at a substantial cost to the NHS. In addition, this long-term hospital stay reduces bed capacity within healthcare settings, an aspect of care where the NHS already experiences significant resource constraints.⁵⁷ Finally, for patients undergoing HDT and ASCT, 1 in 20 (5.0%) patients are admitted to ICU, primarily due to sepsis, which further increases costs associated with the ASCT regimen.^{43, 44} Of note, at the November 2025 advisory board, all five UK-based clinical experts emphasised the considerable resource use and cost associated with ASCT.⁴²

Clinical efficacy of the ASCT regimen

In recent years, with the advance of immunotherapies and biological therapies, the benefit of ASCT consolidation treatment for MCL patients has been put into question.⁵⁸ As outlined above, the ASCT regimen is associated with a substantial treatment burden and its efficacy is associated with limitations. Many patients with MCL will experience refractory disease or relapse following the ASCT regimen.^{22, 52, 53} Once MCL progresses to a r/r state, treatment options are limited and the chances of achieving durable remission are significantly reduced, further impacting patient prognosis.⁵ Survival rates following each line of treatment decline in patients with r/r MCL. Specifically, a UK biobank observational study found that, amongst 588 patients with MCL, median OS decreased from 20.3 months following second-line treatment to just 4.5 months following fourth-line treatment.²¹ Evidence on the impact of r/r MCL on patient QoL is scarce, but it can be reasonably expected that a continued reduction is observed with each subsequent line of treatment, given the worsening prognosis and survival outcomes. As such, the availability of efficacious first-line treatments which are able to delay disease relapse and ultimately improve survival outcomes is crucial and represents a key unmet need for patients with MCL.⁵⁹ Of note, the importance of effective first-line treatments was reiterated by clinical experts at the November 2025 advisory board, with experts noting that given patient prognosis worsens with each relapse, the use of optimal therapies in the first-line treatment setting is critical to enhance patient outcomes.⁴²

Summary of unmet need

In summary, there is a clear unmet need for new, efficacious and tolerable front-line treatment options for patients with MCL which removes the need for ASCT, and thus the vast physical and psychological burden associated with current SoC. Such a treatment would not only improve Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

survival outcomes and relieve the clinical and psychological burden associated with existing SoC, but would also reduce the substantial cost and resource use borne by NHS resulting from lengthy inpatient stays, management of AEs and long-term monitoring and follow up associated with ASCT. This significant unmet need was echoed by UK-based clinical experts at the November 2025 advisory board meeting who referenced the need for a new treatment that improves clinical outcomes and reduces the resource use burden on the NHS,⁴² as well as by MCL patients interviewed about their experience undergoing treatment with ASCT (n=6).²⁷ The unmet need and subsequent desire in the clinical community for an alternative treatment to the ASCT regimen is exemplified by the clinician-driven TRIANGLE trial; (see Section 2) which assessed the efficacy and safety of a new regimen (the ibrutinib regimen; see Section 1.3.6) vs. the ASCT regimen in patients with previously untreated MCL.

Patients consulted as part of a patient research study conducted by the Company clearly indicated their **desire for alternative treatment options** in the front-line MCL setting.²⁷

“There was so many tests and so many drugs and everything surrounded with the stem cell transplant, from preparing for actually taking the stem cells to putting them back in. It was just a really intense, long process. So, if there was an easier alternative, yeah, absolutely.”

– **Patient with MCL who received treatment with ASCT**

“Definitely a hassle. Definitely a burden. It's not something that I would recommend anyone else to go through knowing what I know now.” – **Patient with MCL who received treatment with ASCT**

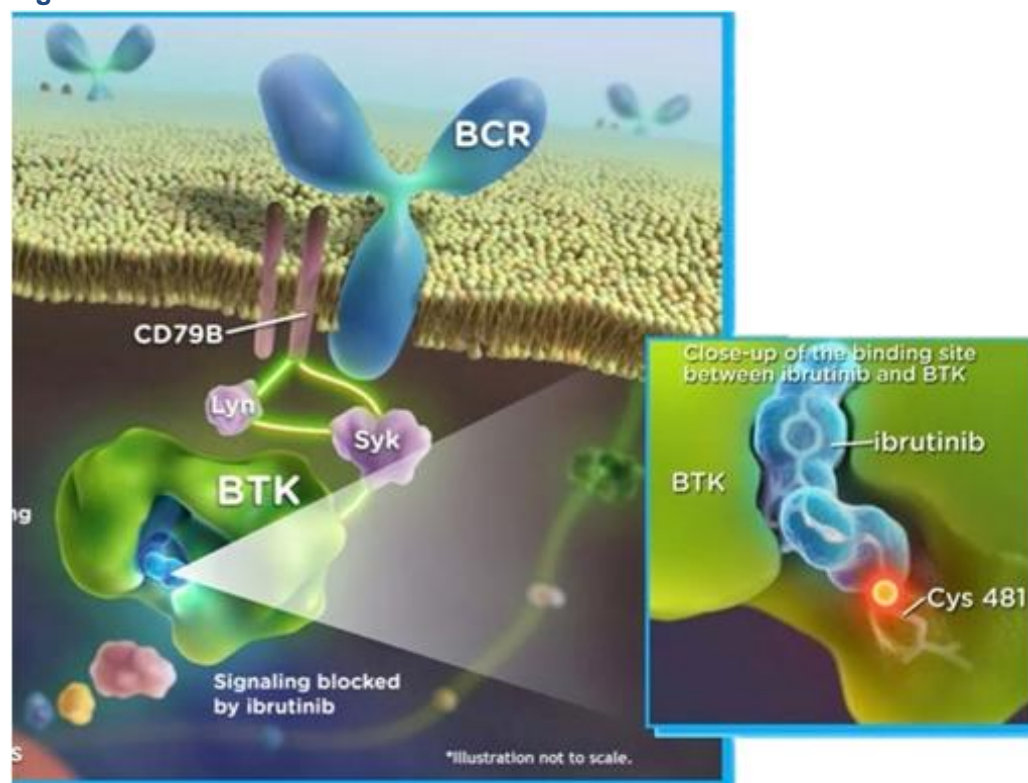
“It's as bad as I thought... I wouldn't do it again. I wouldn't do it even if the consultant said I think they say it is the best chance of putting this into a longer remission.” – **Patient with MCL who received treatment with ASCT**

“I think if it was something that was known to be effective, I would go for something else. Yeah. Be it either tablets or infusion. I think the consultant in passing said, if it comes back, we've now got a tablet we can give you that will sort it out. Didn't go into details, but I thought, “well, that's reassuring”... Given the opportunity to do something else that works, I would do something else [other than the transplant].” – **Patient with MCL who received treatment with ASCT**

1.3.6 **Proposed positioning of the ibrutinib regimen in MCL**

Ibrutinib is an orally available, irreversible covalent inhibitor of Bruton's tyrosine kinase (BTK), a key signalling kinase in the B-cell receptor (BCR) pathway for tumour cell survival and proliferation.¹ Ibrutinib forms a stable covalent bond with a cysteine residue (Cys-481) in the BTK active site, shown in Figure 3, leading to sustained inhibition of BTK enzymatic activity.¹

Figure 3: Ibrutinib mechanism of action



Abbreviations: BCR: B cell antigen receptor; BTK: Bruton's tyrosine kinase; Cys: cysteine; Syk: spleen tyrosine kinase.

Source: Ayyildiz (2014).⁷

BTK is an important signalling molecule of the BCR and cytokine receptor pathways. BTK's role in signalling through the BCR activates pathways crucial for B-cell trafficking, chemotaxis, and adhesion.¹ Ibrutinib impacts several key pathways and functions within B-cells, including those involved in the pathogenesis of MCL. Ibrutinib's inhibition of BTK blocks BCR signalling, induces apoptosis, and blocks B-cell migration and adhesion.¹

Specifically, ibrutinib inhibits:⁶⁰

- BCR activation of nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB)
- BCR activation of integrins (adhesion)
- Chemokine networks (migration/homing)

Ibrutinib in combination R-CHOP alternating with R-DHAP (or R-DHAox) without ibrutinib, followed by ibrutinib with or without rituximab maintenance, (the ibrutinib regimen) received marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) in August 2025 for the treatment of adult patients with previously untreated MCL who would be eligible for ASCT.¹

As such, it is anticipated that, if recommended by NICE, the ibrutinib regimen would be positioned in line with its full marketing authorisation within in the MCL pathway as an alternative first-line treatment to the ASCT regimen for ASCT-eligible adult patients with previously untreated MCL. This positioning is in line with the population assessed in the TRIANGLE trial, the

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principal evidence base informing the clinical evidence for the ibrutinib regimen in this submission (see Section 2).

Based on positioning ibrutinib in line with its full marketing authorisation, the only relevant comparator to the ibrutinib regimen in this indication is the ASCT regimen; comprising rituximab-based immunochemotherapy for induction, HDT-ASCT for consolidation and rituximab for maintenance, as described in Section 1.3.4.¹ The proposed positioning and relevant comparator to the ibrutinib regimen was validated by UK clinical experts, consulted as part of this submission.^{6, 42}

Value of the ibrutinib regimen

The reimbursement of the ibrutinib regimen in untreated MCL would introduce the first new treatment option for this patient population since the establishment of the ASCT regimen 20 years ago.⁶¹ The results of the TRIANGLE trial demonstrate that the ibrutinib regimen is associated with improved efficacy compared to the ASCT regimen in patients with untreated MCL (see Section 2). This is evidenced through earlier response to treatment, improved FFS, PFS and OS compared to ASCT, indicating that, across clinically significant efficacy measures, the ibrutinib regimen is superior to SoC with the ASCT regimen.³⁰ This improved efficacy demonstrates that the ibrutinib regimen can delay disease progression, ultimately resulting in improved survival outcomes for patients with MCL in the UK. These results are particularly important given the existing poor prognosis for patients treated with the ASCT-regimen in UK clinical practice. This is supported by feedback received from patients with MCL and their caregivers (n=10), who noted that “increased life expectancy and “slowing disease progression” are the most important outcomes for new MCL treatments.²⁷

As outlined in Section 1.3.5, the ASCT regimen is associated with significant toxicity, with the effects on patients’ lives often long lasting. The ibrutinib regimen has demonstrated a superior tolerability profile compared to the ASCT regimen (see Section 2.12), allowing patients to avoid serious complications associated with ASCT, including severe infections.^{26, 30} This improved tolerability profile will also positively impact patient HRQoL by decreasing the frequency, severity and duration of AEs, thereby lowering the treatment burden and maintaining patient QoL. Importantly, the removal of the need for ASCT, and thus the long-term recovery following ASCT, will greatly benefit patients and minimise the wider impact on other aspects of patients’ lives (e.g. work, finances).²⁷

The avoidance of the ASCT regimen would also drastically reduce the considerable resource use associated with the current SoC. As detailed in Section 1.3.5, treatment with the ASCT regimen is incredibly resource intensive to the NHS, with long inpatient admissions and extensive follow-up across several months.²⁶ This long-term stay in hospital comes at a substantial cost to the NHS. In contrast, the ibrutinib regimen offers greater ease of administration, and removes the requirement for overnight stays and intensive inpatient management following the induction phase. Of note, a recent German-based study developed a clinical model for first-line patients with MCL to assess the impact on hospital duration and healthcare resource use of omitting the HDT and ASCT phase of treatment by instead adopting the TRIANGLE ibrutinib regimen (see Section 2).⁶² The study identified that by omitting HDT and ASCT, ≥23 hospitalisation days can be eliminated from the treatment pathway. The elimination of long hospital stays and follow up monitoring of patients not only reduces the burden on limited hospital beds in the NHS, but also reduces disruptions to both patients’ and caregivers’ lives, and leads to improved work productivity through reduced absence. The value of lower-burden treatment options with fewer Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

hospital visits and side effects was confirmed by all patients who had undergone ASCT and their caregivers (n=10) consulted by the Company.²⁷ Likewise, UK-based clinical experts at the November 2025 advisory board emphasised that the introduction of the ibrutinib regimen into UK clinical practice would be hugely cost saving in terms of reducing resource use compared to the ASCT regimen, including through the reduction of intensive care unit (ICU) stays, inpatient admission, follow-up visits and scans. These resource savings are reflected within the economic model, as detailed in Section 3.5.⁴²

Of note, as of 2025, ESMO clinical practice guidelines have recognised the transformative potential of ibrutinib for patients with untreated MCL, and as such have recommended ibrutinib in combination with R-CHOP alternating with R-DHAP or R-DHAOx induction therapy, followed by two years of ibrutinib and three years of rituximab maintenance therapy as an option for patients with untreated MCL who are ASCT-eligible.⁵ This precedent from ESMO reflects that the ibrutinib regimen is anticipated to represent a highly impactful treatment option for patients with untreated MCL that will meet the unmet needs outlined in Section 1.3.5.

In summary, if recommended, the ibrutinib regimen will address the significant unmet need in untreated MCL patients by providing patients and their clinicians with an effective treatment option which can delay disease progression and offer an improved safety profile compared to the highly toxic current SoC with the ASCT regimen. Furthermore, the ibrutinib regimen would reduce the burden of frequent and lengthy hospital stays, allowing patients and their caregivers to work, spend time with friends and maintain their way of life for longer, whilst also helping to free up value NHS resources.

1.4 *Equality considerations*

No special considerations including issues related to equity or equality are relevant to this submission.

2 Clinical effectiveness

TRIANGLE provides direct efficacy and safety evidence on the ibrutinib regimen vs. existing SoC in UK clinical practice, in a population generalisable to patients in UK clinical practice, as validated by UK clinical experts^{42, 63}

- The Phase III TRIANGLE trial is a randomised, open-label, three-arm, parallel group, study conducted in multiple sites across Europe (EU)^a in patients ≥18 years of age and ≤65 years of age with untreated MCL who are eligible for high intensity therapy.⁶³
- TRIANGLE provides direct evidence comparing the ibrutinib regimen (Arm I) with current SoC, the ASCT regimen (Arm A), thus eliminating the need for indirect treatment comparisons and facilitating the robust generation of evidence on the relative efficacy of the two treatments.⁶³
- Data presented within this submission are based on the most recent clinical cut-off (CCO) (09 May 2024) of TRIANGLE assessed in the Full Analysis Set (FAS). The FAS included patients who provided explicit consent for their data to be included in HTA submissions or were deceased.⁶³ Further details on the FAS are provided within Section 2.3.1.

Treatment with the ibrutinib regimen substantially prolongs FFS, PFS and OS vs. existing SoC with the ASCT regimen in patients with untreated MCL

- FFS was the primary endpoint in TRIANGLE; FFS is a key measure of disease control that measures treatment efficacy based on PR and CR only, considering stable disease at the end of induction immunochemotherapy as well as progression or death as a sign of treatment failure.^{63, 64}
- At the time of the CCO, at a median time on study of [REDACTED] and [REDACTED] months in Arm I and Arm A respectively, patients treated with the ibrutinib regimen had a nominally significant 36.1% (hazard ratio [HR]: 0.639 [98.33% confidence interval (CI): 0.428, 0.953], p-value: 0.0068) reduction in the risk of stable disease at the end of induction, progressive disease or death vs. patients treated with the ASCT regimen.^{30, 63}
 - This result indicates that the ibrutinib regimen extends FFS in patients with untreated MCL, leading to delayed progression to second-line treatment. As prognosis significantly worsens upon progression to second-line treatment this finding translated to improved survival outcomes in patients with previously untreated MCL.
 - These results were found to be robust across various subgroup analyses explored; most analyses demonstrated that the ibrutinib regimen (Arm I) was associated with at least numerical improvements in FFS vs. the ASCT regimen (Arm A).⁶³
- At the latest CCO, median OS was not reached in either treatment arm, however almost twice as many OS events had occurred in Arm A vs. Arm I (60 vs. 33, respectively). Importantly, treatment with the ibrutinib regimen was associated with a nominally significant and clinically meaningful 47.8% (HR: 0.522 [95% CI: 0.341, 0.799], nominal p-value: 0.0023) reduction in the risk of death compared to the ASCT regimen.⁶³
- The OS results are further supported by the consistently numerically improved survival rates in Arm I vs Arm A observed from 6 months ([REDACTED] vs. [REDACTED]) up to 84 months ([REDACTED] vs. [REDACTED]). In addition, the KM OS curves demonstrate a clear and early separation in favour of Arm I over Arm A from as early as 6 months.^{30, 63}

^aTRIANGLE also included patients from Israel. However, these patients were not included in the Full Analysis Set informing the efficacy and safety data presented in this submission.

- PFS results were consistent with FFS results; treatment with the ibrutinib regimen was associated with prolonged PFS compared to patients treated with the ASCT regimen; a nominally significant 36.7% (HR: 0.633 [98.33% CI: 0.424, 0.946], p-value: 0.0060) reduction in the risk of progressive disease or death was observed in patients in Arm I vs. Arm A.⁶³
 - As disease progression is associated with worsening symptoms and therefore an increased clinical burden, as well as an increased risk of death, extending the time to progression is expected to translate to improvements in patient QoL and overall improvements in survival.²¹ These improvements are crucial given MCL is associated with one of the worst prognosis out of all NHLs.²⁸
- Furthermore, patients treated with the ibrutinib regimen experienced at least the same high rate and depth of response as patients treated with the ASCT regimen. These results demonstrate that the ibrutinib regimen is able to achieve at least the same depth of response as existing SoC without imparting the substantial toxicity burden, and associated reduction in QoL, currently experienced with the ASCT regimen (see Section 1.3.5).⁶³
 - The overall response rate (ORR) was comparable but numerically higher for patients in Arm I vs. Arm A (96.3% vs. 92.2%, respectively).⁶³
 - Complete response rates (CRR) were comparable but numerically higher for patients in Arm I vs. Arm A (67.2% vs. 64.7%, respectively).⁶³
- Together, these results demonstrate that treatment with the ibrutinib regimen is associated with a clear survival benefit in patients with previously untreated MCL vs. existing SoC with the ASCT regimen.

Patients can be exposed to the ibrutinib regimen for five times as long as the ASCT regimen before experiencing a similar toxicity profile, thereby demonstrating that the ibrutinib regimen is associated with an improved tolerability profile vs. the ASCT regimen

- At the CCO, the median duration of study treatment was 28.45 months for patients in Arm I vs. 5.16 months for patients in Arm A.⁶³ This is equivalent to a treatment exposure that is more than 5-fold longer for patients in Arm I compared with patients in Arm A.⁶³
- Despite this, over the whole study follow-up, the proportion of patients experiencing at least one Grade ≥ 3 treatment-emergent AE (TEAE) was comparable across treatment arms (93.2% vs. 93.3% for patients in Arm I and A, respectively).⁶³
- Furthermore, the proportion of fatal AEs experienced by patients, whilst low across treatment arms, was twice as high in patients in Arm A vs. Arm I (4.1% vs. 2.3% in Arm A and I, respectively), further highlighting the increased toxicity associated with the ASCT regimen over the ibrutinib regimen.⁶³
- These results highlight that the ibrutinib regimen is able to minimise the acute toxicities and related mortality-risk associated with existing SoC with the ASCT regimen. The importance of avoiding these AEs was highlighted by feedback received from UK clinical experts and statements during patient interviews who noted that reducing the acute toxicity associated with the ASCT regimen is a key consideration for care.^{27, 42}

The results of TRIANGLE demonstrate that if reimbursed, the ibrutinib regimen will address the significant unmet need in patients with untreated MCL for a treatment option with improved efficacy and a more manageable safety profile vs. existing SoC with the highly toxic ASCT regimen

- Overall, the results of TRIANGLE demonstrate that the ibrutinib regimen is able to delay time to treatment failure, extend time to progression and ultimately improve survival in patients with untreated MCL vs. existing SoC in UK clinical practice (the ASCT regimen).^{30, 63} As disease progression is associated with worsening symptoms and therefore an

increased clinical burden, extending the time to progression is also expected to translate into improvements in patient QoL.

- Additionally, the safety data demonstrate that the ibrutinib regimen is associated with a comparable safety profile vs. the ASCT regimen when assessed over a 5-times longer duration, thereby suggesting that the ibrutinib regimen is associated with a more manageable tolerability profile.^{30, 63}
- These findings combined suggest that the ibrutinib regimen has the potential to satisfy the existing unmet need for a treatment option with improved efficacy and a reduced toxicity burden vs. existing SoC in patients with previously untreated MCL.

2.1 Identification and selection of relevant studies

A SLR was conducted to identify relevant clinical evidence on the efficacy and safety of treatments for adult patients with previously untreated MCL eligible for ASCT. The original SLR search was conducted on the 13th September 2024 and subsequently updated twice, on the 9th May 2025 and the 30th October 2025, respectively. The SLR adhered to established methods for conducting systematic reviews and was reported in accordance with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement.⁶⁵⁻⁶⁸

Overall, the clinical SLR and its associated updates, following de-duplication of results, a total of 5,388 records across all searched were screened. After exclusion of records not meeting the eligibility criteria, 89 records were included in the SLR. An additional 16 records were identified via hand searches including conference, registry and bibliography searches, of which 14 were included based on the eligibility criteria.

Overall, 103 records were included in the SLR, of which 55 records reported on 40 unique studies evaluating induction regimens with or without consolidation/maintenance. The remaining 48 records reported the efficacy of ASCT only. A complete list of the 55 included records that report on studies evaluating induction regimens with or without consolidation/maintenance is presented in Appendix B.1. A risk of bias assessment was conducted on all included studies to standards recommended by NICE and are presented in Appendix B.1. The quality assessment of the four randomised controlled trials (RCTs) was performed using the revised Cochrane Risk of Bias (RoB) tool 2.0.⁶⁶ The Downs and Black checklist was used to assess the bias in single arm studies and the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool was used to assess non-randomised comparative observational studies.⁶⁹

Full details of the SLR methodology used to identify the clinical evidence relevant to ibrutinib in this submission, including the search and PICO strategy, PRISMA flow diagram, list of included studies, and list of excluded studies at full-text review, is provided in Appendix B.

2.2 List of relevant clinical effectiveness evidence

Of the 40 unique studies identified, only one interventional trial provided evidence on the clinical efficacy and safety of ibrutinib with immunochemotherapy in the patient population of interest for this evaluation (patients with previously untreated MCL): TRIANGLE. TRIANGLE is an investigator-initiated, Phase III, randomised, open-label, international, multicentre, three-arm, parallel group trial assessing the efficacy and safety of ibrutinib with immunochemotherapy vs the ASCT regimen in patients with previously untreated MCL who are eligible for ASCT.³⁰

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Ibrutinib in combination with R-CHOP alternating with R-DHAP (or R-DHAox) without ibrutinib, followed by ibrutinib maintenance therapy holds a marketing authorisation for use in adult patients with previously untreated MCL who would be eligible for ASCT.¹ As detailed in Section 1.2 and in line with the SmPC for ibrutinib, rituximab may be added to ibrutinib maintenance treatment as per national treatment guidelines.¹ TRIANGLE was the registrational trial supporting the licence application for ibrutinib in the indication of relevance to this submission and therefore forms the principal source of effectiveness data for this submission.³⁰

TRIANGLE

The clinical effectiveness and safety of ibrutinib with immunochemotherapy for patients with untreated MCL was assessed in TRIANGLE.

This submission is focused on data from the primary analysis, which is from the most recent clinical cut-off (CCO) of TRIANGLE (09 May 2024). TRIANGLE was an investigator-initiated trial, therefore, per Europe (EU) General Data Protection Regulation (GDPR), re-consent of TRIANGLE patients was required to use TRIANGLE data for submission to health technology assessment (HTA) bodies, such as NICE.⁷⁰ The vast majority (93% [809/870]) of the intention-to-treat (ITT) population either provided explicit consent for their data to be included in HTA submissions or were deceased at the time of CCO (09 May 2024), henceforth referred to as the Full Analysis Set (FAS).³⁰ As such, data presented within this submission are based on the FAS. Further details on the reasons for non-reconsent are provided in Section 2.4.1. Importantly, baseline characteristics were highly consistent across the ITT and FAS analysis sets, as supported by feedback received from UK clinical experts, who noted that the ITT and FAS analysis sets indicate strong alignment between populations based on baseline characteristics.⁶ The clinical experts noted that there were no clinically meaningful differences between the two patient populations. A side-by-side comparison of the baseline characteristics of patients in the ITT and FAS is presented in Appendix K.1.⁶³

An overview of TRIANGLE is provided in Table 4, with the methodology and results of the trial presented in the sections that follow.

Table 4: Clinical effectiveness evidence

	TRIANGLE (NCT02858258)
Study design	An investigator-initiated, Phase III, randomised, open-label, international, multicentre, three-arm, parallel group trial assessing whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT
Population	Adult patients aged 18–65, with previously untreated, stage II–IV MCL, with at least one measurable lesion (or bone marrow only), ECOG PS ≤2, and suitable for high-dose treatment including high-dose cytarabine-containing therapy
Intervention(s)	Arm I Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAox (Cycles 2, 4 and 6) - Ibrutinib 560 mg QD on days 1–19 of R-CHOP cycles Maintenance: - Ibrutinib 560 mg QD for two years

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	TRIANGLE (NCT02858258)
	Rituximab (according to national treatment guidelines)^a
Comparator(s)	Arm A Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAOx (Cycles 2, 4 and 6) ASCT conditioning: - High-dose therapy (THAM [fractionated total body irradiation, cytarabine and melphalan] or BEAM [carmustine, etoposide, cytarabine and melphalan]^b) and ASCT Maintenance: - Rituximab (according to national treatment guidelines)^a Arm A+I^c Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAOx (Cycles 2, 4 and 6) - Ibrutinib 560 mg QD on days 1–19 of R-CHOP cycles ASCT conditioning: - High-dose therapy (THAM or BEAM^b) and ASCT Maintenance: - Rituximab (according to national treatment guidelines)^a
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	- FFS - PFS - OS - Response rates: - Overall response rate (ORR) - Partial response (PR) - Complete response rate (CRR) - Conversion rate of PR to CR during-follow up after end of induction therapy - AEs and serious AEs
All other reported outcomes	N/A

^a As evidence supporting rituximab maintenance treatment was not yet established during the development of the study protocol, rituximab maintenance was not considered a study treatment in TRIANGLE. However, upon its implementation in national treatment guidelines, rituximab maintenance therapy was administered to patients across all three study arms per the recommendations of the site's study group. Rituximab was administered at the end of induction for Arm I and in the case of PR or CR following ASCT in Arm A. ^b Choice of THAM or BEAM was stratified per trial site before trial activation at site. ^c Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib and is therefore not relevant to clinical decision making in the UK.

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Abbreviations: ASCT: autologous stem cell transplant; BEAM: carmustine, etoposide, cytarabine and melphalan; CHOP: cyclophosphamide, doxorubicin; DHAox: dexamethasone, high-dose cytarabine and oxaliplatin; DHAP: dexamethasone, high-dose cytarabine, platinum; MCL: mantle cell lymphoma; OS: overall survival; PFS: progression-free survival; QD: one daily; THAM: fractionated total body irradiation, cytarabine and melphalan.

Source: European MCL Network (2023) TRIANGLE Protocol.⁷¹

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design

The Phase III TRIANGLE trial is a randomised, open-label, three-arm, parallel group, study conducted in multiple sites across Europe and Israel^b in patients ≥ 18 years of age and ≤ 65 years of age with untreated MCL.⁵ An overview of TRIANGLE trial design is provided in Figure 4.

TRIANGLE included patients with previously untreated MCL eligible for ASCT, with patients randomised to the following treatment arms in a 1:1:1 ratio:

- **Arm I: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)/rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin [R-DHAox]) with ibrutinib followed by 2-years of ibrutinib maintenance $\pm$ rituximab**
- **Arm A: R-CHOP/R-DHAP followed by HDT-ASCT $\pm$ rituximab maintenance**
- *Arm A+I: R-CHOP/R-DHAP with ibrutinib followed by HDT-ASCT and 2-years of ibrutinib maintenance $\pm$ rituximab*

At the time of randomisation, patients were stratified according to study group and MIPI risk group (low, intermediate, high).

For Arm A and Arm A+I, HDT with THAM or BEAM was only given to patients in complete or partial remission after induction immunochemotherapy. For patients who did not achieve remission at the end of induction immunochemotherapy (treatment failure) patients remained in the study for progression and survival follow-up.⁷¹ For Arm I and Arm A+I, maintenance therapy with ibrutinib was only given to patients who achieved complete response (CR) or partial response (PR) at the end of induction therapy or following ASCT, respectively.⁷¹ For all treatment arms, in the event of progressive disease (proven by CT scan), study treatment was stopped, and patients remained in study for survival follow-up. Any salvage therapy according to individual institutional standard could be used after stopping study treatment.⁷¹

With regards to rituximab maintenance treatment, evidence supporting the use of rituximab in this treatment setting was not established when the protocol was developed for TRIANGLE.⁷¹ Therefore, rituximab maintenance was not considered a study treatment in TRIANGLE.³⁰ However, following the publication of evidence supporting rituximab maintenance treatment,⁷² and upon its implementation into the national treatment guidelines for a participating country, rituximab maintenance was administered to patients across all arms per the recommendation of

^b The FAS does not include patients from Israel.

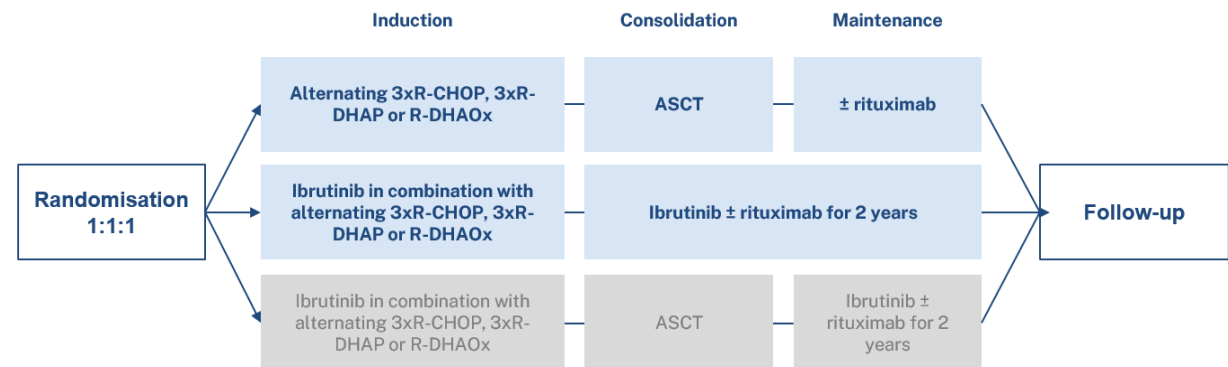
the site's study group.³⁰ This ensured the decision to administer rituximab maintenance was consistent across all treatment arms to avoid treatment-related bias. Application and management of rituximab maintenance therapy followed the standards of the participating study groups.³⁰

The maximal trial participation period per individual patient was set to 10 years:⁷³

- **Arm I:** 18 weeks induction therapy, 2 years ibrutinib maintenance^c, observation until progression and follow-up until the end of the trial
- **Arm A:** 18 weeks induction therapy, 6 weeks ASCT, observation until progression and follow-up until the end of the trial
- *Arm A+I: 18 weeks induction therapy, 6 weeks ASCT, 2 years ibrutinib maintenance^c, observation until progression and follow-up until the end of the trial*

As ibrutinib is licensed in the UK in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy^c, the use of ibrutinib in combination with ASCT is off-label.¹ Arm A+I of TRIANGLE is therefore not relevant to decision-making in the UK and as such the study methodology and results presented for the remainder of this submission are for the Arm I and Arm A only. For completeness, the results for Arm A+I are provided within the clinical study report (CSR) for TRIANGLE, provided in the reference pack accompanying this submission.

Figure 4: TRIANGLE trial design



According to the recently completely recruited LyMa trial, rituximab maintenance could have been added to all three study arms depending on national guidelines.

Abbreviations: ASCT: autologous stem cell transplant; CHOP: cyclophosphamide, doxorubicin; DHAP: dexamethasone, high-dose cytarabine, platinum.

Source: Dreyling (2024).⁵

^c Rituximab may be added to maintenance ibrutinib monotherapy as per national treatment guidelines.

2.3.2 Trial methodology

TRIANGLE methodology is summarised in Table 5.

Table 5: Summary of TRIANGLE trial methodology

Trial name	TRIANGLE (NCT02858258)
Location	165 sites across 13 European countries (Czech Republic, Germany, Italy, Portugal, the Netherlands, Belgium, Denmark, Finland, Norway, Sweden, Poland, Spain, and Switzerland) and Israel ^a
Trial design	A Phase III, randomised, open-label, multicentre, three-arm, parallel group, trial assessing whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT All patients were randomised in a 1:1:1 ratio to one of three treatment arms: • Arm I • Arm A • Arm A+I Further details of the treatment regimens included in each arm are provided within the 'method of study drug administration' row below.
Key eligibility criteria for patients	The key inclusion and exclusion criteria for TRIANGLE are summarised below. A full list of inclusion and exclusion are provided within the CSR, included in the reference pack accompanying this submission. Inclusion criteria: • Histologically confirmed diagnosis of MCL according to WHO classification • Suitable for high-dose treatment including high-dose cytarabine-containing therapy • Stage II-IV disease (Ann Arbor) • Age ≥18 years and ≤65 years • Previously untreated MCL • At least 1 measurable lesion (or bone marrow only) • ECOG/WHO performance status ≤2 • The following laboratory values at screening (unless related to MCL): ○ Absolute neutrophil count ≥1000 cells/μL ○ Platelets ≥100,000 cells/μL ○ Transaminases (AST and ALT) ≤3 x ULN ○ Total bilirubin ≤2 x ULN unless due to known Morbus Meulengracht (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 • Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods together with one of the barrier methods while on study; this should be maintained for 90 days after the last dose of study drug and 12 months after the last dose of rituximab Exclusion criteria: • Known CNS involvement of MCL • Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon

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Method of study drug administration	Arm I: R-CHOP: - Induction: IV rituximab 375 mg/m² on day 0 or 1, IV cyclophosphamide 750 mg/m² on day 1, IV doxorubicin 50 mg/m² on day 1, IV vincristine 1.4 mg/m² on day 1, and oral prednisone 100 mg on days 1–5 R-DHAP or R-DHAOx induction: - Induction: IV rituximab 375 mg/m² on day 0 or 1, IV or oral dexamethasone 40 mg on days 1–4, IV cytarabine 2 × 2 g/m² for 3 h every 12 h on day 2, and IV cisplatin 100 mg/m² over 24 h on day 1 (alternatively IV oxaliplatin 130 mg/m² on day 1), SC G-CSF 5 µg/kg daily from day 6 until recovery of WBC > 2.5 G/l (alternatively pegfilgrastim may be applied once on day 6) Ibrutinib: - Induction: 560 mg (4 x 140 mg capsules) orally QD on days 1–19 of R-CHOP cycles - Maintenance: 560 mg (4 x 140 mg capsules) orally QD for 2 years - Ibrutinib maintenance was only given to patients who achieved complete or partial response after induction immunochemotherapy Rituximab:^b - Maintenance: rituximab maintenance was only given to patients who achieved complete or partial response after induction immunochemotherapy Arm A: R-CHOP: - Induction: IV rituximab 375 mg/m² on day 0 or 1, IV cyclophosphamide 750 mg/m² on day 1, IV doxorubicin 50 mg/m² on day 1, IV vincristine 1.4 mg/m² on day 1, and oral prednisone 100 mg on days 1–5 R-DHAP or R-DHAOx: - Induction: IV rituximab 375 mg/m² on day 0 or 1, IV or oral dexamethasone 40 mg on days 1–4, IV cytarabine 2 × 2 g/m² for 3 h every 12 h on day 2, and IV cisplatin 100 mg/m² over 24 h on day 1 (alternatively IV oxaliplatin 130 mg/m² on day 1), SC G-CSF 5 µg/kg daily from D6 until recovery of WBC > 2.5 G/l (alternatively pegfilgrastim may be applied once on day 6) ASCT: - Stem cell mobilisation and harvest 5-10 µg/kg G-CSF on day 6 of DHAP cycle 3 until completion of stem cell harvest - Conditioning THAM - Total body irradiation with a total of 10 Gray (day –7, to day –5), IV cytarabine 2x1.5 g/m², every 12h for 30 minutes (day –4 and day –3), and IV melphalan 140 mg/m² (day –2) for 1 hour - Peripheral stem cells (2.0 × 10⁶/kg body weight CD34+ cells) transfused on day 0 (2 days after melphalan) - Conditioning BEAM - Combined chemotherapy with IV carmustine 300 mg/m² (day –7) for 1 hour,^c IV cytarabine 2x200 mg/m², every 12h for 30 minutes (day –6 to day –3), IV etoposide 2x100 mg/m², every 12h for 1 hour (day –6 to day –3) and IV melphalan 140 mg/m² (day –2) for 1 hour - Peripheral stem cells (2.0 × 10⁶/kg body weight CD34+ cells) transfused on day 0 (2 days after melphalan) - Only one of THAM or BEAM conditioning prior to ASCT was applied to patients who achieved complete or partial remission after induction

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	immunochemotherapy Rituximab:^b Maintenance: rituximab maintenance was only given to patients who achieved complete or partial response after induction immunochemotherapy
Primary endpoint	The primary endpoint of TRIANGLE was FFS, defined as the time from randomisation to stable disease at end of induction immunochemotherapy, progressive disease, or death from any cause, whichever came first.
Secondary endpoints	- OS - PFS - ORR - CRR - PR to CR conversion rate - TEAEs - SAEs - AESIs - Other significant AEs
Pre-planned subgroups	Pre-specified subgroup analyses of the key TRIANGLE trial endpoints were performed for FFS. The following subgroups were considered: - MIPI risk group (low, intermediate, high) - Ki-67 index ($\geq 30\%$, $< 30\%$) - Cytology of MCL (blastoid or pleomorphic, classic or small cell, not done) - p53 expression ($> 50\%$, $\leq 50\%$) - Remission status (CR, PR) at end of induction immunochemotherapy (for DOR) - Remission status after ASCT months after end of induction immunochemotherapy (for DOR from ASCT) - Sex - Rituximab maintenance^b
Duration of study and follow-up	The study was initiated on 25 July 2016 (which corresponds to the date the first patient signed the informed consent form). At the latest CCO the median time on study was ■■■ months and ■■■ months for Arm I and Arm A, respectively.

^a The FAS does not include patients from the ITT in the Israeli study group as it was not possible to re-consent these patients due to the ongoing geopolitical situation. ^b As evidence supporting rituximab maintenance treatment was not yet established during the development of the study protocol, rituximab maintenance was not considered a study treatment in TRIANGLE. However, upon its implementation in national treatment guidelines, rituximab maintenance therapy was administered to patients across all three study arms per the recommendations of the site's study group. Rituximab was administered at the end of induction for Arm I and in the case of PR or CR following ASCT in Arm A. ^c The availability of carmustine could be challenging at some sites. Instead, TEAM (Thiotepa 5 mg/kg twice a day on Day -7) could be considered based on a retrospective EBMT comparison.⁷⁴

Abbreviations: ALT: alanine aminotransferase; AE: adverse event; ASCT: autologous stem cell transplant; AST: aspartate aminotransferase; BEAM: chemotherapy regimen (carmustine, etoposide, cytarabine, melphalan); CCO: clinical cut off; CNS: central nervous system; CR: complete response; CRR: complete response rate; DOR: duration of response; EU: European Union; FFS: failure-free survival; ICH: International Conference on Harmonisation; IV: intravenous; MCL: mantle cell lymphoma; OS: overall survival; ORR: objective response rate; PFS: progression-free survival; PR: partial response; QD: once daily; SAE: serious adverse event; THAM: total body irradiation; ULN: upper limit of normal.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

2.3.3 **Baseline characteristics**

The baseline demographics and disease characteristics presented are based on the FAS from the 09 May 2024 CCO, as described in Section 2.3.1. A summary of the baseline demographic and disease characteristics of patients in Arm I and Arm A of TRIANGLE is provided in Table 6 below.

Overall, baseline demographic characteristics were well balanced across treatment arms, as supported by feedback received from five UK clinical experts during the November 2025 advisory board.⁴² Across both treatment arms, baseline demographics such as sex, weight and body mass index (BMI) were well balanced and reflective of UK clinical practice. Patients had a median age of 57 years (range 27, 65) across both treatment arms; which is consistent with UK clinical practice in which ASCT is only suitable for patients ≤ 65 years (see Section 1.3.2).⁶³ Furthermore, as MCL most commonly occurs in men, the higher proportion of males in TRIANGLE (Arm I: 79.9%, Arm A: 76.2%; Table 6) is in line with UK clinical practice (see Section 1.3.2).⁶³

In addition, disease characteristics, including MIPI risk group, ECOG PS and Ann Arbor stage of MCL, were highly aligned across treatment arms.⁶³ The majority of patients presented with low risk disease as measured by MIPI (57% in Arm I and Arm A) and an ECOG PS of either 0 (70% in Arm I and 72% in Arm A) or 1 (28% in Arm I and 27% in Arm A).⁶³ This is aligned with the population of patients who would be fit enough to receive HDT-ASCT in UK clinical practice. Furthermore, the majority of patients presented with stage IV disease (84% in Arm I and 88% in Arm A).⁶³ This is reflective of the UK patient population, as the majority (up to 95%) of patients with MCL are diagnosed at an advanced stage of disease with multiple nodal and/or extra nodal sites of involvement.^{4, 18} The often late-stage diagnosis of MCL is reflective of the non-specific symptoms, which delay diagnosis, and the disease's aggressive nature (see Section 1.3.2).⁶³

In TRIANGLE, over half of patients received rituximab maintenance, this is slightly lower than the anticipated use in UK clinical practice; feedback received from five UK clinical experts indicated that 85% of patients in both arms would be anticipated to receive rituximab maintenance in clinical practice.^{42, 63} Whilst the proportion of patients receiving rituximab maintenance therapy was slightly lower in TRIANGLE than the expected usage in UK clinical practice, the use of rituximab maintenance was well balanced between treatment arms (60% vs 63% in Arm I and A, respectively). Therefore, this is not anticipated to impact the generalisability of the observed relative treatment effect of Arm I vs. Arm A from TRIANGLE to UK clinical practice. In order to understand the uncertainty associated with this discrepancy, an analysis was conducted in which TRIANGLE data (both Arm I and Arm A) were adjusted to reflect the proportion of patients estimated to receive rituximab maintenance therapy in UK clinical practice. The methods of this adjustment, and the subsequent results are presented in Section 2.9. The following sections present the unadjusted FAS analyses.

Overall, the baseline demographic and disease characteristics of patients in Arm I and Arm A of the FAS were found to be well balanced between treatment arms and aligned to the population of patients who would be anticipated to receive ibrutinib in UK clinical practice. This was supported by feedback received from five UK clinical experts who noted that the baseline demographic and disease characteristics of the FAS population were generalisable to ASCT-eligible patients with untreated MCL in the UK, with the exception of the slightly reduced rituximab maintenance usage.⁴²

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Table 6: Baseline demographics and disease characteristics in TRIANGLE (Full Analysis Set)

Baseline Characteristic	Arm I (N=268)	Arm A (N=269)
Age, years		
Mean (SD)		
Median (range)	57.0 (27, 65)	57.0 (31, 65)
≥65 years, n (%)	8 (3.0%)	17 (6.3%)
Sex, n (%)		
Female	54 (20.1%)	64 (23.8%)
Male	214 (79.9%)	205 (76.2%)
Race, n (%)		
White	268 (100%)	264 (98.1%)
Other	0	5 (1.9%)
Weight, kg		
Mean (SD)		
Median (range)		
BMI, kg/m²		
Mean (SD)		
Median (range)		
MIPI risk group		
Low risk	152 (56.7%)	153 (56.9%)
Intermediate risk	76 (28.4%)	75 (27.9%)
High risk	40 (14.9%)	41 (15.2%)
ECOG PS		
0	187 (70.0%)	191 (71.8%)
1	75 (28.1%)	71 (26.7%)
2	5 (1.9%)	4 (1.5%)
Rituximab maintenance		
Yes	160 (59.7%)	168 (62.5%)
No	108 (40.3%)	101 (37.5%)
Ann Arbor stage		
I	0	1 (0.4%)
II	16 (6.0%)	8 (3.0%)
III	26 (9.7%)	22 (8.2%)
IV	226 (84.3%)	236 (88.4%)

Abbreviations: BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; FAS: Full Analysis Set; MIPI: MCL international prognostic index; PS: performance status; SD: standard deviation.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

2.4 Statistical analysis and study groups in the relevant clinical effectiveness evidence

2.4.1 Study population and patient disposition

Patients were enrolled in TRIANGLE between 29 July 2016 and 28 December 2020 across 165 sites in 14 countries.^{63, 75}

Analysis sets

A summary of the analysis sets included in TRIANGLE is presented in Table 7.

TRIANGLE was conducted by the EU MCL network group across 13 European countries and Israel. As noted previously in Section 2.2, per EU GDPR legislation, study patients had to provide explicit permission for their data to be included in a dossier for global HTA submissions. As a result, the FAS presented in this dossier is limited to patients who either provided explicit consent in an Informed Consent Form (ICF) for their data to be included or were deceased.³⁰ At the 09 May 2024 CCO, 93% of patients originally randomised met these criteria. Consequently, data for 22 patients in Arm I and 19 patients in Arm A were not included in the FAS analysis set and are not included within this submission.⁶³ The following reasons were provided by the EU MCL network group for why consent could not be obtained:³⁰

- Withdrawal of consent prior to consenting for their data to be included in HTA submissions: Arm I: █ patients, Arm A: █ patients
- Lost to follow-up: Arm I: █ patients, Arm A: █ patients
- Refusal to consent: Arm I: █ patients, Arm A: █ patients
- Other: Arm I: █ patients, Arm A: █ patients

It should be noted that owing to the geopolitical situation in Israel throughout the consenting period (Q3 2023 to Q2 2024), consent was not obtained from any of the Israeli patients for their data to be included in HTA submissions.³⁰ As such, no Israeli patients are included in the FAS presented within this submission; the exclusion of these patients from the FAS is not anticipated to impact the generalisability of the results to patients in the UK, as supported by feedback received from UK clinical experts.⁶

Table 7: Analysis sets in TRIANGLE

Analysis set name	Analysis set definition	Arm I, n	Arm A, n
Intent-to-treat	All randomised patients with confirmed MCL who started induction immunochemotherapy according to the randomly allocated treatment arm	290	288
Full Analysis Set	All randomised patients who have provided explicit consent for their data to be included by the Applicant for global HTA submissions as per the European General Data Protection Regulation (GDPR) and patients who were deceased	268	269
Safety Analysis Set	All patients of the FAS who received at least 1 dose of study treatment. Patients are presented according to their actual treatment received regardless of their randomised treatment arm	265 ^a	268

^a Three patients who were randomly assigned to Arm I received ASCT and therefore were considered part of Arm A+I for safety analysis and reporting.

Abbreviations: ASCT: autologous stem cell transplant; FAS: Full Analysis Set; HTA: health technology assessment; MCL: mantle cell lymphoma.

Source: Dreyling (2024),⁵ EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

Patient disposition

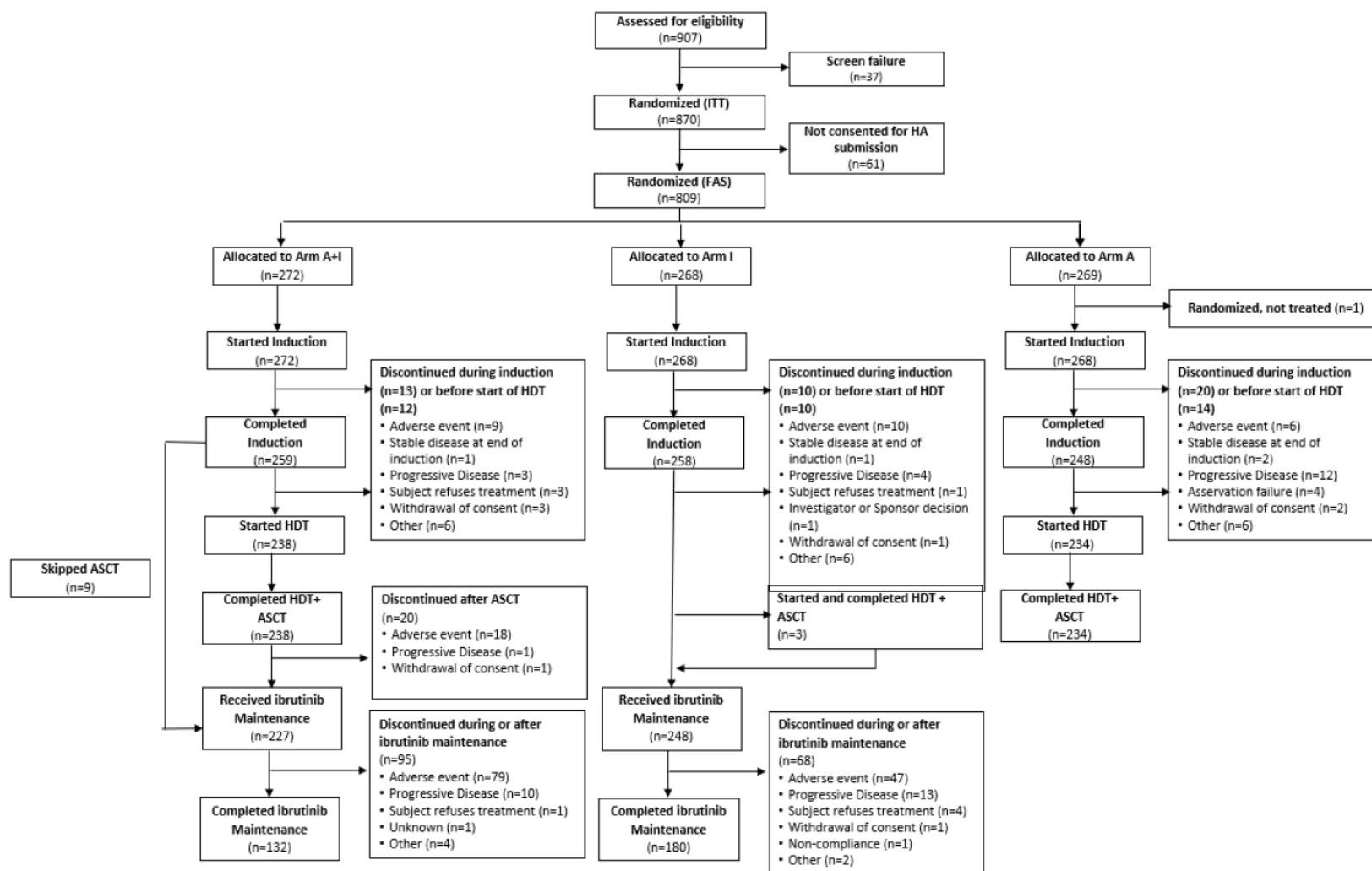
As of the 09 May 2024 CCO, a total of 809 (93% of ITT) patients were randomised and either provided explicit consent for their data to be included in a dossier for global HTA submissions or were deceased (268 patients to Arm I, 269 patients to Arm A and 272 patients to Arm A+I) and were thus included in the FAS.⁶³ A summary of patient disposition is presented in Figure 5. Out of 809 patients, 127 patients (15.7%) had died and were considered to have completed the study (33 [12.5%] patients in Arm I, 60 [22.4%] patients in Arm A and 34 [12.4%] patients in Arm A+I), and 665 (82.2%) patients remained ongoing. Seventeen (2.1%) patients discontinued participation, all of whom discontinued due to withdrawal of consent.⁶³

Of the 809 patients in the FAS, 808 (99.9%) patients received study treatment (one participant in Arm A did not receive study treatment). All patients had either discontinued or completed study treatment. The majority of patients completed induction immunochemotherapy treatment with or without ibrutinib (Arm I: 258 [96.3%]; Arm A: 248 [92.2%]). Subsequently, 234 (87.0%) patients in Arm A started and completed HDT followed by ASCT. Of the 248 patients in Arm I who completed the induction phase and continued study treatment in the maintenance phase, a total of 180 (72.6%) patients completed ibrutinib maintenance treatment.⁶³

Overall, a total of 262 (32.4%) patients^d discontinued their study treatment regimen, with AEs (21.3% in Arm I and 2.2% in Arm A) and progressive disease (6.3% in Arm I and 4.5% in Arm A) being the most common reasons for treatment discontinuation. With the maintenance period being the longest treatment phase (24 months compared to approximately 18 weeks in the induction phase), most study treatment discontinuations occurred during the maintenance period.⁶³

^d This includes patients in Arm A+I.

Figure 5: Patient disposition from TRIANGLE (Full Analysis Set)



Abbreviations: ASCT: autologous stem cell transplant; FAS: Full Analysis Set; HDT: high-dose therapy; HTA: health technology assessment; ITT: intention-to-treat.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

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2.4.2 Statistical methods

The statistical methods of TRIANGLE are summarised in Table 8.

The statistical analysis plan (SAP) pre-specified in the protocol (version 1.1, 18 December 2015) was developed by the study sponsor (European MCL Network), prior to study start. The protocol-specified primary analysis used a one-sided 5% overall significance level across three pairwise comparisons, corresponding to a one-sided 1.67% significance level per comparison after Bonferroni correction for multiple comparisons. A one-sided hypothesis test using the log-rank test statistic for FFS was performed for each comparison: Arm A vs Arm I, Arm A+I vs Arm A, and Arm A+I vs Arm I. However, considering the hypothesis testing of Arm A vs I was one sided to detect superiority of A vs. I, superiority of I vs A couldn't be concluded from the protocol-specified analyses.

The Medical Products Agency advised the Company to perform supplementary analyses in accordance with EMA guidance to provide a comprehensive evaluation of the study data. As such, supplementary analyses were performed to support regulatory assessment and decision making. While these supplementary analyses were not part of the prespecified SAP, the supplementary SAP was prepared prior to the transfer of the full patient-level dataset to the Company.⁶³

The TRIANGLE CSR therefore includes not only the results of the original pre-specified (one-sided tests at 0.05/3 significance level for each test), but also supplementary analyses based on two-sided alpha at 5% significance level (i.e., two-sided test at 1.667% significance level for each pairwise test). The two-sided tests were used to analyse the efficacy data presented in this submission, given they are powered to detect superiority of either the ASCT regimen or the ibrutinib regimen and are described in Table 8 below. As this significance test was not pre-specified, results deemed significant through the two-sided tests are referred to as nominally significant throughout the submission.

Table 8: Statistical methods for the primary analysis of TRIANGLE

Trial name	TRIANGLE
Hypothesis objective	Primary - The primary objective of the trial was to establish one of three study arms, R-CHOP/R-DHAP followed by ASCT (control arm A), <i>R-CHOP + ibrutinib/R-DHAP followed by ASCT and followed by ibrutinib maintenance^a (experimental arm A+I)^b</i>, and R-CHOP + ibrutinib/R-DHAP followed by ibrutinib maintenance^a (experimental arm I) as future standard based on the comparison of FFS assessed by central medical EU MCL Network case evaluation of investigator assessment Secondary - The secondary efficacy objective was to compare the efficacy of the three treatment groups in terms of secondary efficacy endpoints - Another secondary objective was to determine the safety and tolerability of ibrutinib during the entire treatment period and to compare the safety profile of the three treatment groups in terms of secondary toxicity endpoints

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Trial name	TRIANGLE
Statistical analysis	Analyses of the primary and secondary endpoints presented within this submission were conducted on the Full Analysis Set (FAS), comprised of patients from the intention-to-treat (ITT) analysis set who consented at the time of the CCO. Further details on the FAS are provided in 2.4.1. As the one-sided tests pre-specified within the protocol (version 1.1. 18 December 2015) were powered to detect superiority of the Arm A vs. Arm I (or the superiority of A+I vs. A or A+I vs. I but not the superiority of Arm I vs. Arm A), supplementary analyses with two-sided statistical tests were pre-specified in the supplementary SAP in line with the convention for regulatory decision-making purposes. These tests were pre-specified prior to receipt of patient level data. As the two-sided tests were powered to detect superiority of either Arm A or Arm I, these tests were used to analyse the efficacy data presented in this submission in line with the analyses described in the supplementary SAP, and are described in more detail below. Analysis of primary endpoint • Derivation of FFS used 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 counted for FFS evaluation • Two-sided unstratified log-rank tests for statistical significance at the 5% level (with a 2-sided 1.67% significant level for each treatment comparison) were conducted. Results were provided in the form of Arm I vs. Arm A as compared with Arm A vs. Arm I • An unstratified Cox's regression model with study treatment (Treatment groups) as the sole explanatory variable were performed to provide hazard ratio with two-sided 95% CIs Assumptions: • Noninformative censoring was assumed for all types of censoring • Identical baseline hazards between treatment groups Analysis of secondary endpoints As the analyses for the secondary endpoints were pre-specified as descriptive in the protocol (multiplicity control was not pre-specified for secondary endpoints), all analyses of secondary endpoint were descriptive rather than inferential in nature. • The analysis of the PFS endpoint was conducted using the same approach as for the FFS endpoint including use of the prespecified statistical methodology of tSPRT for controlling the overall alpha for the planned sequential analyses within each pairwise comparison • OS was described by Kaplan-Meier plots with all groups presented in one plot. The OS distribution and median OS with its two-sided 95% CI was estimated using the Kaplan-Meier method. OS was analysed using the unstratified log-rank test for

Trial name	TRIANGLE
	treatment comparison • ORR and CRR were estimated according to the crude proportion of confirmed responders (PR or CR) and summarised by treatment arm. CRR, ORR, and PR to CR conversion rates were compared using relative risk with their associated two-sided 95% CIs Safety analyses All safety analyses were conducted on the safety analysis set based on actual treatment received, unless otherwise specified. Safety was analysed using the incidence and severity of AEs and laboratory test results. The baseline value for safety analyses was defined as the value collected at the time closest to and prior to the start of study treatment Subgroups For the primary efficacy endpoint (FFS), subgroup analyses were performed with respect to the following subgroups with sufficient sample size. ○ Sex (male/female) ○ MIPI risk group (low/medium/high) ○ Ki-67 index (<30%/≥30%) ○ Cytology (blastoid or pleomorphic/classic or small cell/not assessed) ○ p53 expression (≤50%/>50%) ○ Rituximab maintenance (yes/no) The subgroup analyses were performed using the multivariate Cox regression model that included treatment group and subgroup indicator as main effects and treatment-by-subgroup interaction in the model. Statistical tests were done on the treatment-by-subgroup interaction terms. Hazard ratios between each pair (A vs. I, A+I vs. A, and A+I vs. I)^b of the three treatment groups within each subgroup level and their CI were calculated using non-stratified Cox regression model. Subgroup analysis results were presented graphically in a forest plot.
Sample size, power calculation	The following assumptions were used to estimate the sample size and the trial duration as per the pre-specified protocol, as such these assumptions relate to the ITT population rather than the FAS population. • Randomisation period of up to 5 years • Additional follow-up period of up to 5 years • Randomisation rate of 174 per year • Allocation ratio of 1:1:1 • Drop-out rate 5% of randomised patients • Three pairwise log-rank tests for FFS with local one-sided significance level 0.05/3; overall significance level one-sided 5% • FFS curve for control arm A as estimated from the experimental arm of MCL Younger trial of the European MCL Network (clinical cut-off date April 7, 2013) • Power 95% to detect an FFS superiority of A vs. I (hazard ratio [HR] 0.60, 5-year FFS: 64.8% vs. 48.5%) • Power 90% to detect an FFS superiority of A+I vs. A and of A+I vs. I (HR 0.60, 5-year FFS: 77.1% vs. 64.8%)

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Trial name	TRIANGLE
	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 Up to 870 patients from up to 250 international sites were planned to be enrolled.^c The maximal trial duration will 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. The sample size and trial duration calculations were done using the Planning and Evaluation of Sequential Trials Version 3 software to adjust for the sequential statistical design.
Data management, patient withdrawals	In general, the study consists of the following study phases: Screening Phase: Period of up to 28 days (i.e., upon informed consent) prior to first treatment Treatment Phase: The overall treatment phase is defined as the period between the date of the first dose of study drug and the date of the last dose of study drug (or date of ASCT when applicable) Observation or Follow-up: From after the last dose of study drug (or date of ASCT when applicable) until death, loss to follow up, withdrawal of consent or end of the study, whichever occurs first Unless specified otherwise, the baseline value is defined as the last non-missing value collected within 28 days before or on the administration of the first dose of study medication. For patients who have been randomised but not treated, the randomisation date will be used as the reference date for baseline value calculation. Safety assessments were presented chronologically by study day as described below. Unless specified otherwise, the date of first dose of study treatment (randomisation date for patients who have been randomised but not treated) was used as the reference date for study day calculation. Data censoring was applied for the outcome analysis as follows: - In patients with complete or partial response at the end of induction therapy and without progression or death, FFS was censored at the last adequate disease assessment date. Patients without any lymphoma disease evaluation during or at the end of induction were censored one day after randomisation - For PFS, patients alive without progression at latest follow-up will be censored at the latest lymphoma assessment date - In patients without documented death during observation time, OS was censored at the last contact date alive

^a Rituximab maintenance was added as per national treatment guidelines. ^b Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib and is therefore not relevant to clinical decision making in the UK. ^c A total of 809 patients provided explicit consent for their data to be included in HTA submissions or were deceased and are included in the FAS.

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; CCO: clinical cut off; CMH: Cochran-Mantel-Haenszel; FFS: failure-free survival; HR: hazard ratio; I: ibrutinib; ITT: intention to treat; MCL: mantle cell lymphoma; MUE: median unbiased estimate; OS: overall survival; PFS: progression-free survival; PR: partial response; CR: complete response; ORR: objective response rate; CI: confidence interval; tSPRT: truncated sequential probability ratio test; SAP: statistical analysis protocol.

Source: J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

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Definition of outcome measures

A variety of outcomes were employed in TRIANGLE to explore the efficacy of ibrutinib with immunochemotherapy vs. ASCT with immunochemotherapy in patients with untreated MCL. Definitions for these outcomes are presented in Table 9.

Table 9: Definitions for outcome measures in TRIANGLE

Outcome measure	Definition
Primary outcome	
FFS	Defined as the time from randomisation to stable disease at the end of induction immunochemotherapy, progressive disease, or death from any cause, whichever occurred first. FFS was assessed by central medical EU MCL Network case evaluation of investigator assessment.
Key secondary outcomes	
OS	Defined as the time from randomisation to death. In patients without documented death during observation time, overall survival was censored at the last contact date alive. If the last contact date is before randomisation, OS was censored one day after randomisation.
PFS	Defined as the time to progression or death from any cause. Patients alive without progression at latest follow-up were censored at the latest lymphoma assessment date. PFS was calculated from randomisation. PFS was assessed by central medical EU MCL Network case evaluation of investigator assessment.
Overall response rate	Defined as the proportion of patients with a best overall response of CR or PR during the study. Missing and non-evaluable responses were treated as a non-response. Response assessments were determined by the central medical EU MCL Network case evaluation of investigator assessment based on the Revised Response Criteria for Malignant Lymphoma. ⁷⁶
Complete response rate	Defined as the proportion of patients with a best overall response of CR during the study. Missing and non-evaluable responses were treated as a non-response. Response assessments were determined by the central medical EU MCL Network case evaluation of investigator assessment based on the Revised Response Criteria for Malignant Lymphoma. ⁷⁶
PR to CR conversion rates	Defined as the percentage of patients with documented CR during follow up after end of induction immunochemotherapy among those with PR at the end of induction immunochemotherapy.

Abbreviations: CR: complete response; EU: European; FFS: failure-free survival; MCL: mantle cell lymphoma; OR: overall response; OS: overall survival; PFS: progression-free survival; PR: partial response.

Source: J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).⁷³

2.5 Critical appraisal of the relevant clinical effectiveness evidence

TRIANGLE was critically appraised using the revised Cochrane RoB tool 2.0 based on the Dreyling 2024 study publication.^{66, 75} This risk of bias assessment contains five distinct domains, where each domain is judged as having a low risk of bias, some concerns, or high risk of bias, with an overall judgment for the study derived from the domain-level evaluations.

The results from the quality assessment are presented in Table 10. These results show that TRIANGLE is associated with a low risk of bias across all domains assessed, demonstrating the study to be of high quality, despite its open-label nature.

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Table 10: Quality assessment of TRIANGLE using the revised Cochrane Risk of Bias tool

Domain	Risk of Bias	Justification
Bias arising from the randomisation process	Low	Randomisation was implemented in the electronic data capture system, blocked and stratified according to study groups and MIPI risk groups and used computer-generated random numbers with unpredictable seed. In addition, baseline characteristics were well balanced between the arms.
Bias due to deviations from intended interventions	Low	The primary analysis on the FAS was done via intention to treat principals. Discontinuations due to reasons such as progression, AEs, MCL diagnosis rejection, patient decision, COVID-19 death and suicide were small.
Bias due to missing outcome data	Low	Efficacy analyses were performed on the FAS via the intention-to-treat principal. Outcome data was collected for nearly all randomised patients.
Bias in measurement of the outcome	Low	Response assessments were performed by the investigator, based on physical examinations, preplanned CT scans, laboratory results, and bone marrow examinations applying the Revised Response Criteria for Malignant Lymphoma. FFS, OS and PFS are objective outcomes, so differential ascertainment is unlikely.
Bias in selection of the reported result	Low	The outcomes in the trial were reported according to pre-specified analysis plans. The timing of interim analyses was pre-specified in the protocol and the disclosure of results was permitted after formal decision of each statistical test.

Abbreviations: AE: adverse event; CT: computed tomography; FFS: failure-free survival; ITT: intention-to-treat; MCL: mantle cell lymphoma; MIPI: MCL international prognostic index; mITT: modified intention-to-treat; OS: overall survival; PFS: progression-free survival.

2.6 Clinical effectiveness results of the relevant studies

Efficacy results for the primary and key secondary endpoints for the FAS from the latest CCO (09 May 2024) of TRIANGLE are provided in Sections 2.6.1–2.6.4 below.

2.6.1 FFS (primary endpoint)

- After a median time on study of ■■■ and ■■■ months in Arm I and Arm A, respectively, patients in **Arm I were associated with a nominally significant 36.1% reduction in the risk of stable disease at the end of induction, progressive disease or death** (i.e. prolonged FFS) vs. patients in Arm A.^{30, 63}
- As treatment guidelines for MCL state that stable disease is an indication for salvage treatment, and is therefore a sign of treatment failure, the observed improvements in FFS demonstrate the **superior efficacy of the ibrutinib regimen** compared with existing SoC with the ASCT regimen in patients with previously untreated MCL.⁶⁴

The primary endpoint of TRIANGLE is FFS, defined as the time from randomisation to stable disease at end of induction, progressive disease or death from any cause, whichever occurred first, as assessed by central EU MCL Network case evaluation of investigator assessment.⁶³

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As unanimously agreed by five clinical experts consulted during a November 2025 advisory board, FFS represents a key endpoint for the measure of treatment efficacy in MCL.⁴² FFS is similar to PFS, however it measures treatment efficacy based on PR and CR only and therefore considers achieving stable disease at the end of induction immunochemotherapy as a sign of treatment failure, in addition to progressed disease and death. As such, FFS represents an extension of PFS, in which stable disease is also considered an event. According to current treatment guidelines for MCL, failure to achieve treatment response (defined as PR or CR) to induction immunochemotherapy is an indication for salvage treatment, as only patients achieving at least a PR can proceed to the next treatment phase.^{5, 64} Therefore, FFS is a more appropriate measure of disease control and treatment efficacy than PFS in this patient population, as validated by five UK clinical experts.⁴² The importance of the inclusion of stable disease at the end of induction as a treatment failure event (alongside disease progression or death) in MCL, is demonstrated by its widespread use as either a primary or secondary endpoint in investigator-initiated clinical trials in MCL.³⁸⁻⁴¹

A summary of FFS results for the FAS at the May 2024 CCO is provided in Table 11 and a Kaplan-Meier (KM) plot for FFS is presented in Figure 6.

After a median time on study of [REDACTED] and [REDACTED] months in Arm I and Arm A respectively, median FFS was not reached in either arm, however, the number of events observed were significantly higher in Arm A (87/269 [including 5 stable disease at end of induction]) vs. Arm I (61/268 [including 1 stable disease at end of induction]).³⁰ These differences translated to a nominally significant 36.1% reduction in the risk of stable disease at the end of induction, progressive disease or death in Arm I vs. Arm A (hazard ratio [HR]: 0.639 [98.33% confidence interval [CI]: 0.428, 0.953], p-value: 0.0068).⁶³ This reduction in risk is supported graphically by the KM curves for FFS which demonstrate a clear and early separation in KM curves favouring Arm I over Arm A.⁶³ In addition, FFS rates were consistently higher in Arm I vs Arm A from month 6 ([REDACTED] vs [REDACTED], respectively) up to month 84 ([REDACTED] vs [REDACTED]).³⁰

Overall, these results demonstrate that treatment with the ibrutinib regimen is associated with extended FFS and therefore improved treatment efficacy in patients with untreated MCL, compared to treatment with existing SoC in the UK clinical practice: the ASCT regimen. For patients with MCL, efficacious treatments which extend FFS in the first-line setting is a key treatment goal. Treatment guidelines for MCL state that stable disease is a sign of treatment failure, and consequently requires salvage treatment and progression to second-line therapy.⁶⁴ A prospective real-world analysis of outcomes in 588 patients with MCL in the UK found that median event-free survival (defined as time to next treatment or death) dropped significantly from 46 months for first-line treatment to 15 months for second-line treatment, highlighting the need for efficacious first-line treatments which are able to keep patients in remission for longer.²¹ As such, the extended FFS observed in Arm I in TRIANGLE demonstrates that treatment with the ibrutinib regimen delays disease progression and is ultimately anticipated to translate to extended survival. Furthermore, given that prognosis is significantly worse in the second-line setting, extending FFS is anticipated to be associated with reduced fears relating to treatment failure and associated worsening prognosis, and hence a reduced psychological burden on patients.

Table 11: FFS (Full Analysis Set)

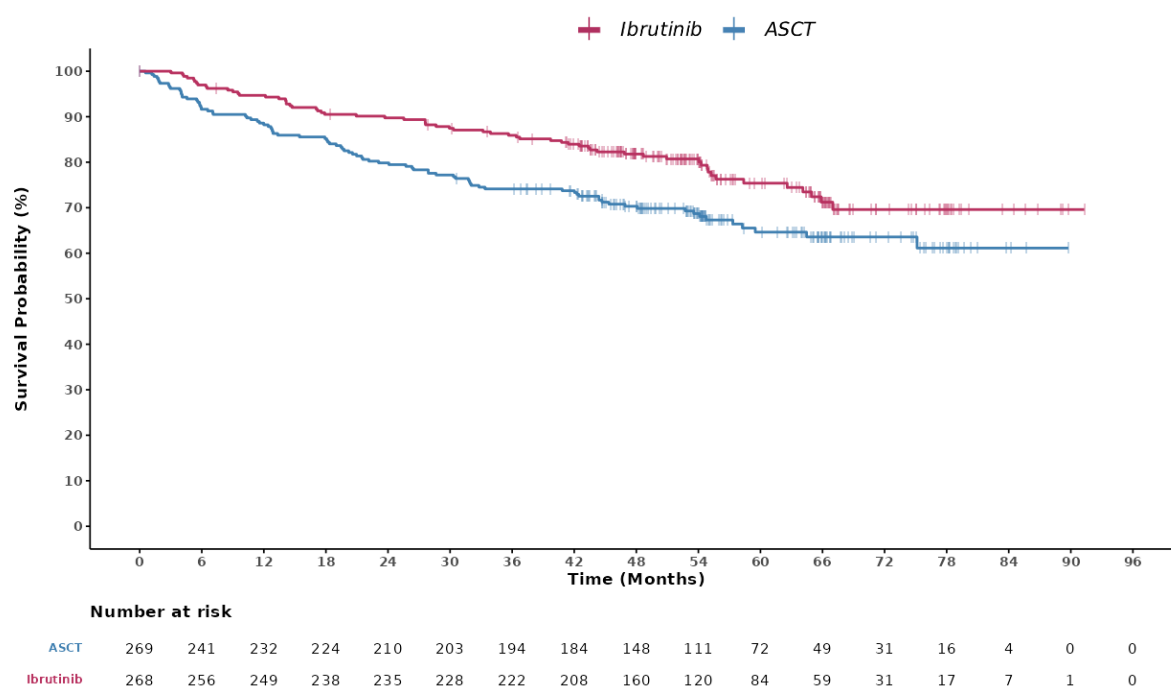
FFS results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	61 (22.8%)	87 (32.3%)
Stable disease at the end of induction	1 (0.4%)	5 (1.9%)
Disease progression	49 (18.3%)	60 (22.3%)
Death	11 (4.1%)	22 (8.2%)
Number of events censored, n (%)	207 (77.2%)	182 (67.7%)
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)		
Range ^a		
Hazard ratio (2-sided 98.33% CI) ^b	0.639 (0.428, 0.953)	
p-value ^c	0.0068	
FFS rate (95% CI)		
6-month		
12-month		
24-month		
36-month		
48-month	0.818 (0.765, 0.860)	0.703 (0.643, 0.755)
60-month	0.754 (0.688, 0.808)	0.646 (0.578, 0.707)
72-month		
84-month		

Percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators, ^a Censored observation, ^b Hazard ratio is from an unstratified Cox regression model and HR < 1 favours Arm I vs A, ^c 2-sided p-value is from an unstratified log-rank test.

Abbreviations: CI: confidence interval; FAS; full analysis set; FFS: failure-free survival; HR: hazard ratio; NE: not estimable.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

Figure 6: KM plot for FFS based on assessment by the central EU MCL Network case evaluation (Full Analysis Set)



Abbreviations: A: Arm A; EU: European; FFS: failure-free survival; I: Arm I; KM: Kaplan-Meier; MCL: mantle cell lymphoma.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.6.2 OS (secondary endpoint)

- At the latest CCO, **almost twice as many OS events had occurred in Arm A vs. Arm I.** These results translated to **nominally significant 48% reduction in the risk of death** observed in patients receiving the ibrutinib regimens vs. the ASCT regimen.³⁰
- As the ASCT regimen is the current SoC in UK clinical practice, these results demonstrate that the ibrutinib regimen could address the existing unmet need for an alternative treatment option that extends survival in patients with untreated MCL.³⁰

OS, defined as the time from randomisation to death, was a key secondary endpoint in TRIANGLE.³⁰ A summary of OS results in the FAS at the May 2024 CCO is provided in Table 12. A KM plot of OS is presented in Figure 7.

After a median time on study of [REDACTED] months for patients in Arm I and [REDACTED] months for patients in Arm A, median OS was not reached in either treatment arm.³⁰ Despite this, the available OS data demonstrate improved survival following treatment with the ibrutinib regimen; almost twice as many events occurred in Arm A vs. Arm I (60 events [22.3%] vs. 33 events [12.3%], respectively).⁶³ These results translated to a nominally significant and clinically meaningful 48% reduction in the risk of death for patients receiving the ibrutinib regimen compared with the ASCT regimen (HR: 0.522 [95% CI: 0.341, 0.799], nominal p-value: 0.0023).⁶³ The OS results are further supported by the consistently numerically improved survival rates in Arm I vs Arm A observed from 6 months ([REDACTED] vs. [REDACTED]) up to 84 months ([REDACTED] vs. [REDACTED]).³⁰ In addition, the KM OS curves demonstrate a clear and early separation in favour of Arm I over Arm A from as early as 6 months.⁶³ Of note, the initial drop in the OS KM curve in Arm A observed in Figure 7 at approximately 6 months correlates to the receipt of treatment with HDT followed by ASCT in this treatment group.⁶³ This provides evidence of the high toxicity and resultant mortality-risk

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associated with the ASCT regimen, which represents current SoC in UK clinical practice. An equivalent drop in OS was not observed when patients commenced treatment with ibrutinib, providing clear evidence that the ibrutinib regimen is associated with a more manageable toxicity profile and reduced mortality-risk vs. existing SoC.

Together, these results demonstrate that treatment with the ibrutinib regimen is associated with a clear survival benefit in patients with previously untreated MCL vs. existing SoC with the ASCT regimen.^{5, 40, 41} These survival benefits are particularly important in light of the fact that MCL has the poorest prognosis of all types of NHL, with a median OS of approximately 4 years.⁷⁷ Furthermore, the number one treatment goal highlighted by patients with MCL as part of patient research is “increased life expectancy”, highlighting that extended survival is the most important factor for patients when choosing a treatment.²⁷

Table 12: OS (Full Analysis Set)

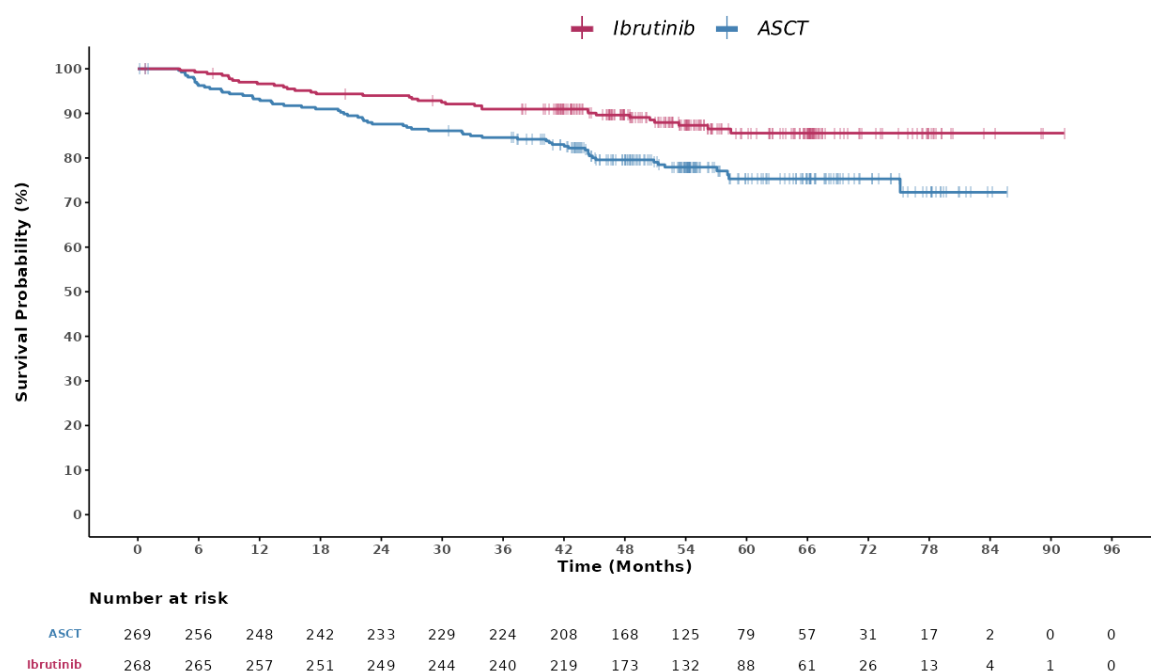
OS Results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	33 (12.3%)	60 (22.3%)
Number of events censored, n (%) ^a	235 (87.7%)	209 (77.7%)
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	██████████	████████████████
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	██████████	██████████
Range ^b	██████████	██████████
Hazard ratio (2-sided 95% CI) ^c	0.522 (0.341, 0.799)	
p-value ^d	0.0023	
Survival rate (95% CI)		
6-month	████████████████	████████████████
12-month	████████████████	████████████████
24-month	████████████████	████████████████
36-month	████████████████	████████████████
48-month	0.896 (0.852, 0.928)	0.796 (0.741, 0.840)
60-month	0.856 (0.800, 0.897)	0.753 (0.690, 0.805)
72-month	████████████████	████████████████
84-month	████████████████	████████████████

^a In patients without documented death during observation time, overall survival was censored at the last contact date alive, percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators, ^b Censored observation, ^c Hazard ratio is from an unstratified Cox regression model and HR < 1 favours Arm I vs A, ^d 2-sided p-value is from an unstratified log-rank test.

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; NE: not estimable; OS: overall survival.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

Figure 7: KM plot for OS (Full Analysis Set)



Abbreviations: A: Arm A; I: Arm I; KM: Kaplan-Meier; OS: overall survival.

Source: J EMA. Assessment Report: Imbruvica (2025).⁶³

2.6.3 PFS (secondary endpoint)

- At the latest CCO, a **nominally significant 36.7% reduction in the risk of progressive disease or death** was observed in patients in **Arm I vs. Arm A**.⁶³ Disease progression is associated with worsening symptoms and therefore an increased clinical burden, as well as an increased risk of death.
- These results indicate that treatment with the ibrutinib regimen may translate to improvements in patient QoL and overall improvements in survival vs. existing SoC with the ASCT regimen.

PFS, defined as the time from randomisation to progression or death from any cause, assessed by central EU MCL Network case evaluation of investigator assessment, was a key secondary endpoint in TRIANGLE.⁶³ A summary of PFS results is provided in Table 13 and a KM plot of PFS is presented in Figure 8.

At the latest CCO, median PFS was not reached in either treatment arm. A numerically higher number of events were however observed in Arm A vs. Arm I (87 [32.3%] vs 60 [22.4%], respectively).⁶³ These differences translated to a nominally significant 36.7% (HR: 0.633 [98.33% CI: 0.424, 0.946], p-value: 0.0060) reduction in the risk of disease progression or death in Arm I compared to Arm A.⁶³ This reduction in risk is supported graphically by the KM curves for PFS which demonstrate a clear and early separation in KM curves favouring Arm I over Arm A.⁶³ In addition, PFS rates were consistently numerically higher in Arm I vs. Arm A from month 6 (■ vs ■, respectively) up to month 84 (■ vs ■, respectively).³⁰

The PFS results are consistent with the FFS results presented in Section 2.6.1, supporting that patients treated with the ibrutinib regimen experience extended PFS, translating to longer periods without disease progression or death compared to patients treated with existing SoC with the ASCT regimen. As disease progression is associated with worsening symptoms and therefore an

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increased clinical burden, as well as an increased risk of death, extending the time to progression is expected to translate to improvements in patient QoL and overall improvements in survival.⁵¹ These improvements are crucial given MCL is associated with the worst prognoses of all types of NHL.

Table 13: PFS (Full Analysis Set)

PFS Results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	60 (22.4%)	87 (32.3%)
Disease progression	49 (18.3%)	63 (23.4%)
Death	11 (4.1%)	24 (8.9%)
Number of events censored, n (%)		
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)		
Median (95% CI)	NE (NE, NE)	NE (77.44 NE)
75% percentile (95% CI)		
Range ^a		
Hazard ratio (2-sided 98.33% CI) ^b	0.633 (0.424, 0.946)	
p-value ^c	0.0060	
PFS rate (95% CI)		
6-month		
12-month		
24-month		
36-month		
48-month	0.824 (0.772, 0.865)	0.710 (0.651, 0.761)
60-month	0.760 (0.696, 0.813)	0.655 (0.587, 0.714)
72-month		
84-month		

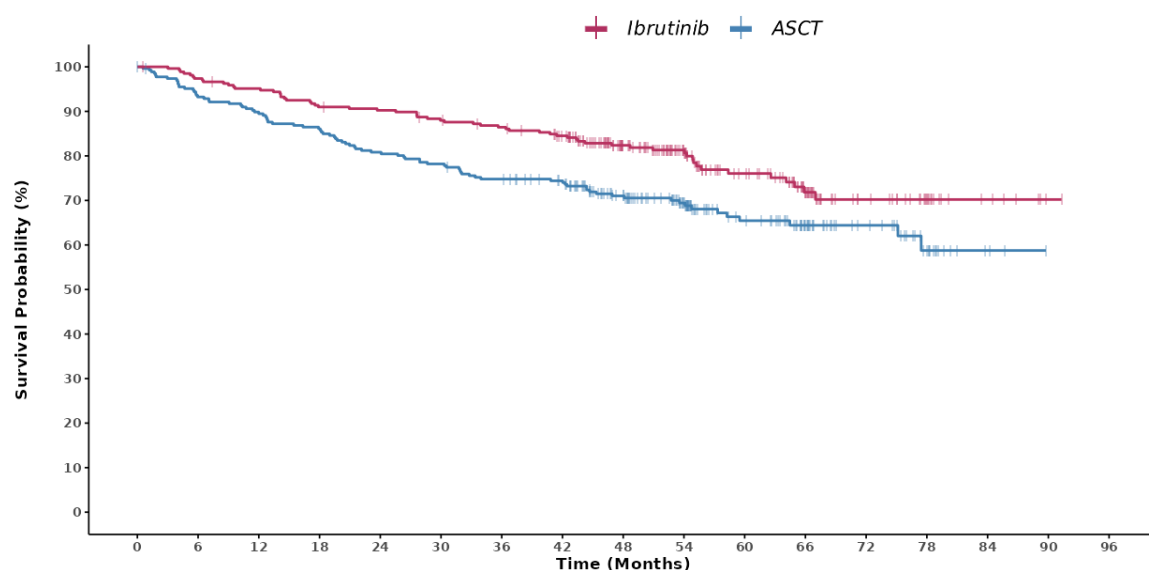
Percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators,

^a Censored observation, ^b Hazard ratio is from an unstratified Cox regression model and HR < 1 favours Arm I vs A, ^c 2-sided p-value is from an unstratified log-rank test.

Abbreviations: CI: confidence interval; FAS: full analysis set; HR: hazard ratio; PFS: progression-free survival.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

Figure 8: KM plot for PFS (Full Analysis Set)



Number at risk

ASCT	269	248	238	229	215	208	198	188	151	114	74	51	32	16	4	0	0
Ibrutinib	268	260	253	242	239	232	226	212	163	122	86	59	31	17	7	1	0

Abbreviations: ASCT: autologous stem cell transplant; KM: Kaplan-Meier; PFS: progression-free survival.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.6.4 Response rates (secondary endpoint)

- The **overall response rate (ORR)** was comparable but numerically higher for patients in Arm I (96.3%) compared to Arm A (92.2%). Similarly, **complete response rates (CRR)** were comparable but numerically higher for patients in Arm I (67.2%) vs. Arm A (64.7%). These results demonstrate that patients treated with the ibrutinib regimen experience at least the same level and depth of response as that experienced by patients on current SoC in UK clinical practice, without imparting the substantial toxicity burden, and therefore the reduced QoL, patients currently experience with the ASCT regimen.⁶³
- **No nominally significant difference** in the PR to CR conversion rate post induction was observed between Arm I (43.5%) and Arm A (50.7%).⁶³

OR and CR rates

Response rates, such as CRR and ORR, are important endpoints in MCL because they directly measure treatment effectiveness by assessing how well a therapy reduces tumour burden. High ORR indicates that a large proportion of patients are responding to treatment; high CRR indicates that a treatment is eliciting a deep response. Response rates are particularly critical given the aggressive nature of MCL and its tendency to relapse.²⁸

CRR and ORR were evaluated based on the Revised Response Criteria for Malignant Lymphoma.⁷⁶ CRR includes patients with a best overall response of CR and ORR includes patients with a best overall response of CR or PR during the study.⁶³ Complete definitions for both endpoints are presented in Table 8; Section 2.4.2. A summary of response rates during the induction phase is provided in Table 14 and a summary of response rates for the overall study period is provided in Table 15; both present data for the FAS at the May 2024 CCO.

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At the end of induction (and prior to ASCT for patients in Arm A), patients experienced comparably high levels of responses across both treatment arms with an ORR of [REDACTED] and [REDACTED] in Arms I and A, respectively. Notably, patients experienced nominally significantly higher CRRs across Arm I ([REDACTED]) vs. Arm A ([REDACTED]) at the end of induction, with a relative risk of [REDACTED] (95% CI: [REDACTED], [REDACTED]; p=[REDACTED]).³⁰ These initial results indicate that patients receiving ibrutinib in addition to immunochemotherapy induction therapy had slightly higher overall response rates and deeper responses, indicating early disease control, vs. those receiving immunochemotherapy induction treatment alone.

Response results were also assessed post-ASCT, however a substantially higher number of patients in Arm I ([REDACTED], [REDACTED]) were reported as “not evaluable” at the post-ASCT timepoint compared with the Arm A ([REDACTED], [REDACTED]).³⁰ This is likely because more patients in Arm I did not have a disease evaluation at this timepoint, as no substantial change in treatment response was expected for these patients compared with their previous assessment at the end of induction. These results are therefore not reported.

Overall, a comparable but numerically higher ORR was observed for patients in Arm I (96.3%) compared with those in Arm A (92.2%), with a relative risk of 1.044 (95% CI: 1.001, 1.089; p-value: 0.0627).⁶³ Similarly, CRR was comparable but numerically higher for patients in Arm I (67.2%) as compared with patients in Arm A (64.7%), with a relative risk of 1.038 (95% CI: 0.919, 1.173; p-value: 0.5851).⁶³

These results demonstrate that patients treated with the ibrutinib regimen are able to achieve at least the same high level and depth of response as currently achieved via existing SoC with the ASCT regimen. The numerically higher ORR and CRR values however indicate that treatment with the ibrutinib regimen may be associated with both an increased likelihood of response and an increased depth of response than treatment with the ASCT regimen. This result is of particular importance to patients as the ibrutinib regimen does not require high intensity chemotherapy and therefore is associated with significantly less toxicity than existing SoC. These results therefore suggest that the ibrutinib regimen is able to achieve at least the same high level of deep responses as existing SoC in UK clinical practice, without imparting the substantial toxicity burden, and therefore the reduced QoL, that patients currently experience with the ASCT regimen (see Section 1.3.4).

Table 14: Summary of CRR and ORR at the end of induction (Full Analysis Set)

Response	Arm I (N=268)	Arm A (N=269)
ORR ^a (CR, PR), n (%)	████████	████████
Relative risk (2-sided 95% CI) ^b	████████████████████	
p-value ^c	████	
CRR ^d , n(%)	████████	████████
Relative risk (2-sided 95% CI) ^b	████████████████████	
p-value ^c	████	
Best overall response, n (%)		
CR	████████	████████
PR	████████	████████
SD	████	████
PD	████	████
NE	████	████

^a ORR is defined as the proportion of subjects with a best response of CR or PR. ^b Relative Risk >1 favours I vs. A. ^c p-value is from the Fisher's exact test. ^d Complete response rate is defined as the proportion of subjects who achieve a best response of CR.

Abbreviations: CI: confidence interval; CR: complete response; CRR: complete response rate; NE: not evaluable; ORR: objective response rate; PR: partial response; PD: progressive disease; SD: stable disease.

Source: J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO; Table tefcr01bmcl and Table teforr01bmcl).³⁰

Table 15: Summary of CRR and ORR (Full Analysis Set)

Response	Arm I (N=268)	Arm A (N=269)
ORR ^a (CR, PR), n (%)	258 (96.3%)	248 (92.2%)
Relative risk (2-sided 95% CI) ^b	1.044 (1.001, 1.089)	
p-value ^c	0.0627	
CRR ^d , n(%)	180 (67.2%)	174 (64.7%)
Relative risk (2-sided 95% CI) ^b	1.038 (0.919, 1.173)	
p-value ^c	0.5851	
Best overall response, n (%)		
CR	180 (67.2%)	174 (64.7%)
PR	78 (29.1%)	74 (27.5%)
SD	1 (0.4%)	3 (1.1%)
PD	3 (1.1%)	11 (4.1%)
NE	6 (2.2%)	7 (2.6%)

^a ORR is defined as the proportion of subjects with a best response of CR or PR. ^b Relative Risk >1 favours I vs. A. ^c p-value is from the Fisher's exact test. ^d Complete response rate is defined as the proportion of subjects who achieve a best response of CR.

Abbreviations: CI: confidence interval; CR: complete response; CRR: complete response rate; NE: not evaluable; ORR: objective response rate; PR: partial response; PD: progressive disease; SD: stable disease.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

PR to CR conversion rate (secondary endpoint)

PR to CR conversion rate was determined based on the proportion of patients whose best overall response improved from PR to CR after the end of induction therapy.⁶³ The complete definition for this endpoint is provided in Table 8; Section 2.4.2 Conversion from PR to CR within a set time frame offers insights into the kinetics of response but is not as clinically meaningful as other endpoints that evaluate the rate of response, such as CRR and ORR (presented above).

A summary of the PR to CR conversion rate after the end of induction therapy is presented in Table 16. Overall, no nominally significant difference in the PR to CR conversion rate between arms was observed (RR: 0.858 [95% CI: 0.670, 1.099], p-value: 0.2389).⁶³ These results suggest that maintenance treatment with ibrutinib ($\pm$ rituximab) is able to convert partial responses to complete responses as effectively as existing SoC with ASCT but without the associated toxicity burden.

Table 16: Summary of PR to CR conversion rate post induction (Full Analysis Set)

Response	Arm I (N=268)	Arm A (N=269)
PR at the end of induction, n	138	150
PR to CR conversion rate, n (%)	60 (43.5%)	76 (50.7%)
Relative risk (2-sided 95% CI) ^a	0.858 (0.670, 1.099)	
p-value ^b	0.2389	

Percentages are calculated with the number of subjects in the full analysis set in each treatment group with PR at end of induction as the denominators. ^a Relative Risk >1 favours I vs. A. ^bp-value is from the Fisher's exact test.

Abbreviations: CR: complete response; PR: partial response.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.7 Subsequent treatments used in the relevant studies

The available subsequent treatment data for patients in Arm I and Arm A of TRIANGLE are presented in Table 17. Further details on subsequent treatments are provided in Section 3.5.2.

Table 17: Subsequent treatments reported in TRIANGLE

Subsequent treatment	Arm I (N=268)	Arm A (N=269)
<i>Subjects with one or more subsequent anticancer therapy</i>		
Antineoplastic agents		
Combinations of antineoplastic agents		
Combinations of antineoplastic agents		
Bendamustine; cytarabine; rituximab		
Cytarabine; dexamethasone; oxaliplatin; rituximab		
Bendamustine; rituximab		
Carmustine; cytarabine; etoposide; melphalan		
Cyclophosphamide; doxorubicin hydrochloride; prednisone; rituximab; vincristine sulphate		
Cyclophosphamide; rituximab	I	I
Bendamustine; bortezomib; rituximab	I	

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Bendamustine; obinutuzumab	████	█
Bortezomib; cyclophosphamide; doxorubicin; prednisone; rituximab	████	█
Bortezomib; cyclophosphamide; rituximab	█	████
Cisplatin; cytarabine; dexamethasone	█	████
Cisplatin; cytarabine; etoposide; methylprednisolone; rituximab	████	█
Cisplatin; dexamethasone; gemcitabine; rituximab	████	█
Cyclophosphamide; doxorubicin hydrochloride; prednisone; vincristine sulphate	████	█
Cyclophosphamide; doxorubicin; prednisone; rituximab; vincristine	████	█
Cyclophosphamide; fludarabine	████	████
Cyclophosphamide; prednisone; rituximab; vincristine sulphate	█	████
Cytarabine; etoposide; melphalan; thiotepa	████	█
Cytarabine; methotrexate	████	█
Fludarabine; melphalan	█	████
Gemcitabine; oxaliplatin	█	████
Gemcitabine; oxaliplatin; rituximab	█	████
Ibrutinib; rituximab	████	█
Lenalidomide; rituximab	████	████
Bruton's tyrosine kinase inhibitors	████	████
Ibrutinib	████	████
Acalabrutinib	█	████
Nemtabrutinib	████	█
Pirtobrutinib	████	████
Tg 1701	█	████
Zanubrutinib	████	████
Antineoplastic cell and gene therapy	████	████
CAR t-cells nos	████	████
Brexucabtagene autoleucel	████	████
Cd20 (clusters of differentiation 20) inhibitors	████	████
Rituximab	████	████
Dexamethasone; rituximab	████	█
Obinutuzumab	████	█
Other antineoplastic agents	████	████
Venetoclax	████	████
Nitrogen mustard analogues	████	████
Cyclophosphamide	████	████
Bendamustine	████	████
Cyclophosphamide; dexamethasone	█	████
Monoclonal antibodies and antibody drug conjugates	████	█
Loncastuximab tesirine	████	█
Purine analogues	█	████
Fludarabine phosphate	█	████
Pyrimidine analogues	████	████

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Gemcitabine hydrochloride		
Cytarabine		
Anthracyclines and related substances		
Doxorubicin		
Pixantrone		
Ethylene imines		
Thiotepa		
Folic acid analogues		
Methotrexate		
Podophyllotoxin derivatives		
Etoposide		
Proteasome inhibitors		
Bortezomib		
Bortezomib; dexamethasone		
Vinca alkaloids and analogues		
Vincristine		
Immunosuppressants		
Other immunosuppressants		
Lenalidomide		
Uncoded		
Allogenic stem cells nos		
Zilovetamab vedotin		
Donor lymphocyte infusion		
Ibrutinib; lenalidomide; rituximab		
Investigational drug		
Uncoded		
Autologous stem cells nos		

Abbreviations: nos: not otherwise specified.

Source: J&J IM. Data on File. TRIANGLE Summary of Subsequent Anticancer Treatment (FAS; May 2024 DCO).⁷⁸

2.8 Subgroup analysis

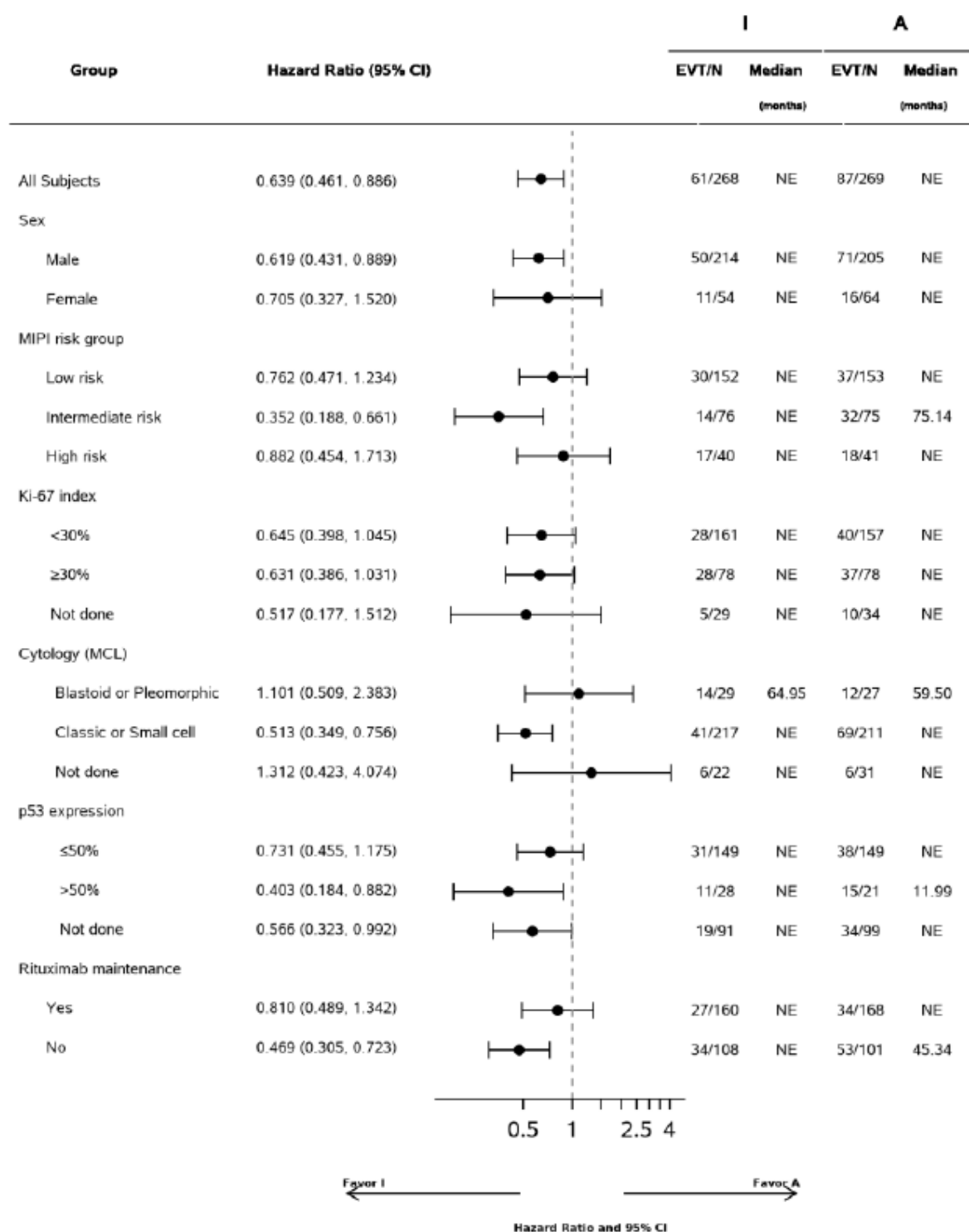
Subgroup analyses were performed on the primary endpoint (FFS) in the FAS analysis set, including clinically relevant subgroups based on baseline clinical disease characteristics, cytology of MCL, p53 expression and receipt of rituximab maintenance.⁶³ The results of the subgroup analyses are provided in Figure 9 below.

At the CCO, subgroup analyses demonstrated that FFS results in the FAS were consistent across almost all subgroups. Most analyses demonstrated that the ibrutinib regimen (Arm I) was associated with at least numerical improvements in FFS vs. the ASCT regimen (Arm A), with the exception of patients in Arm I with a blastoid or pleomorphic MCL who did not show a difference in treatment effect in comparison to patients in Arm A.³⁰ Given that the study was not powered to detect differences in subgroups and owing to the small patients numbers associated with these subgroups however, these results should be interpreted with caution (29 in Arm I and 27 Arm A, respectively).⁶³

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In addition, small differences were observed between rituximab subgroups, although the analysis shows overlapping confidence limits and no indication of substantially different effect sizes between patients who received rituximab maintenance and those who did not. Of note, given that rituximab maintenance was only provided following completion of induction treatment in Arm I or consolidation ASCT in Arm A, these results should be interpreted with caution given the rituximab “yes” subgroup represents an enriched population of patients that successfully completed induction with ibrutinib or consolidation with ASCT.⁶³ It should additionally be noted that use of maintenance rituximab was implemented consistently in each treatment arm and consequently was well balanced across arms (60% vs. 63% in Arms I and A, respectively see Section 2.3.3) and therefore should any differences in treatment effect exist between subgroups they would not impact the relative effects of Arm I vs. Arm A observed during TRIANGLE. Furthermore, for completeness an inverse probability of censoring weighting (IPCW)-adjusted analysis was conducted to estimate the difference in efficacy outcomes between the two treatment regimens if 85% of patients had received rituximab maintenance therapy within the trial. The results of these analyses are presented in Section 2.9.

Figure 9: Forest plot of FFS in subgroup analyses (Full Analysis Set)



Abbreviations: CI: confidence interval; EVT: event; MCL: mantle cell lymphoma; NE: not evaluable.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.9 IPCW-adjusted analyses (rituximab maintenance)

As discussed in Section 2.3.3, over half of patients in TRIANGLE received rituximab maintenance, which is slightly lower than the anticipated use in UK clinical practice (Arm I: 59.7%; Arm A: 62.5%).⁶³ Feedback received from five UK clinical experts indicated that 85% of Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

patients in both arms would be anticipated to receive rituximab maintenance in clinical practice.⁴² As the proportion of patients receiving rituximab maintenance is balanced between trial arms it is not anticipated to impact the generalisability of the relative treatment effect observed between the ibrutinib regimen and the ASCT regimen in TRIANGLE. To minimise uncertainty associated with this slight discrepancy in rituximab maintenance use in TRIANGLE vs. UK clinical practice however an IPCW-adjusted analysis was conducted in which the proportion of patients receiving rituximab maintenance in both arms was adjusted to reflect the anticipated use in UK clinical practice (85%). An overview of the IPCW-adjusted analyses methods are presented below, with full details in the Rituximab Analysis Report provided in the reference pack accompanying this submission.⁷⁹

Method of adjustment

Step 1

An IPCW adjustment approach was implemented in which patients who did not receive rituximab maintenance were artificially censored at the point at which they would have received rituximab maintenance therapy (assumed to be 30-days post-ASCT in Arm A and at the start of ibrutinib maintenance therapy in Arm I).⁷⁹

To adjust for potential bias due to informative censoring, patients that received rituximab maintenance in Arm A and Arm I in TRIANGLE were assigned weights over time, such that these accounted not only for themselves but also participants with similar characteristics in the same study arm (both those at baseline and those measured throughout the trial [time-varying covariates]) who were censored and did not receive rituximab maintenance.⁷⁹

The covariates adjusted for within the analyses were based on clinical expert feedback, the use of variables in comparative efficacy for patients with previously untreated MCL who were eligible for transplant in the literature, and the availability of variables in the dataset.^{80, 81} The final list of covariates included are detailed in Table 18, with further information on the identification of the chosen covariates provided in the Rituximab Analysis Report provided in the reference pack accompanying this submission.⁷⁹

Table 18: Covariates considered within the IPCW-adjusted analysis

Covariates collected at baseline	Covariates collected continuously throughout the trial
• Cytology • Ki-67 • P-53 • Bone marrow involvement • B-symptoms	• LDH • WBC • ECOG PS • Serum Beta-2-microglobulin • Complete responder (yes/no) • Treatment failure (yes/no)

Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; IPCW: inverse probability of censoring; LDH: lactate dehydrogenase; WBC: white blood count.

Stabilised time-dependent weights were estimated for each arm separately, derived from the probability of receiving rituximab maintenance. The probability of receiving rituximab maintenance within each time period was estimated using two logistic regression models.

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- **Model 1 (conditional on baseline covariates and time-varying covariates)** was fitted to all participants who received ASCT in Arm A and ibrutinib maintenance in Arm I, and included all baseline and time-varying covariates in Table 18. A reduced model was also derived using the stepwise variable selection method with a significance level of 25%
- **Model 2 (conditional on the baseline variables selected, if any, in Model 1)** was fitted to all patients in each arm

The inverse probability of receiving rituximab maintenance up to the current timepoint from Model 1 was used for non-stabilised weights. Stabilised weights for each timepoint were then calculated, estimated as a ratio of the probabilities of not receiving rituximab maintenance up to the current timepoint from Model 2 (numerator) and Model 1 (denominator). Patients who experienced early failure or progression, and who consequently did not undergo ASCT in Arm A or receive ibrutinib maintenance in Arm I, were deemed ineligible to receive rituximab maintenance and were assigned a weight of 1 within the analysis.

Step 2

The same approach described above was repeated, but this time patients who did receive rituximab maintenance, were artificially censored at the time they received rituximab maintenance using the panel data, all other assumptions remained the same.

Step 3

To account for the assumption by clinical experts consulted at a November 2025 advisory board that 85% of patients would receive rituximab maintenance therapy, a weight of 85% was assigned to the IPCW-adjusted IPD where all patients received rituximab maintenance (Step 1) while a weight of 15% was assigned to the IPCW-adjusted IPD where no patients received rituximab maintenance (Step 2).⁴² Weighted IPCW-adjusted HRs for Arm I vs. Arm A for FFS and OS (including 95% CI and p-value) and KM curves were derived using a weighted Cox proportional hazards model. The variance was estimated using a robust sandwich variance estimator to account for the induced correlation among weighted individuals.

Results

The results of the IPCW-adjusted analysis are presented alongside the FAS results in Table 19, with the associated KMs for the IPCW-adjusted analysis presented in Figure 10 – Figure 11. After IPCW adjustment to simulate 85% of patients in TRIANGLE receiving rituximab maintenance therapy, Arm I remained nominally significantly superior to the Arm A across all key endpoints assessed. Importantly the FFS and OS HRs observed from the IPCW adjusted analyses were highly consistent with those observed in the unadjusted analyses. These results therefore demonstrate that the relative treatment effect of the ibrutinib regimen vs. the ASCT regimen observed in TRIANGLE is robust to variations in the proportion of maintenance rituximab used, as long as the proportion is consistent across arms.

Table 19: Comparison of results from the IPCW-adjusted and unadjusted analysis (TRIANGLE; FAS)

Endpoint	IPCW-adjusted analysis	Unadjusted analysis
FFS, HR (95% CI)	■ (■) p-value: ■	■ (■) ^a p-value: ■
OS, HR (95% CI)	■ (■)	■ (■)

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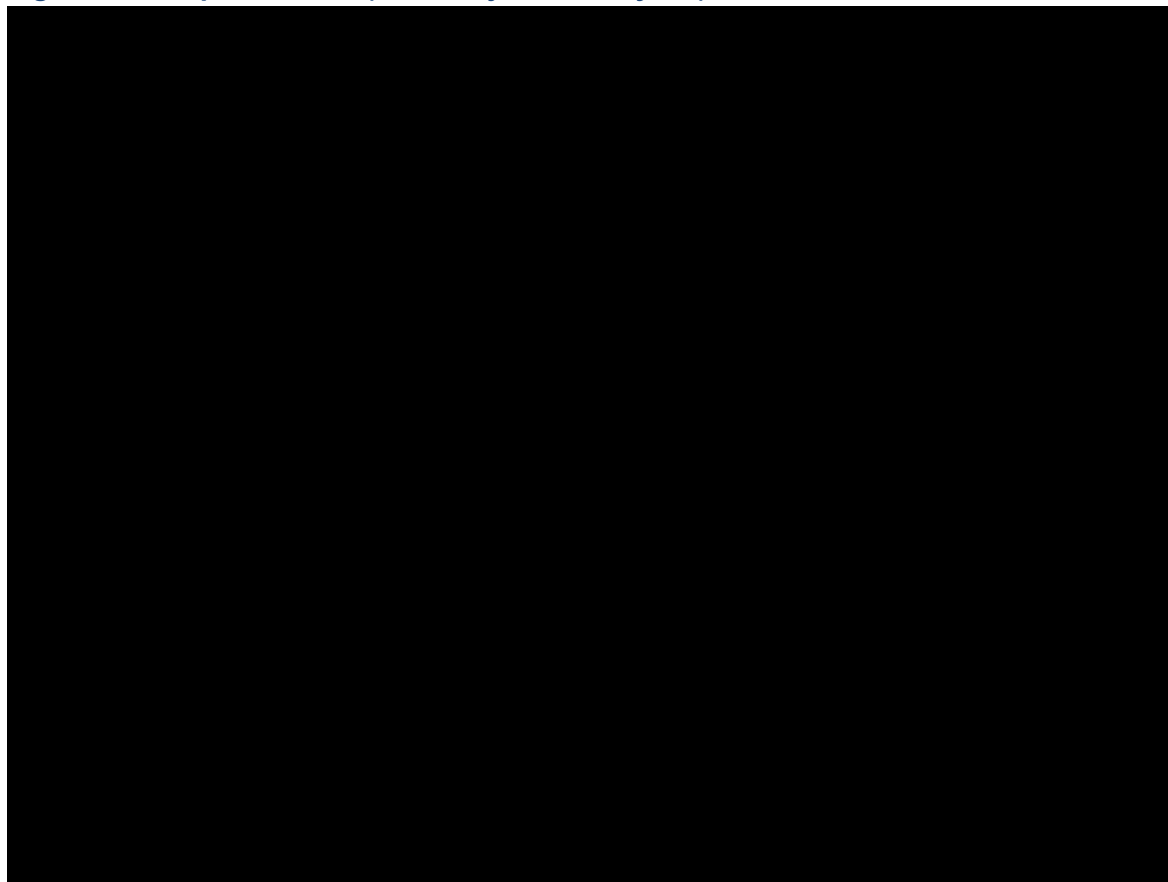
	p-value: [REDACTED]	p-value: [REDACTED]

Footnotes: ^a98.33% CI.

Abbreviations: CI: confidence interval; HR: hazard ratio; FAS: full analysis set; FFS: failure-free survival; OS: overall survival

Source: J&J IM. Data on File. Rituximab Analysis Report.⁷⁹

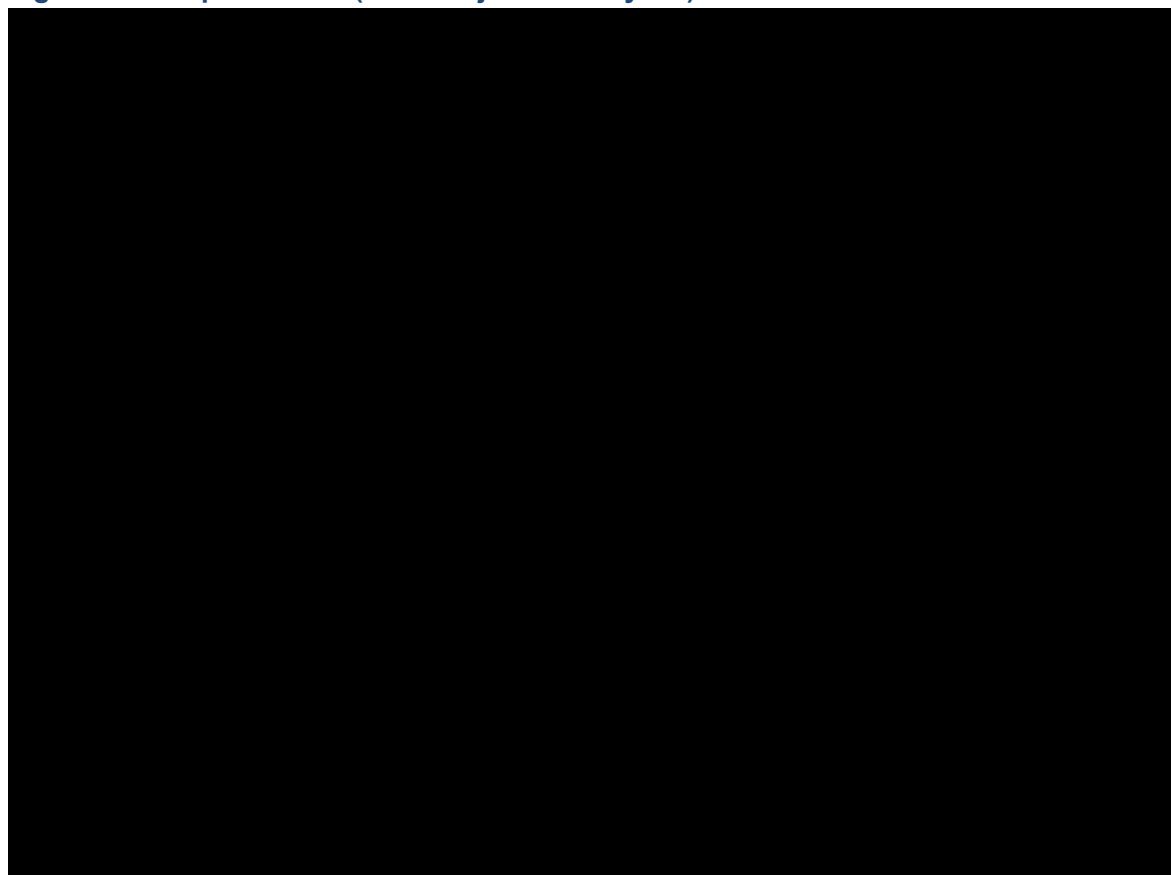
Figure 10: KM plot for FFS (IPCW-adjusted analyses)



Abbreviations: A: Arm A; FFS: failure-free survival; I: Arm I; KM: Kaplan-Meier; MCL: mantle cell lymphoma.

Source: J&J IM. Data on File. Rituximab Analysis Report.⁷⁹

Figure 11: KM plot for OS (IPCW-adjusted analyses)



Abbreviations: A: Arm A; I: Arm I; KM: Kaplan-Meier; MCL: mantle cell lymphoma; OS: overall survival.

Source: J&J IM. Data on File. Rituximab Analysis Report.⁷⁹

Conclusions

The FFS and OS HRs observed from the IPCW adjusted analyses are highly consistent with those observed in the unadjusted analyses. These results therefore provide confidence that the observed relative treatment effect between the ibrutinib and ASCT regimens in TRIANGLE are generalisable to UK clinical practice and therefore suitable for UK-decision making.

2.10 *Meta-analysis*

TRIANGLE was the only relevant interventional study identified by the clinical SLR which provides evidence on the clinical efficacy and safety of ibrutinib with immunochemotherapy in the indication of relevance to this submission, and therefore no meta-analyses were conducted.^{30, 63}

2.11 *Indirect and mixed treatment comparisons*

TRIANGLE provides direct evidence comparing ibrutinib with immunochemotherapy in patients with untreated MCL vs. the only relevant comparator to ibrutinib (the ASCT regimen) in this indication in UK clinical practice.^{30, 63} As such, no indirect treatment comparisons (ITCs) were required.

2.12 Adverse reactions

The safety data presented in the sections below are based on the results of the safety analysis set from the TRIANGLE trial at the latest (August 2024 CCO). The safety analysis set included all patients who had received at least one dose of study treatment in the trial.^{30, 63} Full details on the safety analysis set are presented in Table 7; Section 2.3.1.

2.12.1 Treatment duration and dosage

The median treatment duration for study treatment was 28.45 months for patients in Arm I vs. 5.16 months for patients in Arm A.⁶³ This is equivalent to a treatment exposure that is more than 5-fold longer for patients in Arm I compared with patients in Arm A.⁶³ A summary of treatment duration and dose intensity for ibrutinib in patients in Arm I in TRIANGLE is provided in Table 20.

The intended dose of ibrutinib was 560 mg, administered orally in an alternating pattern of 3 cycles R-CHOP + ibrutinib followed by 3 cycles R-DHAP induction therapy followed by 2 years of ibrutinib maintenance treatment once daily. A total of 265 patients received at least one dose of ibrutinib in Arm I during induction therapy, during which the median number of treatment cycles with ibrutinib (to be given in Cycles 1, 3, and 5) was 3.0 cycles.⁶³ The mean relative dose intensity for ibrutinib during induction was 95.2% and the median dose intensity was 560 mg/day.³⁰ During induction therapy, the majority of patients receiving ibrutinib did not require dose reductions of ibrutinib (251 [94.7%]).⁶³

A total of 245 patients received at least one dose of ibrutinib maintenance therapy in Arm I, with a median treatment duration of 24.0 months.⁶³ The mean relative dose intensity for ibrutinib during maintenance was 92.9% and the median dose intensity was 533.2 mg/day.⁶³ Of note, during maintenance treatment with ibrutinib, the majority of patients did not require dose reductions of ibrutinib (191 [78.0%]).⁶³ Furthermore, only ■ (■■■) patients discontinued study treatment after 6 months, and ■ (■■■) between 6–12 months.³⁰ These data suggest that long-term treatment with ibrutinib is well tolerated, with minimal dose reductions and discontinuations reported amongst patients.

In addition to ibrutinib maintenance therapy, patients also received rituximab maintenance therapy in line with national treatment guidelines. The use of rituximab maintenance therapy was balanced across treatment arms, with 60% of patients in Arm A and 63% of patients in Arm I receiving rituximab maintenance.⁶³

Table 20: Summary of treatment duration and dose intensity in patients receiving ibrutinib (Safety Analysis Set)

	Safety Analysis Set N=265
Induction treatment	
Total number of cycles (n, %)	
1 cycle	7 (2.6%)
2 cycles	5 (1.9%)
≥3 cycles	253 (95.5%)
Mean (SD)	2.9 (0.35)
Median	3.0

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	Safety Analysis Set N=265
Range	1, 4
Dose intensity per protocol (mg/day)^a	
Mean (SD)	533.2 (92.94)
Median	560.0
Range	49, 855
Relative dose intensity per protocol (%)^b	
Mean (SD)	95.2 (16.60)
Median	100.0
Range	9, 153
Maintenance treatment	
Total treatment duration (months)	
<6 months	14 (5.7%)
6–12 months	12 (4.9%)
12–18 months	17 (6.9%)
≥18 months	202 (82.4%)
Mean (SD)	21.3 (6.24)
Median	24.0
Range	0, 29
Dose intensity per protocol (mg/day)^a	
Mean (SD)	461.8 (151.66)
Median	533.2
Range	5, 661
Relative dose intensity per protocol (%)^b	
Mean (SD)	82.5 (27.08)
Median	95.2
Range	1, 118

^a Dose intensity per protocol is calculated as the ratio of total dose administered and planned total treatment duration per protocol, ^b Relative dose intensity per protocol is calculated as the ratio of dose intensity per protocol and 560 mg.

Abbreviations: SD: standard deviation.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.12.2 Summary of treatment-emergent adverse events

A summary of treatment-emergent adverse events (TEAEs) during the induction phase in the Safety Analysis Set is provided in Table 22 and a summary of TEAEs reported for the overall study period in the Safety Analysis Set is provided in Table 21.

A TEAE was defined as an event that was new or worsening at or after the first dose of study drug and up to 30 days following the last dose of study drug (or ASCT when applicable) or until the start of a subsequent anticancer therapy, whichever is earliest. It should however be noted that rituximab maintenance treatment was initiated for patients in Arm A at the time when the treatment-emergent period ended (30 days after the last study treatment or ASCT was

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administered, as applicable). In contrast, it was administered concomitantly with the ibrutinib maintenance treatment for patients in Arm I and was thus captured within the treatment-emergent period for Arm I. This discrepancy arose because, as noted in Section 2.3.1, rituximab maintenance was not considered study treatment, however, upon its implementation in the national guidelines for a participating country, rituximab maintenance was administered to patients, as per the recommendation of the sites study group. The TEAE data presented in this section may therefore be biased against Arm I.

TEAEs leading to discontinuation or dose reductions of ibrutinib were observed in 61 (23.0%) of patients in Arm I.⁶³ Notably, during the induction phase, the incidence of TEAEs leading to ibrutinib discontinuation was relatively low, and the majority of AEs leading to ibrutinib discontinuation were reported during the two-year maintenance phase of treatment with ibrutinib when patients were also receiving treatment with rituximab.⁶³

During the induction phase (prior to the receipt of ASCT in Arm A), similar frequencies of TEAEs, serious TEAEs and TEAEs leading to death were observed in patients treated with ibrutinib in addition to 6 cycles of induction immunochemotherapy (Arm I) as compared to those receiving chemotherapy without ibrutinib (Arm A).⁶³ These results demonstrate that the addition of ibrutinib to the existing immunochemotherapy induction regimen does not increase the toxicity burden on patients.

Overall, the proportion of patients experiencing at least one TEAE was comparable across treatment arms (99.2% vs. 99.6% for patients in Arm I and A, respectively).⁶³ While serious TEAEs were experienced by slightly more patients in Arm I (64.5%) than Arm A (45.9%), these results should be considered within the context that patients in Arm I received treatment for five times longer than those in Arm A (28.45 months vs. 5.16 months, respectively).⁶³ These results therefore demonstrate that ibrutinib can be used for five times as long before resulting in a comparable number of TEAE and serious TEAE to the ASCT-regimen, therefore highlighting its improved tolerability profile vs. existing SoC. Furthermore, the proportion of fatal AEs experienced by patients, whilst low across treatment arms, was twice as high in patients in Arm A vs. Arm I (4.1% vs. 2.3% in Arm A and I, respectively), further highlighting the increased toxicity associated with the ASCT regimen over the ibrutinib regimen.⁶³

COVID-19

The majority of patients were enrolled into TRIANGLE before the COVID-19 outbreak was declared a pandemic by World Health Organisation (WHO) in March 2020. As such, the majority of patients had already completed the approximate 5 months of study treatment in Arm A before March 2020. In comparison, study treatment was still ongoing for patients in Arm I, who were enrolled in or after 2018 and received study treatment with up to 2 years ibrutinib maintenance.⁶³ Therefore, a higher incidence of COVID-19 AEs and serious adverse events (SAEs) was observed in patients in Arm I (■■■■ and ■■■■) as compared with patients in Arm A (■■■■ and ■■■■).³⁰ This is expected as more patients on Arm I were still on study treatment during the COVID-19 outbreak than patients in Arm A. The proportion of patients experiencing a fatal AE of COVID-19 was low in all treatment arms: 4 (1.5%) patients in Arm I and 2 patients (0.7%) in Arm A.⁶³

Table 21: Summary of treatment-emergent adverse events during the induction phase (Safety Analysis Set)

TEAEs, n (%)	Arm I N=265	Arm A N=268
Any TEAE	259 (97.7%)	262 (97.8%)
Grade ≥3	228 (86.0%)	220 (82.1%)
Ibrutinib-related ^a	148 (55.8%)	-
Any serious TEAE	119 (44.9%)	110 (41.0%)
Grade ≥3	90 (34.0%)	89 (33.2%)
Ibrutinib-related ^a	22 (8.3%)	-
Treatment-emergent adverse events leading to death^b	1 (0.4%)	3 (1.1%)
Within 30 days of last dose of study treatment	1 (0.4%)	0
TEAE leading to ibrutinib discontinuation^c	13 (4.9%)	-
TEAE leading to ibrutinib dose reduction^c	10 (3.8%)	-

^a An AE is categorised as related if assessed by the investigator as related or not related to Ibrutinib. The causal relationship of an adverse event to study treatment was 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. ^c Data are not reported for Arm A.

Abbreviations: AE: adverse event; EOT: end of treatment; TEAE: treatment-emergent adverse event.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

Table 22: Summary of treatment-emergent adverse events (Safety Analysis Set)

TEAEs, n (%)	Arm I N=265	Arm A N=268
Any TEAE	263 (99.2%)	267 (99.6%)
Grade ≥3	247 (93.2%)	250 (93.3%)
Ibrutinib-related ^a	212 (80.0%)	-
Any serious TEAE	171 (64.5%)	123 (45.9%)
Grade ≥3	146 (55.1%)	105 (39.2%)
Ibrutinib-related ^a	50 (18.9%)	-
TEAE leading to death^b	6 (2.3%)	11 (4.1%)
Within 30 days of last dose of study treatment	4 (1.5%)	5 (1.9%)
TEAE leading to ibrutinib discontinuation^c	61 (23.0%)	-
TEAE leading to ibrutinib dose reduction^c	43 (16.2%)	-
COVID-19 TEAE	52 (19.6%)	5 (1.9%)
COVID-19 serious TEAE	23 (8.7%)	4 (1.5%)
COVID-19 TEAE leading to death	4 (1.5%)	2 (0.7%)

^a An AE is categorised as related if assessed by the investigator as related or not related to Ibrutinib. The causal relationship of an adverse event to study treatment was 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. ^c Data are not reported for Arm A.

Abbreviations: AE: adverse event; EOT: end of treatment; TEAE: treatment-emergent adverse event

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

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2.12.3 Most common treatment-emergent adverse events

The most frequently reported TEAEs, defined as TEAEs occurring in $\geq 10.0\%$ of patients in either treatment arm, are summarised in Table 23.

The overall incidence of any grade TEAEs was similar between patients in Arm A (99.6%) and Arm I (99.2%), with most patients experiencing a TEAE.⁶³ The most common TEAEs across both arms were blood and lymphatic system disorders. Anaemia was the most common TEAE, reported in 44.9% of patients in Arm I and in 57.8% in Arm A, respectively. The second and third most common TEAE across treatment arms were neutropenia (42.3% in Arm I and 41.0% in Arm A), and thrombocytopenia (39.6% in Arm I and 45.1% in Arm A).⁶³ Considering that patients in Arm I received treatment for five times longer than those in Arm A, the comparable TEAE rates demonstrate that the ibrutinib regimen is associated with improved tolerability vs. the ASCT regimen and comparable tolerability when administered over a significantly longer time period.

Table 23: Summary of most common ($\geq 10.0\%$) treatment-emergent adverse events (Safety Analysis Set)

TEAE, n (%)	Arm I N=265	Arm A N=268
	All grade	All grade
Blood and lymphatic system disorders	199 (75.1%)	221 (82.5%)
Anaemia	119 (44.9%)	155 (57.8%)
Neutropenia	112 (42.3%)	110 (41.0%)
Thrombocytopenia	105 (39.6%)	121 (45.1%)
Febrile neutropenia	37 (14.0%)	71 (26.5%)
Leukopenia	33 (12.5%)	37 (13.8%)
Infections and infestations	186 (70.2%)	137 (51.1%)
Pneumonia	27 (10.2%)	14 (5.2%)
COVID-19	37 (14.0%)	3 (1.1%)
Gastrointestinal disorders	169 (63.8%)	190 (70.9%)
Nausea	84 (31.7%)	105 (39.2%)
Diarrhoea	75 (28.3%)	78 (29.1%)
Vomiting	49 (18.5%)	47 (17.5%)
Constipation	44 (16.6%)	49 (18.3%)
Stomatitis	24 (9.1%)	42 (15.7%)
General disorders and administration site conditions	144 (54.3%)	175 (65.3%)
Pyrexia	57 (21.5%)	89 (33.2%)
Mucosal inflammation	22 (8.3%)	74 (27.6%)
Fatigue	46 (17.4%)	31 (11.6%)
Investigations	153 (57.7%)	155 (57.8%)
Platelet count decreased	87 (32.8%)	91 (34.0%)
Neutrophil count decreased	68 (25.7%)	65 (24.3%)
White blood cell count decreased	24 (9.1%)	38 (14.2%)

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TEAE, n (%)	Arm I N=265	Arm A N=268
	All grade	All grade
Blood creatinine increased	42 (15.8%)	32 (11.9%)
Nervous system disorders	135 (50.9%)	104 (38.8%)
Headache	29 (10.9%)	28 (10.4%)
Peripheral sensory neuropathy	28 (10.6%)	14 (5.2%)
Paraesthesia	28 (10.6%)	14 (5.2%)
Skin and subcutaneous tissue disorders	91 (34.3%)	51 (19.0%)
Rash	36 (13.6%)	15 (5.6%)
Respiratory, thoracic, and mediastinal disorders	83 (31.3%)	63 (23.5%)
Cough	33 (12.5%)	12 (4.5%)
Metabolism and nutrition disorders	89 (33.6%)	96 (35.8%)
Hypokalaemia	37 (14.0%)	43 (16.0%)
Musculoskeletal and connective tissue disorders	85 (32.1%)	57 (21.3%)
Vascular disorders	65 (24.5%)	60 (22.4%)
Hypertension	33 (12.5%)	21 (7.8%)
Renal and urinary disorders	68 (25.7%)	56 (20.9%)
Acute kidney injury	29 (10.9%)	31 (11.6%)
Cardiac disorders	54 (20.4%)	22 (8.2%)
Injury, poisoning, and procedural complications	55 (20.8%)	32 (11.9%)
Ear and labyrinth disorders	39 (14.7%)	27 (10.1%)

Abbreviations: ASCT: autologous stem cell transplant; TEAE: treatment-emergent adverse event.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.12.4 Most common treatment-emergent adverse events related to ibrutinib

Data reporting the causal relationship between an AE to any study treatment was only collected for ibrutinib, whereas information on the relationship between an AE and any other study treatment, including the ASCT regimen, was not collected.⁶³ A summary of the most frequently reported TEAEs related to ibrutinib, defined as occurring in $\geq 5.0\%$ of patients, is provided in Table 24. Overall, 80.0% of patients in Arm I experienced an ibrutinib-related AE. Importantly, no fatal AEs related to ibrutinib were observed in Arm I.⁶³

Table 24: Summary of most common ($\geq 5.0\%$) treatment-emergent adverse events related to ibrutinib (Safety Analysis Set)

TEAE, n (%)	Arm I N=265
	All grade
Blood and lymphatic system disorders	103 (38.9%)
Anaemia	40 (15.1%)

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TEAE, n (%)	Arm I N=265
	All grade
Neutropenia	61 (23.0%)
Thrombocytopenia	29 (10.9%)
Infections and infestations	65 (24.5%)
Pneumonia	13 (4.9%)
Gastrointestinal disorders	35 (13.2%)
Nausea	14 (5.3%)
Diarrhoea	24 (9.1%)
General disorders and administration site conditions	37 (14.0%)
Investigations	66 (24.9%)
Platelet count decreased	20 (7.5%)
Neutrophil count decreased	30 (11.3%)
White blood cell count decreased	57 (21.5%)
Nervous system disorders	36 (13.6%)
Skin and subcutaneous tissue disorders	49 (18.5%)
Rash	19 (7.2%)
Respiratory, thoracic, and mediastinal disorders	25 (9.4%)
Metabolism and nutrition disorders	14 (5.3%)
Musculoskeletal and connective tissue disorders	42 (15.8%)
Muscle spasms	17 (6.4%)
Vascular disorders	24 (9.1%)
Hypertension	14 (5.3%)
Cardiac disorders	27 (10.2%)
Atrial fibrillation	19 (7.2%)

Abbreviations: TEAE: treatment-emergent adverse event.

Source: J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

2.12.5 Serious adverse events

A summary of treatment-emergent serious AEs (TESAEs), defined as Grade 3 or above, occurring in Arms I and A of the Safety Analysis Set is provided in Table 25.

The most frequently reported TESAEs were febrile neutropenia (10.6% in Arm I and 7.1% in Arm A), acute kidney injury (6.8% in Arm I and 5.2% in Arm A), and pneumonia (4.2% in Arm I and 3.0% in Arm A).⁶³ The relatively modest differences in the most common TESAEs between arms, in light of the significantly prolonged treatment exposure in patients in Arm I vs. Arm A, demonstrate that prolonged treatment with ibrutinib does not significantly increase the risk of severe adverse events, compared with short-term treatment with ASCT. Furthermore, the proportion of patients experiencing a Grade 5 TESAE was higher overall in patients in Arm A vs. Arm I. Specifically patients in Arm A experienced death due to infections and infestations, GI disorders, kidney disorders, respiratory, thoracic, and mediastinal disorders at a numerically greater rate than patients in Arm I.⁶³ These results therefore demonstrate that treatment with the ibrutinib regimen reduces the risk of Grade 5 AEs vs. treatment with existing SoC in UK clinical practice; the ASCT regimen.

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Table 25: Summary of treatment-emergent serious AEs (Safety Analysis Set)

TESAE, n (%)	Arm I N=265			Arm A N=268		
	Grade ≥3	Grade 3/4	Grade 5	Grade ≥3	Grade 3/4	Grade 5
Blood and lymphatic system disorders	33 (12.5%)	33 (12.5%)	0	30 (11.2%)	30 (11.2%)	0
Thrombocytopenia	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	6 (2.2%)	0
Febrile neutropenia	28 (10.6%)	28 (10.6%)	0	19 (7.1%)	19 (7.1%)	0
Infections and infestations	72 (27.2%)	56 (21.1%)	4 (1.5%)	36 (13.4%)	27 (10.1%)	6 (2.2%)
Pneumonia	11 (4.2%)	9 (3.4%)	0	8 (3.0%)	7 (2.6%)	1 (0.4%)
COVID-19	12 (4.5%)	9 (3.4%)	2 (0.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Sepsis	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	3 (1.1%)	3 (1.1%)
COVID-19 pneumonia	10 (3.8%)	7 (2.6%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Device related infection	0	0	0	1 (0.4%)	1 (0.4%)	0
Herpes zoster	1 (0.4%)	1 (0.4%)	0	0	0	0
Gastrointestinal disorders	21 (7.9%)	17 (6.4%)	0	23 (8.6%)	16 (6.0%)	4 (1.5%)
Diarrhoea	2 (0.8%)	2 (0.8%)	0	3 (1.1%)	2 (0.7%)	0
Vomiting	9 (3.4%)	7 (2.6%)	0	4 (1.5%)	3 (1.1%)	0
General disorders and administration site conditions	18 (6.8%)	8 (3.0%)	0	13 (4.9%)	7 (2.6%)	1 (0.4%)
Pyrexia	8 (3.0%)	2 (0.8%)	0	8 (3.0%)	4 (1.5%)	0
Investigations	11 (4.2%)	5 (1.9%)	0	11 (4.1%)	7 (2.6%)	0
Platelet count decreased	0	0	0	6 (2.2%)	6 (2.2%)	0
Blood creatinine increased	5 (1.9%)	0	0	4 (1.5%)	0	0
Nervous system disorders	14 (5.3%)	11 (4.2%)	0	7 (2.6%)	5 (1.9%)	0
Respiratory, thoracic, and mediastinal disorders	3 (1.1%)	2 (0.8%)	0	7 (2.6%)	5 (1.9%)	2 (0.7%)
Metabolism and nutrition disorders	11 (4.2%)	11 (4.2%)	0	11 (4.1%)	11 (4.1%)	0
Vascular disorders	5 (1.9%)	4 (1.5%)	0	5 (1.9%)	1 (0.4%)	0
Renal and urinary disorders	25 (9.4%)	13 (4.9%)	0	20 (7.5%)	7 (2.6%)	1 (0.4%)
Acute kidney injury	18 (6.8%)	10 (3.8%)	0	14 (5.2%)	4 (1.5%)	1 (0.4%)
Renal failure	5 (1.9%)	2 (0.8%)	0	4 (1.5%)	2 (0.7%)	0
Cardiac disorders	19 (7.2%)	11 (4.2%)	1 (0.4%)	4 (1.5%)	3 (1.1%)	0

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TESAE, n (%)	Arm I N=265			Arm A N=268		
	Grade ≥3	Grade 3/4	Grade 5	Grade ≥3	Grade 3/4	Grade 5
Atrial fibrillation	12 (4.5%)	8 (3.0%)	0	1 (0.4%)	1 (0.4%)	0
Injury, poisoning, and procedural complications	7 (2.6%)	6 (2.3%)	0	4 (1.5%)	3 (1.1%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (1.9%)	4 (1.5%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)

Abbreviations: AE: adverse event; TEAE: treatment-emergent serious adverse event.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.12.6 Adverse events of special interest – haemorrhage

Haemorrhage was considered an adverse event of special interest (AESI) in TRIANGLE due to previous reports of bleeding-related AEs in patients receiving ibrutinib.⁸² In TRIANGLE, a major haemorrhage event was defined as any treatment-emergent haemorrhagic AE Grade 3 or higher, any serious TEAE of bleeding of any grade, and any treatment-emergent central nervous system (CNS) haemorrhage or hematoma.⁶³ A summary of the treatment-emergent haemorrhagic AEs in the Safety Analysis Set is provided in Table 26.

The incidence of treatment-emergent major haemorrhage events was similar across treatment arms (3.8% in Arm I and 3.4% in Arm A). The most frequently (≥1%) reported any Grade AEs were epistaxis (1.1% in Arm I and Arm A, each) and haematoma (1.1% in Arm I and 0.4% in Arm A). Of note one Grade 5 haemorrhage event occurred in Arm A (gastric haemorrhage) and no Grade 5 events occurred in Arm I.⁶³

Table 26: Incidence of treatment-emergent major haemorrhagic events (Safety Analysis Set)

AESI, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Subjects with any treatment-emergent major haemorrhage events	10 (3.8%)	8 (3.0%)	0	9 (3.4%)	8 (3.0%)	1 (0.4%)
Gastrointestinal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Catheter site haemorrhage	2 (0.8%)	2 (0.8%)	0	0	0	0
Epistaxis	3 (1.1%)	3 (1.1%)	0	3 (1.1%)	3 (1.1%)	0
Gastric haemorrhage	0	0	0	1 (0.4%)	0	1 (0.4%)
Anal haemorrhage	1 (0.4%)	0	0	0	0	0
Blood loss anaemia	0	0	0	1 (0.4%)	1 (0.4%)	0
Haematoma	3 (1.1%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Haemorrhage intracranial	1 (0.4%)	1 (0.4%)	0	0	0	0

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AEI, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Intestinal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Rectal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Subarachnoid haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0

Abbreviations: AEI: adverse event of special interest.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

2.12.7 Other significant adverse events

All other significant AEs reported in TRIANGLE included secondary primary malignancy, cardiac arrhythmias, cardiac failure, hypertension, interstitial lung disease, ischemic stroke, cytopenic AEs, tumour lysis syndrome, leukostasis, hepatotoxicity including hepatic failure and infections.⁶³

The incidence of second primary malignancies during the entire study period was 7.5% (n=20) in Arm I and 4.1% (n=11) in Arm A.⁶³ Non-skin cancer malignancies were generally similar across treatment arms (16 [6.0%] in Arm I and 10 [3.7%] in Arm A). Non-melanoma skin cancer was reported in 3 participants (1.1%) in Arm I, and one participant in Arm A (0.4%); melanoma skin cancer was reported in 1 participant (0.4%) in Arm I, and no participants in Arm A.⁶³

A summary of the remaining significant AEs reported in the Safety Analysis Set is presented in Table 27, demonstrating that these were generally well-balanced between treatment arms. As shown in Table 27, the majority of significant AEs were <Grade 3, and no fatal AEs were reported, except for fatal infections (of which fewer occurred in Arm I [4 deaths] than in Arm A [6 deaths]). Three categories of significant AE were slightly elevated in Arm I vs Arm A: cardiac arrhythmias, interstitial lung disease and infections. These data should however be considered with the context that patients in Arm I had a considerably longer treatment duration than patients in Arm A, 28.45 months vs. 5.16 months, respectively.⁶³ As such, the fact that patients in Arm I only experienced slightly elevated significant AEs versus Arm A despite receiving treatment for over a 5-times longer duration, exemplifies the improved tolerability of the ibrutinib regimen versus the ASCT regimen. Furthermore, the difference in infections can also be attributed to the fact that many more patients in Arm I were still on study treatment during the COVID-19 pandemic, as described in Section 2.12.2.

Table 27: Incidence of other significant AEs (Safety Analysis Set)

Significant AE, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Cardiac arrhythmias						
Atrial fibrillation	26 (9.8%)	10 (3.8%)	0	6 (2.2%)	5 (1.9%)	0
Other cardiac arrhythmia (excluding atrial fibrillation)	34 (12.8%)	7 (2.6%)	0	24 (9.0%)	7 (2.6%)	1 (0.4%)
Cardiac failure	5 (1.9%)	0	0	3 (1.1%)	1 (0.4%)	0

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Significant AE, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Hypertension	36 (13.6%)	14 (5.3%)	0	24 (9.0%)	12 (4.5%)	0
Interstitial lung disease	12 (4.5%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Ischemic stroke	2 (0.8%)	0	0	2 (0.7%)	0	0
Cytopenic AEs	224 (84.5%)	209 (78.9%)	0	233 (86.9%)	225 (84.0%)	0
Tumour lysis syndrome	██████	██████	█	██████	██████	█
Hepatotoxicity including hepatic failure	5 (1.9%)	0	0	2 (0.7%)	0	0
Infections	186 (70.2%)	72 (27.2%)	4 (1.5%)	137 (51.1%)	56 (20.9%)	6 (2.2%)

Abbreviations: AE: adverse event.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

2.12.8 Deaths

At the 09 May 2024 CCO, there was a total of 93 deaths, with more deaths occurring in Arm A (60 deaths, 22.4%) compared with Arm I (33 deaths, 12.5%).⁶³ Notably, patients in Arm A were on treatment for a five times shorter duration than those in Arm I, yet nearly double the number of deaths occurred in Arm A, underscoring the high toxicity and regimen-related mortality associated with ASCT, as well as the reduced treatment efficacy versus the ibrutinib regimen.

Of note, 30 (11.2%) deaths in Arm A and 14 (5.3%) in Arm I were attributed to disease progression (PD). The higher rate of PD-related deaths in Arm A emphasises the importance of extending the time patients spend without disease progression to improving survival outcomes in this patient population. Of relevance, efficacy data presented in Section 2.6 demonstrate that the ibrutinib regimen is associated with a nominally significant 36.7% (p-value: 0.0060) reduction in the risk of disease progression, thereby delaying progression and improving survival outcomes.⁶³

When considering fatal TEAEs, almost twice as many Grade 5 TEAEs occurred in patients in Arm A compared to Arm I (4.1% vs. 2.3%, respectively).⁶³ This is despite the fact that patients in Arm I had a significantly longer study drug exposure (greater than five-fold, see Section 2.12.1) and therefore a correspondingly longer treatment-emergent period.⁶³ In addition, there was an increase in early fatal events shortly after the end of induction treatment for patients treated with ASCT regimen, which correlates to the early decrease observed in the OS KM curves (see Section 2.6.2).⁶³ This is likely reflective of the toxicity-related burden of disease for HDT and ASCT, which can lead to treatment-related mortality.

There were 4 (1.5%) COVID-19 related deaths in Arm I and 2 (0.7%) in Arm A. As noted in Section 2.12.2 however, the majority of patients were enrolled before the COVID-19 outbreak was declared a pandemic by WHO in March 2020, therefore, a high proportion of patients had already completed the approximate 5 months of study treatment in Arm A before March 2020, while study treatment was still ongoing for patients in Arm I, who received study treatment with up to 2 years ibrutinib maintenance, with or without rituximab maintenance.⁶³

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2.13 **Ongoing studies**

TRIANGLE is ongoing, but the Company is not aware of any plans from the European MCL network for future data cuts in the ITT analysis to be made available during or shortly after this submission. Importantly, consistent with the derivation of the FAS (see Section 2.4.1), no further data cuts will be available for the purpose of HTA. There are no other ongoing studies for ibrutinib in the population of interest to this appraisal.

2.14 **Interpretation of clinical effectiveness and safety evidence**

A significant unmet need exists in patients with previously untreated MCL for new, efficacious and tolerable front-line treatment options which remove the need for ASCT, and thus the vast physical and psychological burden associated with current SoC

MCL is an aggressive and incurable lymphoma associated with poor prognosis.⁸³ Whilst current treatment options prolong survival, nearly half of patients with newly diagnosed MCL will eventually experience disease relapse.²² Once MCL progresses to a r/r state, treatment options become limited and the chances of achieving durable remission are significantly reduced, further impacting patient prognosis.⁵ With each line of subsequent treatment, survival rates decline in patients with MCL.²¹ There therefore remains a critical unmet need for first-line treatment options with improved efficacy that are able to delay disease progression and ultimately improve survival outcomes for patients with untreated MCL, as supported by feedback from five UK clinicians elicited during the November 2025 advisory board.⁴²

Furthermore, existing SoC in UK clinical practice, the ASCT regimen, imparts a substantial clinical burden and has a detrimental impact on patients QoL.^{26, 27, 55, 56} This toxic and complex treatment causes severe side effects and is associated with considerable healthcare resource use.²⁶ Nearly half (46%) of patients will experience at least one side effect following ASCT treatment.³⁷ Furthermore, treatment with ASCT involves conditioning with HDT, which causes a wide range of side effects including sore mouth, nausea, vomiting, diarrhoea, constipation, anaemia and thrombocytopenia.^{26, 27} Another significant concern is the risk of severe infection due to immunosuppression, which can result in serious complications or even death.²⁶ These AEs significantly impact patients' QoL causing patients considerable anxiety surrounding treatment.^{26, 27}

Beyond the severe side effects, patients undergoing ASCT must also endure the complex treatment procedure. ASCT involves hospitalisation for up to a month, followed by intensive post-treatment monitoring, including weekly follow-ups and blood transfusions.^{26, 27} During this period, it is common for patients to see an increase in symptoms, such as fatigue and treatment-related pain.^{43, 44} It can take patients up to six months to recover and return to normal day to day life (such as work).^{26, 55} This lengthy recovery and associated follow-up further highlights the significant physical and psychological long-term burden existing SoC places on patients.²⁷

Combined, these factors demonstrate that a substantial unmet need exists in patients with untreated MCL for an additional first-line treatment option which is associated with improved efficacy and a more tolerable safety profile than existing SoC. The substantial unmet need and therefore desire in the clinical community for an alternative treatment to the ASCT-regimen is underscored by the investigator-initiated nature of TRIANGLE (the pivotal evidence base for the ibrutinib regimen in patients with untreated MCL). Results from TRIANGLE demonstrate that the

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ibrutinib regimen is an effective treatment option that has the potential to reduce the substantial existing clinical burden in patients with MCL.

Principal findings of TRIANGLE

As noted above, the pivotal evidence for ibrutinib with immunochemotherapy in patients with untreated MCL in this submission is provided by TRIANGLE. TRIANGLE is an investigator-initiated randomised, open-label, three-arm, parallel group, Phase III trial in patients with untreated MCL.

Efficacy evidence from TRIANGLE demonstrate that treatment with the ibrutinib regimen substantially prolongs FFS, PFS and OS vs. existing SoC, whilst avoiding the significant toxicity burden associated with the ASCT regimen

The primary endpoint of TRIANGLE was FFS. At the latest CCO after a median time on study of [REDACTED] and [REDACTED] months in Arm I and Arm A respectively, TRIANGLE found that patients treated with the ibrutinib regimen had a nominally significant 36.1% (HR: 0.639 [98.33% CI: 0.428, 0.953], p-value: 0.0068) reduction in the risk of stable disease at the end of induction, progressive disease or death (i.e. prolonged FFS) vs. patients treated with the ASCT regimen.^{30, 63} As treatment guidelines for MCL state that stable disease is an indication for salvage treatment, and is therefore a sign of treatment failure, the observed improvements in FFS demonstrate that ibrutinib with immunochemotherapy is a more efficacious first-line treatment than existing SoC with the ASCT regimen in UK clinical practice.

The observed improvement in FFS were found to be consistent across a range of subgroups explored; most analyses demonstrated that the ibrutinib regimen (Arm I) was associated with at least numerical improvements in FFS vs. the ASCT regimen (Arm A).⁶³ A small difference in FFS was observed between rituximab subgroups. However, it should be noted that patients who received rituximab represent an enriched patient population: rituximab was only provided as maintenance therapy following successful completion of induction treatment in Arm I or consolidation ASCT in Arm A.⁶³ Additionally, use of rituximab maintenance was well balanced between treatment arms (60% vs. 63% in Arms I and A, respectively) and therefore any differences in treatment effect resulting from its use would not impact the relative efficacy estimates obtained from TRIANGLE; as demonstrated by the rituximab maintenance adjusted analyses presented in 2.9. These results therefore provide confidence that the observed relative treatment effect between the ibrutinib and ASCT regimens in TRIANGLE are generalisable to UK clinical practice and therefore suitable for UK-decision making and therefore adjusted analyses are not required to inform the cost-effectiveness analyses.

PFS results were consistent with FFS results; a nominally significant 36.7% reduction in the risk of progressive disease or death was observed in patients treated with ibrutinib regimen compared to the ASCT regimen (HR: 0.633 [98.33% CI: 0.424, 0.946], p-value: 0.0060).⁶³ While the median PFS was not reached in either treatment arm, the KM curves for PFS demonstrated a clear and early separation favouring Arm I over Arm A.⁶³ The extended PFS observed with the ibrutinib regimen in TRIANGLE is a critical outcome for patients with MCL as it delays the need for subsequent therapies, which are associated with declining survival rates and reduced HRQoL.^{5, 21, 22}

The observed FFS and PFS results were found to translate to a nominally significant and clinically meaningful improvement in survival (OS) for patients treated with the ibrutinib regimen

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compared to existing standard of care with the ASCT regimen.⁶³ Whilst median OS was not reached in either treatment arm, at a median time on study of [REDACTED] months and [REDACTED] months for patients in Arm I and Arm A, respectively, patients in Arm A had experienced almost twice as many OS events vs. Arm I (22.3% vs 12.3%, respectively).^{30, 63} These results translated to a nominally significant and clinically meaningful reduction in the risk of death for patients receiving the ibrutinib regimen compared with the ASCT regimen (HR: 0.522 [95% CI: 0.341, 0.799], nominal p-value: 0.0023).⁶³ The OS results are further supported by the consistently numerically improved survival rates in Arm I vs Arm A observed from 6 months ([REDACTED] vs. [REDACTED]) up to 84 months ([REDACTED] vs. [REDACTED]).³⁰ Furthermore, the KM OS curves demonstrate a clear and early separation in favour of Arm I over Arm A from as early as 6 months.⁶³ Together, these results demonstrate that treatment with the ibrutinib regimen is associated with a clear survival benefit in patients with previously untreated MCL vs. existing SoC with the ASCT regimen.

Furthermore, patients treated with ibrutinib regimen are able to avoid the HDT related toxicity experienced in patients treated with the ASCT regimen. The high levels of toxicity are demonstrated by the sharp initial drop in OS KM curves in Arm A compared with Arm I at 6 months, which correlates to receipt of treatment with HDT followed by ASCT in Arm A.⁶³ Overall, these OS results combined highlight that the avoidance of toxicity related mortality and improved disease control (prolonged FFS and PFS) experienced by patients treated with the ibrutinib regimen translate to prolonged survival in patients with previously untreated MCL.

Regarding response rates, the ORR was comparable but numerically higher for patients in Arm I (96.3%) compared with Arm A (92.2%). Similarly, CRR was comparable but numerically higher for patients in Arm I (67.2%) and Arm A (64.7%).⁶³ These results demonstrate that patients treated with the ibrutinib regimen experience at least the same high rate and depth of response as that experienced by patients receiving the ASCT regimen.³⁰ Furthermore, no nominally significant difference in PR to CR conversion rates post induction was observed between Arm I (43.5%) and Arm A (50.7%).⁶³ These results demonstrate that maintenance treatment with ibrutinib is able to convert partial responses to complete responses as effectively as existing SoC with ASCT but without the associated toxicity burden.

Safety data from TRIANGLE demonstrate that the ibrutinib regimen is associated with an improved tolerability profile; patients can be exposed to the ibrutinib regimen for five times as long before experiencing a similar toxicity profile to the ASCT regimen, thus alleviating the substantial HRQoL burden associated with existing treatment

Median treatment duration was 28.45 months for patients receiving the ibrutinib regimen vs. 5.16 months for patients receiving the ASCT regimen.⁶³ This is equivalent to a treatment exposure more than 5-fold longer for patients in Arm I compared with patients in Arm A.⁶³ Despite the significantly longer treatment-emergent period for patients treated with the ibrutinib regimen, rates of TEAEs were similar across treatment arms; 99.2% of patients in Arm I and 99.6% of patients in Arm A reported experiencing at least 1 TEAE, of which 93.2% and 93.3%, respectively, were Grade ≥3.⁶³ Notably, when considering fatal TEAEs, fewer Grade 5 TEAEs were experienced by patients in Arm I (6 events [2.3%]) compared with Arm A (11 [4.1%]).³⁰ Finally, more than twice as many deaths were reported in patients in Arm A vs. Arm I (22.4% vs. 12.5%, respectively).⁶³ Together, these results demonstrate that the ibrutinib regimen is able to minimise the acute toxicity-related mortality-risk associated with existing SoC with the ASCT regimen. The importance of the avoidance of such acute toxicities was highlighted by feedback received from UK clinical experts who noted that ASCT was extremely toxic with severe and prolonged side effects that have a significant detrimental impact on patient quality of life.⁶ This Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

was supported by the patients themselves who reported the widespread and significantly life-altering burden that ASCT, and the range of AEs associated throughout the ASCT process, imparts on their lives (Section 1.3.5).²⁷

Although the investigators did not collect HRQoL data within TRIANGLE, the outcomes presented are expected to translate to improvements in patients HRQoL and psychological status. The avoidance of the acute toxicity and associated mortality risk associated with the HDT-ASCT regimen will likely result in a reduced toxicity burden as well as reduced anxiety, due to a reduced fear of death in patients. Furthermore, given that disease progression is associated with worsening symptoms and prognosis, extending the time to progression is expected to translate to improvements in patient HRQoL, as patients are able to remain in a state with a reduced clinical burden for longer.

Strengths and limitations of the clinical evidence base

TRIANGLE is a high-quality, large, randomised, Phase III clinical trial which provides direct evidence on the ibrutinib regimen versus existing SoC in UK clinical practice

TRIANGLE is a large, randomised, Phase III clinical trial conducted by the European MCL network, an expert collective of 15 national and multinational lymphoma study groups.⁸⁴ TRIANGLE is a high-quality trial (as assessed via the Cochrane Risk of Bias tool; see Section 2.5), that provides robust, direct evidence on the efficacy and safety of the ibrutinib regimen (Arm I) vs. the ASCT regimen (Arm A) in patients with untreated MCL. As the ASCT regimen represents SoC in this patient population in UK clinical practice, TRIANGLE provides robust direct evidence on the relative efficacy of the two treatments, thus eliminating the need for indirect treatment comparisons and hence minimising uncertainty.

Despite the international nature of TRIANGLE, results are highly generalisable to UK clinical practice, as supported by patients baseline characteristics and treatment regimens received. Whilst rituximab maintenance usage was slightly lower versus anticipated use in UK clinical practice, sensitive analyses demonstrated that this did not impact the generalisability of results to UK clinical practice

Overall, the baseline demographic and disease characteristics of patients in TRIANGLE were considered highly generalisable to the population of patients expected to receive ibrutinib with immunochemotherapy in UK clinical practice. Across both treatment arms, baseline demographics such as age, sex, weight and BMI were well balanced and reflective of UK clinical practice. Furthermore, all disease characteristics, including MIPI risk group, ECOG PS, therapy and Ann Arbor stage of MCL, were well balanced across treatment arms and considered broadly reflective of a population of patients who would be fit enough to receive ASCT in UK clinical practice, as supported by feedback received from five UK clinical experts.^{30, 42, 63}

While the trial did not include any UK-based sites, treatment recommendations are largely aligned between UK and European guidelines (see Section 1.3.4), suggesting that the results are unlikely to be materially impacted by this geographic difference. Overall, the trial population and treatment regimens support the applicability of the findings to UK clinical practice. It is however acknowledged that the use of maintenance rituximab within TRIANGLE is slightly reduced compared to usage in UK clinical practice, as evidence supporting treatment with rituximab maintenance was not yet established at the start of the trial. The potential impact of this was explored within subgroup analyses, however the enriched nature of the rituximab-treated population rendered these findings inconclusive. Importantly, however, as rituximab usage was Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

evenly distributed across treatment arms (60% vs. 63% in Arms I vs. A, respectively), any differences in treatment effect would not impact the generalisability of the relative treatment effect between Arm I and Arm A observed in TRIANGLE, to UK clinical practice.⁶³ This was demonstrated via the results of rituximab-adjustment analysis presented in Section 2.9, whereby the FFS and OS HRs, adjusted to align to the estimates proportion of patients expected to receive rituximab maintenance therapy in UK clinical practice [85%]), were highly aligned to those in the unadjusted analysis (see Table 19;Section 2.9). These results therefore provide confidence that conclusions regarding the comparative effectiveness of the ibrutinib regimen vs. the ASCT regimen in TRIANGLE are reflective of what would be observed in UK clinical practice.

Despite median OS not being reached at the latest CCO, results from TRIANGLE provide compelling evidence that the ibrutinib regimen is associated with clinically meaningful improvements in patient survival versus the ASCT regimen over a significant follow-up period of ~■ years

As expected, given the first-line indication of the ibrutinib regimen and substantial follow up required to obtain mature survival data, median OS was not reached at the time of the latest CCO. Despite this, the TRIANGLE data demonstrate that the ibrutinib regimen is associated with nominally significant improvements across all key survival endpoints assessed (FFS, PFS and OS) compared to the ASCT regimen.⁶³ Specifically, at a median study duration of ■ and ■ months in Arm I and Arm A, respectively, OS data demonstrated a nominally significant and clinically meaningful reduction in the risk of death in patients in Arm A vs. Arm I.^{30, 63} The OS results were further supported by the consistently numerically improved survival rates in Arm I vs Arm A observed from 6 months up to 84 months alongside the clear and early separation in favour of Arm I over Arm A from as early as 6 months in the OS KM curves.⁶³ Together, these initial results demonstrate that treatment with the ibrutinib regimen is associated with a clear survival benefit in patients with previously untreated MCL vs. existing SoC with the ASCT regimen based on the available data. Clinical experts consulted at the November 2025 advisory board highlighted the promising results of the ibrutinib regimen in TRIANGLE and emphasised the potential for the ibrutinib regimen to replace the ASCT regimen which they anticipated would have a strong positive impact on patient quality of life.⁴²

As TRIANGLE is an investigator initiated trial, there are some unavoidable limitations in terms of data availability; however, the data remain generalisable and relevant to UK clinical practice, as validated by UK clinical experts⁴²

An unavoidable limitation of TRIANGLE is its open-label nature and lack of blinding. Due to the omission of ASCT and the earlier start of maintenance in the ibrutinib arm, blinding of neither the ASCT arm nor the ibrutinib arm was feasible, based on the methods of treatment administration. As noted above however, despite this limitation TRIANGLE was still deemed to be of high quality based on the Cochrane RoB tool 2.0; see Section 2.5).⁶⁶ A further limitation, due to the investigator-initiated nature of the trial, was that some outcomes were not captured, including HRQoL data.

Finally, as TRIANGLE was an investigator-initiated trial, per EU GDPR, reconsent of TRIANGLE patients was required to use TRIANGLE data for submission to HTA bodies, such as NICE.⁷⁰ This ultimately meant that 93% of patients from the ITT population were included in the FAS presented within this submission. Although an unavoidable limitation, the percentage of patients who did not provide reconsent was low and comparable between treatment arms. Additionally, baseline characteristics between the ITT and FAS analysis sets were highly consistent (see

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Appendix K.1).⁶³ This, along with supportive clinical expert opinion, indicates that there are no clinically meaningful differences between the two analysis sets and therefore use of the FAS over the ITT is not anticipated to have a meaningful impact on results.⁶ Furthermore all patients enrolled in the trial who were treated in Israel did not re-consent, owing to the geopolitical situation in Israel throughout the consenting period (Q3 2023 to Q2 2024).³⁰ As the baseline characteristics and management of MCL in Israel is likely to be the most different compared to the UK, the exclusion of these patients is only anticipated to increase the generalisability of the study results to patients in UK clinical practice.

Overall, data from TRIANGLE are robust and generalisable to UK clinical practice, as reinforced by feedback received from UK clinical experts.⁴² The comprehensive study design, with consistent results across multiple endpoints, enhances confidence in the validity of the outcomes.

Summary

The results of TRIANGLE demonstrate that, if reimbursed, the ibrutinib regimen will address the significant unmet need in patients with untreated MCL for a treatment with improved efficacy and a more manageable safety profile vs. existing SoC with the highly toxic ASCT regimen

The results of TRIANGLE demonstrate that treatment with the ibrutinib regimen can address several key areas of existing unmet need in patients with untreated MCL. Firstly, treatment with the ibrutinib regimen substantially prolongs FFS, PFS and OS vs. existing SoC with the ASCT regimen. Ibrutinib therefore represents a highly efficacious treatment which delays disease progression and improves survival outcomes for patients with untreated MCL. These results are particularly important considering that MCL is an incurable disease with the poorest prognosis of all types of NHL.^{5, 28, 40, 41} Furthermore, this addresses the top priorities for patients with MCL given patients report that three most important factors when choosing a treatment are increased life expectancy, seeing a clear improvement from the treatment and slowing the diseases progression.²⁷ In addition to improved survival, the ibrutinib regimen is associated with a more manageable tolerability profile, enabling patients to avoid the significant acute-toxicity burden associated with the ASCT regimen. In particular, the ibrutinib regimen is able to reduce the risk of AE-related mortality. Overall, the results of TRIANGLE demonstrate that, if reimbursed, the ibrutinib regimen will address the significant unmet need in patients with untreated MCL for a treatment option with improved efficacy and a more manageable safety profile vs. existing SoC with the highly toxic ASCT regimen.

3 Cost effectiveness

Summary of the cost-effectiveness model

- A cost-utility model was developed to determine the cost-effectiveness of the ibrutinib regimen vs. the ASCT regimen for the treatment of patients with untreated MCL who are eligible for ASCT from a UK NHS and personal social services (PSS) perspective.
- In line with a prior economic evaluation accepted by NICE as being suitable for decision-making assessing a similar fixed duration regimen of ibrutinib with immunochemotherapy in an untreated B-cell lymphoma patient population [TA891], the model was a semi-Markov model comprised of four mutually exclusive health states: (i) failure-free on first-line treatment (FF 1L), (ii), progression-free on second-line treatment (PF 2L), (iii) progressed disease (PD) and (iv) death.
 - All patients entered the model in the FF 1L health state and began active 1L treatment.
- The model had a 21 day cycle length (with half cycle correction). A lifetime time horizon of 43 years (given a starting age of 57 years) was used to sufficiently capture the remaining lifetime of patients from the initiation of their treatment.

Model inputs

Transition probabilities

- TRIANGLE (the pivotal evidence base for the ibrutinib regimen in the target indication for this appraisal) and RAY-3001 (a Phase III trial evaluating the efficacy of ibrutinib among patients with r/r MCL who had received at least one rituximab-containing chemotherapy regimen) were the primary sources of clinical data informing transition probabilities between health states within the economic model.^{30, 85}
- Transitions from **FF 1L to Death** (pre-failure mortality on first-line treatment) were modelled separately for each regimen using pre-failure mortality data from Arm I and Arm A of TRIANGLE, respectively. Due to low pre-failure event numbers, a pre-failure annual mortality rate (AMR) was derived for each arm, thus deriving a constant probability of pre-failure death for each regimen (■■■■% and ■■■■% per cycle probability, for the ibrutinib and ASCT regimen, respectively).
- Transitions from **FF 1L to PF 2L** (failure on first-line treatment) were modelled separately for the ibrutinib regimen and the ASCT regimen using time-to-failure (TTF) data from Arm I and Arm A of TRIANGLE, respectively. The exponential was selected in the base case for TTF for the ibrutinib regimen (see Section 3.3.2). Similarly, the gamma extrapolation was selected for the ASCT regimen.
- Transitions from **PF 2L to Death** were modelled using an AMR derived from the ibrutinib arm of RAY-3001 (one prior line subgroup) to derive a constant probability of pre-progression death (■■■■% per cycle).
- Transitions from **PF 2L to PD** (progression on second-line treatment) for patients receiving second-line treatment with ibrutinib (regardless of first-line treatment) were modelled using time-to-progression (TTP) data from the ibrutinib arm of RAY-3001 (one prior line of therapy subgroup). Standard parametric distributions were fitted to RAY-3001 TTP KM data to act as a 'reference' curve to inform TTP in the model; the log-logistic was selected in the base case (see Section 3.3.4).
 - Differential weighted HRs were applied to this reference curve to derive the final modelled TTP curves for the ibrutinib and ASCT regimens, respectively, based on the subsequent treatment distributions and relative efficacy between subsequent treatments used in the 2L setting in UK clinical practice (see Section 3.3.4).
- Transitions from **PD to Death** (mortality on third-line treatment) were modelled for patients receiving third-line treatment using post-progression survival (PPS) data from the ibrutinib arm of RAY-3001 (one prior line subgroup). Parametric distributions were fitted to the PPS data; the exponential was selected for the base case curve (see Section 3.3.5).

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- Crucially, OS landmark survival estimates predicted by the semi-Markov model (based on the base case modelling approach) were closely aligned with the clinical expert estimates of OS for both the ibrutinib regimen and the ASCT regimen, with any difference between clinical expert estimates and the model-predicted estimates remaining less than <2.5% across all landmark timepoints. These findings demonstrate that the long-term predictions of OS from the model align closely with expected outcomes in UK clinical practice, thereby demonstrating that the model is associated with high external validity in relation to the modelling of long-term survival estimates.

Other model inputs

- To account for the impact on patient HRQoL and resource use resulting from AEs experienced by patients on first-line treatment, AEs were included in the FF 1L health state of the model, informed by safety data from TRIANGLE for both the ibrutinib regimen and the ASCT regimen (Section 3.4.4 and Section 3.5.4).
- In the absence of utility data from TRIANGLE, health state utility values (HSUVs) were sourced from the literature. The HSUV for the FF 1L health state was derived from the SHINE trial.⁸⁶ HSUVs for the PF 2L and PD health states were aligned with accepted HSUVs for BTKis reimbursed in the second-line setting (ibrutinib; TA502¹¹ and zanubrutinib; TA1081).^{51, 85, 87} HSUVs were treatment-independent (Section 3.4).
- Costs in the model (acquisition, administration, subsequent treatments, routine care and monitoring, AEs and ASCT complications and terminal care costs) were aligned with the established sources of costs within the NHS, the NICE reference case and prior appraisals in non-Hodgkin's B-cell lymphoma.⁸⁸⁻⁹³

Summary of cost-effectiveness results

- Overall, the base case with-patient access scheme (PAS) incremental cost-effectiveness ratios (ICERs) demonstrated the ibrutinib regimen to be a cost-effective use of NHS resource at a willingness-to-pay (WTP) threshold of £30,000 per quality-adjusted life year (QALY).
- In the base case probabilistic analyses, the ibrutinib regimen was associated with ■■■ life years gained (LYG) and ■■■ QALYs vs. the ASCT regimen, highlighting the significant improvements in both quality and length of life that the ibrutinib regimen may offer to patients in this setting compared to the ASCT regimen. Alongside a cost-saving of £■■■, the ibrutinib regimen was found to be dominant versus the ASCT regimen
- It should be noted that these base case results omit important benefits that cannot be captured in the QALY, including the significantly reduced toxicity associated with the ibrutinib regimen and subsequent anticipated improvements in patient HRQoL given the lack of inclusion of treatment dependent HSUVs for the FF 1L health state. The introduction of the ibrutinib regimen would also provide the significant value of hope to both patients and caregivers of an additional effective and more tolerable treatment choice in this setting. This value is not captured in the existing QALY calculations.
- Probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) and scenario analyses were conducted to assess uncertainty in the economic analysis and demonstrated that the base case cost-effectiveness results were robust to uncertainties in key model inputs and assumptions

These results demonstrate that, if recommended, the ibrutinib regimen would address the significant unmet need for patients with untreated MCL, by providing patients and their clinicians with an additional, convenient, more effective treatment option that allows patients to avoid the highly invasive and toxic ASCT procedure and its associated lengthy inpatient stays. In addition to the significant benefits for patients, the ibrutinib regimen represents a cost-effective use of NHS resources which would result in cost-savings to the NHS.

3.1 Published cost-effectiveness studies

An SLR was conducted to identify all relevant economic evaluations for the treatment of adult patients with untreated MCL, regardless of transplant eligibility status. Searches were performed in December 2023, and subsequently updated in May 2025 and October 2025. Full details of the SLR search strategy, study selection process and results of included studies, alongside the associated PRISMA diagram, are reported in Appendix E.

No cost-effectiveness analyses in patients with untreated MCL who are eligible for ASCT were identified via the SLR and its subsequent updates. One unique cost-effectiveness analysis in patients with untreated MCL who were ineligible for ASCT and one unique cost-effectiveness analysis in patients with untreated MCL who are ineligible for haematopoietic stem cell transplantation (HSCT) were identified; further details of these cost-effectiveness analyses are provided in Appendix E.

3.2 Economic analysis

No relevant economic evaluations comparing the ibrutinib regimen to the ASCT regimen from a UK perspective were identified in the SLR. As such, a *de novo* cost-effectiveness analysis was conducted for the purpose of this evaluation. The model is described in detail below.

The aim of the economic analysis was to determine the cost-effectiveness of the ibrutinib regimen vs. the ASCT regimen for treating untreated MCL. The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS), taking into account direct costs and benefits only.

The economic evaluation was approached as follows, in line with the NICE reference case:⁹⁰

- Health outcomes were measured both in terms of life years gained (LYG) and quality-adjusted life years (QALYs) gained
- All relevant costs were considered including treatment acquisition costs, treatment administration costs, AEs costs, subsequent treatment costs, resource use and monitoring costs and end-of-life costs (see Section 3.5)
- The primary outcome measure for the economic evaluation was the incremental cost-effectiveness ratio (ICER: cost per QALY gained) for the comparison of the ibrutinib regimen vs. the ASCT regimen
- To ensure all potentially relevant costs and benefits for the intervention and comparator were captured the model utilised a lifetime time horizon (given a starting age of 57, this was equivalent to 43 years, allowing the cohort to reach up to 100 years of age).
- The discount rate was set to 3.5% for both costs and benefits.

3.2.1 Patient population

The population of interest is adult patients with untreated MCL who are eligible for ASCT, which is in line with the decision problem for this submission, the licensed indication for ibrutinib in the UK and the patient population of the FAS of TRIANGLE.^{30, 82}

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Age and sex are included in the model to determine general population mortality and utility inputs. Mean body weight and body surface area (BSA) are also included in the model to calculate drug acquisition costs for intravenous (IV) treatments (see Section 3.5.1).

The characteristics of patients entering the model were based on the baseline characteristics of the TRIANGLE FAS population, pooled across Arm I and Arm A.³⁰ A summary of the patient baseline characteristics used in the economic model are presented in Table 28.

Table 28: Summary of baseline characteristics used in the economic model

Characteristic	MCL population	Source
Median age, years	57	TRIANGLE (FAS, pooled Arm I and Arm A)
Proportion of female patients, %	21.97%	
Mean body weight, kg	████	
Mean BSA, m ²	████	

Abbreviations: BSA: body surface area; FAS: Full Analysis Set; MCL: mantle cell lymphoma.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³⁰

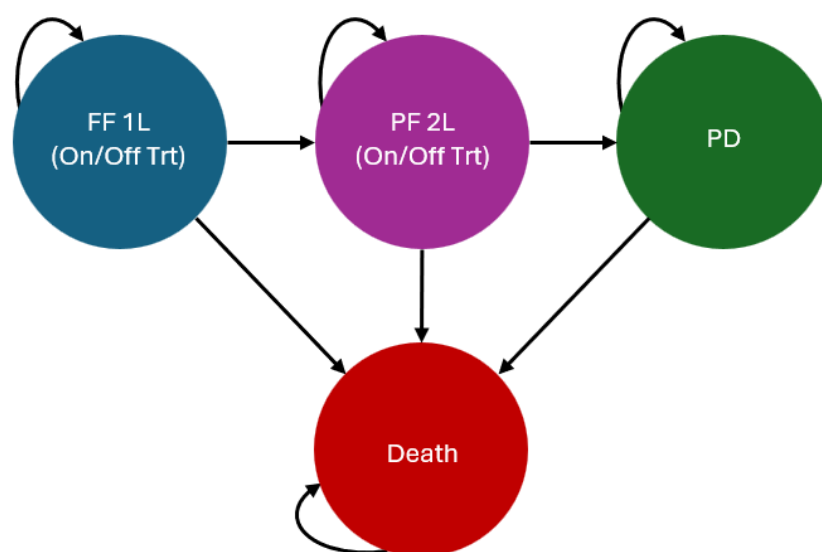
3.2.2 *Model structure*

A semi-Markov model, illustrated in Figure 12, was developed in Microsoft Excel. The semi-Markov model consists of four mutually exclusive health states:

- **Failure-free on first-line (1L) treatment (FF 1L):** Patients in this health state are alive and failure-free on 1L treatment. Patients who are failure-free have not experienced stable disease at the end of induction, progressive disease or death from any cause (in line with the definition of FFS in the TRIANGLE trial detailed in Section 2.6.1)
 - As both the ibrutinib and ASCT regimen are fixed-duration treatments, patients may be either on or off active treatment in this state
- **Progression-free on second-line (2L) treatment (PF 2L):** Patients in this health state are alive and pre-progression on 2L treatment
 - Patients may be either on or off active treatment in this state
- **Progressed disease (PD):** Patients in this health state have progressed disease and are receiving third-line (3L) treatment.
 - Patients remain on their 3L treatment until death.
- **Death:** Patients who have died within the model time horizon

The model explicitly considers up to three lines of active treatment as OS is estimated through summing the time spent in each of the alive health states (FF 1L, PF 2L and PD).

Figure 12: Semi-Markov model diagram



Abbreviations: 1/2L: first/second line; FF: failure-free; FFS: failure-free survival; PD: progressive disease; PF: progression-free; Trt: treatment; TTF: time to failure.

Justification for choice of model structure

A semi-Markov model was deemed the most appropriate model structure to robustly and transparently capture the costs and benefits associated with the ibrutinib regimen. The choice of model structure was driven by several key considerations.

Given the pronounced improvement in FFS and low number of OS events associated with the ibrutinib regimen in TRIANGLE, despite the long-term follow-up (54.9-month median follow-up), it was necessary to choose a modelling approach that could reduce uncertainty in long-term OS estimates. A Markov model enables additional external data sources to be incorporated to more robustly model long-term OS estimates.³⁰ In this instance, use of a Markov model structure enabled external IPD from the RAY-3001 trial, the principal evidence source informing the reimbursement of ibrutinib in the 2L setting in MCL by NICE [TA502], to be incorporated into the economic model.⁸⁹ Use of the RAY-3001 data enabled data specific to each line of treatment to be leveraged, thus reducing the dependency of long-term OS estimates on the TRIANGLE data alone and ultimately reducing uncertainty in long-term OS estimates.⁸⁹ Details of how the RAY-3001 trial was utilised to inform transition probabilities in the economic model are provided in Section 3.3.

Available data from TRIANGLE were reviewed to ensure that the model appropriately captured the clinical profile of ibrutinib and ASCT in 1L MCL. The TRIANGLE endpoints were consistent with the key aspects identified that affect patient outcomes and decisions around subsequent treatments in MCL in the UK.⁴² The semi-Markov model structure explicitly considers efficacy and costs in up to two subsequent lines of active therapy to capture the relapsing and refractory nature of MCL. The availability of IPD data from TRIANGLE also allowed the model to incorporate treatment-line specific efficacy including time-to-failure (TTF) at first line and pre-failure mortality. The cost-effectiveness SLR did not identify any economic evaluations or assessments by NICE in the population of interest to this appraisal: untreated patients with MCL who are eligible for ASCT. Therefore, the approach chosen was aligned to models accepted by NICE as appropriate for decision making in B cell lymphoma indications of the same intervention Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

which also used a Markov approach.^{88, 89} As mentioned in Section 3.1, the SLR did identify a cost-effectiveness analysis in patients with untreated MCL who were ineligible for HSCT, which also used a Markov approach.⁹⁴

The most relevant model identified was in TA891 which assessed ibrutinib plus venetoclax for patients with untreated CLL. Owing to the lack of availability of models in untreated MCL, this model was deemed the most relevant as it assessed a similar patient population (first-line untreated patients with a B-cell lymphoma) and also included a fixed-duration ibrutinib regimen as first-line treatment. TA891 utilised a four-health state semi-Markov model, with some differences on how the transitions in first line treatment were estimated.⁸⁸ Importantly, in the appraisal of TA891, the committee noted that there were limitations with the approach taken to model pre-failure mortality. In the semi-Markov model presented in this submission, these limitations were addressed by capturing mortality during FF 1L on the basis of separate estimates of time to treatment failure (TTF), defined as stable disease at the end of induction immunochemotherapy, or progressive disease, whichever came first (patients who experienced a pre-failure mortality event were censored), and time to pre-failure death, derived directly from the IPD data available from TRIANGLE (see Section 3.3). NICE TA502 for the reimbursement of ibrutinib in r/r MCL also used a three-state Markov model.⁸⁹ These two TAs therefore demonstrate that the model structure utilised in this submission is appropriate for decision making.

Patient journey through the model

All patients enter the model via the FF 1L health state and begin receiving active first-line treatment consisting of either the ibrutinib regimen or the ASCT regimen (full details of the treatment regimens are provided in Section 3.2.3). Patients can either remain in this state, fail first-line treatment and progress to the PF 2L health state, or die, during each 21-day cycle. As first-line treatment with either the ASCT regimen or the ibrutinib regimen are fixed-duration treatments, patients may be off active treatment while they are in FF 1L state. Collectively, transitions from the FF 1L health state are informed by FFS. As noted in Section 2.6.1, FFS is a more stringent endpoint than PFS which includes stable disease at the end of induction immunochemotherapy as an event, in addition to progressed disease and death. Stable disease following induction immunochemotherapy is an indication for salvage treatment based on treatment guidelines for MCL, as only patients achieving at least a PR can proceed to the next treatment phase.^{64, 95} As such, stable disease is a marker of lack of treatment efficacy, making FFS a measure more closely aligned with UK clinical practice. This was validated by feedback received from five UK clinical experts consulted at the November 2025 advisory board.⁴²

Within any given cycle patients could fail first-line treatment and transition from the FF 1L health state to the PF 2L health state. Upon treatment failure patients enter the PF 2L health state and begin the next line of active therapy. Patients in the PF 2L state remain in this state until disease progression or death. As in the FF 1L health state, some second-line treatments reimbursed in the UK are fixed duration, and patients may either remain on active treatment if receiving a treat-to-progression regimen (e.g., BTK inhibitor) or until the end of treatment if on a fixed-duration regimen (e.g., R-BAC [rituximab, bendamustine, and cytarabine]) whilst in this state. Upon disease progression, patients enter the PD health state and receive third-line treatment. Patients remain in the PD state until death. Death can occur at any time in the model and is an absorbing health state.

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The model follows patients in the PF 2L and PD health states to facilitate the consideration of time-varying transition probabilities, which were applied relative to the timepoint at which a patient first enters these health states.

The per-cycle transitions included in the economic model are depicted via the nine arrows in Figure 12. The sources informing these transition probabilities and their corresponding derivation methods, are described in full in Section 3.3.

Features of the economic analysis

Costs and health-related utilities were allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The following costs were considered in the model: drug acquisition and administration applied for the duration of active treatment (determined by dosing regimen and treatment duration data from clinical trials), routine follow-up care and costs of unplanned events such as AEs, progression, and terminal care costs. Effectiveness measures included life years (LYs) and QALYs. The ICER of the ibrutinib regimen vs. the ASCT regimen was evaluated in terms of the incremental cost per QALY gained.

As noted above, given that no prior NICE appraisals were identified for untreated patients with MCL eligible for ASCT (see Section 3.1), the most relevant economic evaluations included in prior NICE appraisals were deemed to be TA891, assessing fixed-duration ibrutinib plus venetoclax for patients with untreated chronic lymphocytic leukaemia (CLL) and TA502 assessing ibrutinib for patients with r/r MCL.⁸⁸ A comparison of the key features of the economic analysis presented in this submission compared with the economic analyses presented in TA891 and TA502 is provided in Table 29.

Table 29: Features of the economic analysis

Factor	Previous evaluation		Current evaluation	
	TA502 ¹¹	TA891 ⁸⁸	Chosen values	Justification
Model structure	Markov model	Semi-Markov model	Semi-Markov model	In line with the approach used in the only other model for ibrutinib fixed-duration regimen in a B-cell lymphoma appraised by NICE, a semi-Markov model was deemed the most appropriate to robustly and transparently capture the costs and benefits associated with the ibrutinib and the ASCT regimen and subsequent treatments available in UK clinical practice, as well as capturing the natural disease course and key clinical outcomes in MCL⁸⁸ Additionally, given the low number of OS events in the ibrutinib arm of TRIANGLE, despite the long-term follow-up, it was deemed necessary to choose a modelling approach that could provide flexibility in how long-term OS was estimated via incorporating external data to enable data specific to each line of treatment to be leveraged, thus reducing dependency of long-term OS estimates on the TRIANGLE data alone and ultimately reducing uncertainty in long-term OS estimates Additional justification for the choice of model structure is provided in the 'Justification for choice of model structure' section above
Time horizon	15 years	- FCR-unsuitable and high-risk patients: 30 years - FCR-suitable patients: 40 years	Lifetime (43 years)	In line with the NICE reference case, to ensure that all potentially relevant costs and benefits associated with the intervention and comparators were captured, a lifetime time horizon was chosen. Given the model had a starting age of 57, 43 years was deemed sufficient to capture the remaining lifetime of patients (up to 100 years) from the initiation of their treatment ⁹⁰
Cycle length	4-weeks	28-days	21-days	Aligned with the length of a treatment cycle during the induction phase of the ibrutinib regimen in TRIANGLE ³⁰
Half cycle correction	Included	Included (except for treatment acquisition costs and	Included	In line with recommended best practice to reduce the systemic overestimation and underestimation of costs and other

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		administration costs that are assumed to occur at the start of each model cycle)		outcomes, half cycle correction was included in the base case analysis ⁹⁶
Discount rate	3.5% for both costs and benefits	3.5% for both costs and benefits	3.5% for both costs and benefits	In line with the NICE reference case ⁹⁰
Perspective	NHS England and Wales	NHS/PSS in England	NHS/PSS in England	In line with the NICE reference case ⁹⁰
Source of utilities	PFS and PD state: Pooled EQ-5D data from RAY-3001 and SPARK-2001 were used to inform utility in both the PFS and PD health state. A mixed model analysis was carried out to determine the mean QoL pre and post progression for patients in the ibrutinib arm of the two studies^{87, 95}	PF state: Based on EQ-5D data collected in the GLOW trial PD state: Alternative values sourced from published literature and previous CLL submissions - Disutilities associated with AEs were sourced from previous CLL submissions	FF 1L state: Based on EQ-5D data collected in the ibrutinib arm of SHINE adjusted to the TRIANGLE patient population⁸⁶ PF 2L and PD state: Pooled EQ-5D data from RAY-3001 and SPARK-2001^{85, 87} - Disutilities associated with AEs were sourced from previous CLL submission and Lloyd et al. 2006^{88, 97}	FF 1L state:⁸⁶ No utility data were collected in TRIANGLE, and no utility data were identified in the SLR of HRQoL for patients with untreated MCL eligible for ASCT who received the same treatment as patients in TRIANGLE. Data from the SHINE trial were however identified in ASCT-ineligible patients with MCL which UK clinical experts deemed to be more suitable than HSUVs in other lymphomas, particularly given that it was in an untreated MCL population receiving an ibrutinib containing regimen at first-line. Additionally, IPD for SHINE were available and therefore SHINE HSUVs could be adjusted for key covariates, where available, to align with the TRIANGLE patient population. As such, owing to the paucity of HSUVs in this setting, adjusted HSUVs from SHINE were considered to represent the best available evidence. PF 2L and PD state: Feedback received from UK clinical experts indicated that the majority of patients with r/r MCL in the UK receive a BTKi at 2L.⁴² Therefore, in the absence of utility data from the TRIANGLE trial, HSUVs for the PF 2L and PD health states were aligned to the accepted utility values for these health states informing the only two BTKis reimbursed in the 2L setting by NICE (ibrutinib; TA502¹¹ and zanubrutinib; TA1081).^{51, 85, 87} Further details on the selection of HSUVs are provided in Section 3.4.2.
Source of costs	eMIT, MIMS, BNF and NHS reference costs	MIMS, BNF and NHS reference costs	BNF, eMIT, PSSRU, NICE NG52 and NHS reference costs	Established sources of costs within the NHS. In line with the NICE reference case and previous appraisals ^{11, 88, 90-93}

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Measure of health effects	QALYs	QALYs	QALYs	In line with the NICE reference case ⁹⁰

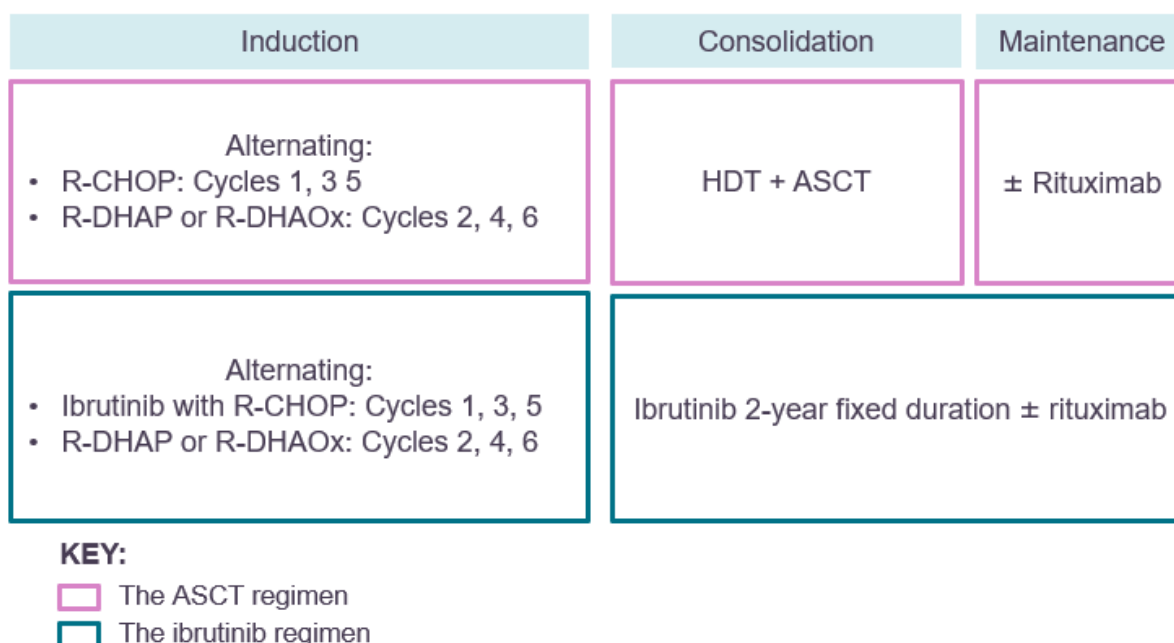
Abbreviations: 1/2L: first/second-line; AE: adverse event; ASCT: autologous stem-cell transplantation; BNF: British National Formulary; BTKi: Bruton's tyrosine kinase inhibitor; CLL: chronic lymphocytic leukaemia; eMIT: electronic market information tool; EQ-5D: EuroQol five dimensions; FCR: fludarabine, cyclophosphamide and rituximab; FF: failure-free; FFS: failure-free survival; IPD: individual patient data; MCL: mantle cell lymphoma; MIMS: Monthly Index of Medical Specialities; NG: NICE guidance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; PD: progressed disease; PF: progression-free; PPS: post-progression survival; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; QALY: quality-adjusted life-year; r/r: relapsed or refractory; SLR: systemic literature review; TA: technology appraisal; UK: United Kingdom.

3.2.3 Intervention technology and comparators

Ibrutinib regimen

As described in Section 1.1, the intervention included in the cost-effectiveness model was the ibrutinib regimen. The economic model assumed that patients on the ibrutinib regimen receive induction and maintenance treatments for a fixed duration, in line with the ibrutinib license, summarised in the dark blue boxes in Figure 13 and described in full in Table 30.⁸²

Figure 13: Treatment regimens in 1L MCL



Abbreviations: 1L: first-line; ASCT: autologous stem cell transplantation; HDT: high dose therapy; MCL: mantle-cell lymphoma; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and platinum.

Table 30: The ibrutinib regimen

Regimen component	Dose	Dosing regimen
Induction		
R-CHOP	Intravenous (IV) rituximab 375 mg/m ² on day 0 or 1, IV cyclophosphamide 750 mg/m ² on day 1, IV doxorubicin 50 mg/m ² on day 1, IV vincristine 1.4 mg/m ² on day 1, and oral prednisone 100 mg on days 1–5	Cycles 1, 3, 5
R-DHAP or R-DHAOx ^{a, b}	IV rituximab 375 mg/m ² on day 0 or 1, IV or oral dexamethasone 40 mg on days 1–4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on day 2, and IV cisplatin 100 mg/m ² over 24 h on day 1 or alternatively IV oxaliplatin 130 mg/m ² on day 1	Cycles 2, 4, 6
Ibrutinib	560 mg (4 x 140 mg capsules) orally every day (QD)	Days 1–19 of R-CHOP cycles
Maintenance		

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Ibrutinib	560 mg (4 x 140 mg capsules) orally QD In total, ■■■ of patients are modelled to receive ibrutinib maintenance treatment, based on the proportion of patients who achieved complete or partial response after induction immunochemotherapy in TRIANGLE	2-years fixed duration
Rituximab ^c	375 mg/m ² IV infusion given Q2M	Up to 3 years ^d

^a Patients received either R-DHAP or R-DHAox as part of their induction therapy, with proportions of patients receiving each informed by clinical expert opinion, in the absence of available data from TRIANGLE, as detailed in Section 3.5.1. ^b Pegfilgrastim was assumed to be given once on Day 6 on relevant cycles. ^c Rituximab maintenance is optional, with the proportion of patients receiving rituximab maintenance therapy in the model aligned to that received in TRIANGLE, as detailed in Section 2.3.1 and presented in Section 3.5.1. ^d As described in Section 1.3.4, duration of rituximab maintenance therapy varies in UK clinical practice. Based on feedback received from UK clinical experts at the November 2025 advisory board, 90% of patients were modelled to receive rituximab maintenance therapy for 2 years and 10% were modelled to receive rituximab maintenance therapy for 3 years.^{24, 42}

Abbreviations: IV: intravenous; Q2M: every two months; QD: every day; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAox: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and platinum.

ASCT regimen

As described in Section 1.1, the ASCT regimen is the only relevant comparator to the ibrutinib regimen in this appraisal. Patients were modelled to receive consolidation and maintenance treatment in line with TRIANGLE. However, given the predominant use of the NORDIC induction regimen in UK clinical practice, as highlighted by feedback received from UK clinical experts at the November 2025 advisory board, the ASCT regimen was modelled to include two potential induction regimens: alternating R-CHOP with R-DHAP or R-DHAox (20% of patients) or the NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine) (80% of patients).⁴² The proportion of patients receiving each induction regimen was aligned to usage in UK clinical practice. As feedback received from UK clinical experts indicated that these induction regimens are associated with equivalent efficacy, as supported by the BSH guidelines, only cost differences were modelled for these two induction regimens.^{4, 42} The ASCT regimen is summarised in the pink boxes in Figure 13 and detailed in full in Table 31.

Table 31: The ASCT regimen

Regimen component	Dose	Dosing regimen
Induction		
<i>R-CHOP alternating with R-DHAP or R-DHAox</i>		
R-CHOP	Intravenous (IV) rituximab 375 mg/m ² on Day 0 or 1, IV cyclophosphamide 750 mg/m ² on Day 1, IV doxorubicin 50 mg/m ² on Day 1, IV vincristine 1.4 mg/m ² on Day 1, and oral prednisone 100 mg on Days 1–5	Cycles 1, 3, 5
R-DHAP or R-DHAox ^{a, b}	IV rituximab 375 mg/m ² on Day 0 or 1, IV or oral dexamethasone 40 mg on Days 1–4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on Day 2, and IV cisplatin 100 mg/m ² over 24 h on Day 1 or alternatively IV oxaliplatin 130 mg/m ² on Day 1	Cycles 2, 4, 6
<i>NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine)</i>		
Maxi-CHOP ^b	IV rituximab 375 mg/m ² on Day 1, IV cyclophosphamide 1,200 mg/m ² on Day 1, IV doxorubicin 75 mg/m ² on Day 1 and IV vincristine 1.4 mg/m ² (maximum dose 2 mg) on Day 1	Cycles 1, 3, 5

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R-cytarabine ^b	IV rituximab 375 mg/m ² on Day 1, IV cytarabine 3g/m ² every 12 hours (total 4 doses) on Days 1 and 2	Cycles 2, 4, 6
Consolidation		
Stem cell mobilisation and harvest	5-10 µg/kg G-CSF until completion of stem cell harvest	Day 6 of R-DHAP or R-DHAox cycle 3
THAM ^c	- Total body irradiation with a total of 10 Gray (Day -7, to Day -5), cytarabine 2x1.5 g/m², Q12h (Day -4 and Day -3), and melphalan 140 mg/m² (Day -2) - Peripheral stem cells (2.0 x 10⁶/kg body weight CD34+ cells) transfused on Day 0 (2 days after melphalan)	
BEAM ^c	- Combined chemotherapy with carmustine 300 mg/m² (Day -7), cytarabine 2x200 mg/m², Q12h (Day -6 to Day -3), etoposide 2x100 mg/m², q12h (Day -6 to Day -3) and melphalan 140 mg/m² (Day -2) - Peripheral stem cells (2.0 x 10⁶/kg body weight CD34+ cells) transfused on Day 0 (2 days after Melphalan)	
Maintenance		
Rituximab ^d	375 mg/m ² IV infusion given Q2M	Up to 3 years ^e

Footnotes: ^a Patients received either R-DHAP or R-DHAox as part of their induction therapy, with proportions of patients receiving each informed by clinical expert opinion, in the absence of available data from TRIANGLE, as detailed in Section 3.5.1. ^b Pegfilgrastim was assumed to be given once on Day 6 of relevant cycles. ^c Only one of THAM or BEAM conditioning prior to ASCT was applied to patients who achieved complete or partial remission after induction immunochemotherapy. ^d Rituximab maintenance is optional, with the proportion of patients receiving rituximab maintenance therapy in the model aligned to that received in TRIANGLE, as detailed in Section 2.3.1 and presented in Section 3.5.1. ^e As described in Section 1.3.4, duration of rituximab maintenance therapy varies in UK clinical practice. Based on feedback received from UK clinical experts at the November 2025 advisory board, 90% of patients were modelled to receive rituximab maintenance therapy for 2 years and 10% were modelled to receive rituximab maintenance therapy for 3 years.^{24, 42}

Abbreviations: ASCT: autologous stem cell transplantation; BEAM: carmustine, cytarabine, etoposide and melphalan; G-CSF: granulocyte colony-stimulating factor; h: hour; IV: intravenous; Q12h: every 12 hours; Q2M: every two months; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAox: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and platinum; THAM: total body irradiation, cytarabine and melphalan.

3.3 Clinical parameters and variables

Summary of health states and transitions

As detailed in Section 3.2.2, the economic model is a semi-Markov model comprising four mutually exclusive health states: FF 1L, PF 2L, PD, and death. All patients enter the model in the FF 1L health state and begin active 1L treatment. Transitions through the semi-Markov model (i.e., movement between health states in each given cycle) are informed by transition probabilities.

For the **FF 1L** state, which includes patients who are failure-free in 1L (on/off treatment), two transitions were modelled:

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- FF 1L to Death (pre-failure mortality on 1L treatment)
- FF 1L to PF 2L (failure on 1L treatment)

Likewise, for the **PF 2L** state, which includes patients who are alive, who experienced failure during 1L treatment and are progression-free on 2L treatment, two transitions were modelled:

- PF 2L to Death (pre-progression mortality on 2L treatment)
- PF 2L to PD (progression on 2L treatment)

For the **PD** state, which includes patients who have progressed after receiving 2L treatment, only one transition from PD to Death (mortality on 3L treatment) was modelled.

Summary of clinical inputs informing the transition probabilities

Data from TRIANGLE were leveraged to inform the 1L treatment efficacy and mortality within the model.^{30, 63} As discussed in depth in Section 2, TRIANGLE represents the pivotal evidence base for the ibrutinib regimen in the target indication for this appraisal.

Given the aim of TRIANGLE was to evaluate treatments in the 1L treatment setting, TRIANGLE did not routinely collect the treatment efficacy data required to inform transitions from the PF 2L and PD health states in the model. Additionally, as detailed in Section 2.6.1, only a small number of treatment failure events had occurred as of the latest data cut of TRIANGLE (CCO: 09 May 2024) and thus use of post-failure data in TRIANGLE would be limited in its ability to robustly inform transitions beyond the 1L setting.⁴² A key strength of a Markov model is that it permits the use of external data sources outside of the core clinical trial (TRIANGLE) to be incorporated; as such, an alternative data source, with more mature PFS and post-progression data was explored to inform transitions on later treatment lines (i.e., transitions from the 2L and PD states).

Specifically, the RAY-3001 trial was identified as a suitable data source to inform transition probabilities for later treatment lines.⁸⁵ As discussed in more detail in Section 3.3.3, RAY-3001 was a randomised, open-label, multicentre, Phase III trial evaluating the efficacy of ibrutinib among patients with r/r MCL who had received at least one rituximab-containing chemotherapy regimen.⁸⁵ RAY-3001 was the principal evidence source for the clinical effectiveness of ibrutinib in the NICE appraisal of ibrutinib in the 2L MCL setting.¹¹ As the majority of MCL patients are expected to receive a BTKi as a 2L treatment following failure on 1L therapy in UK clinical practice, RAY-3001 represents an appropriate data source that provides more mature PFS and post-progression data to inform transition probabilities for subsequent treatment lines. At the November 2025 advisory board, clinical experts unanimously agreed that RAY-3001 was a more suitable source of data than TRIANGLE to model transitions beyond the 1L setting, given the fact that patients were receiving a BTKi in the second-line setting in line with UK clinical practice, and the increased maturity and granularity of the second and third-line data vs. TRIANGLE.⁴²

An overview of the data sources and approaches used to inform each transition probability in the semi-Markov model is presented in Table 32 below. In summary, TRIANGLE and RAY-3001 were the primary sources of clinical data informing transition probabilities between health states within the economic model.^{30, 63, 85} The subsequent sections provide further detail on the methodology used to derive each of the transition probabilities incorporated in the economic model.

Of note, where extrapolation of trial data was required, standard parametric survival analysis techniques were utilised, in line with the guidance provided in NICE technical support document Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

(TSD) 14.⁹⁸ Specifically, standard parametric survival analysis techniques were conducted on IPD from TRIANGLE (see Section 3.3.2) and RAY-3001 (see Section 3.3.4 and Section 3.3.5).³⁰ The standard parametric survival analyses consisted of fitting exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma distributions to the observed data from the relevant trial.³⁰ The analytical process subsequently consisted of testing the various statistical distributions and assessing their fits over the observed trial period and beyond to ensure reliable projection of the clinical outcomes. The distributions were selected in line with NICE TSD 14 guidance on the analysis of survival outcomes for economic evaluations alongside clinical trials.⁹⁸ The selection of the most appropriate distributions in the base case analysis was based on consideration of the following:

- **Graphical assessment of fit:** Visual inspection regarding how well the predicted extrapolation captured the shape of the observed KM data
- **Statistical fit:** Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC) statistics were generated for each extrapolation, the best fit to the observed data is the extrapolation with the lowest AIC and BIC
- **Clinical plausibility and external validation of long-term predications:** Interviews with clinical experts were conducted, where clinical experts were asked to provide their most likely estimates of the proportion of patients in clinical practice expected to be failure-free and alive at 10, 15 and 20 years following treatment with the ibrutinib regimen or the ASCT regimen.

Table 32: Summary of the transition probabilities applied in the semi-Markov model

Transition	Source	Approach
FF 1L to Death (pre-failure mortality on 1L treatment)	Pre-failure mortality data from TRIANGLE (modelled separately for the ibrutinib regimen and the ASCT regimen from Arm I and Arm A, respectively)	AMR derived from TRIANGLE data used to derive constant probability of pre-progression death, capped by general population mortality. ^a Further details are provided in Section 3.3.1.
FF 1L to PF 2L (failure on 1L treatment)	TTF from TRIANGLE (modelled separately for the ibrutinib regimen and the ASCT regimen from Arm I and Arm A, respectively)	Standard parametric functions were fitted to the observed KM curves. Further details are provided in Section 3.3.2.
PF 2L to Death (pre-progression mortality on 2L treatment)	Pre-progression mortality data from RAY-3001 (one prior line of therapy subgroup; ibrutinib arm)	AMR derived from RAY-3001 used to derive constant probability of pre-progression death, capped by general population mortality. ^a Further details are provided in Section 3.3.4.
PF 2L to PD (progression on 2L treatment)	TTP data from RAY-3001 (one prior line of therapy subgroup; ibrutinib arm)	Standard parametric functions were fitted to the TTP KM curve from RAY-3001, to act as a reference curve to inform TTP in the economic model. Differential weighted HRs were then applied to this curve to derive the final modelled TTP curves. These weighted HRs were based on the subsequent treatment distributions provided in Section 3.5.2, and data/assumptions around the relative efficacy between subsequent treatments. Further details are provided in Section 3.3.4.

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PD to Death (mortality on 3L treatment)	PPS from RAY-3001 (one prior line of therapy subgroup; the ibrutinib arm)	Standard parametric functions were fitted to the observed KM curve, capped by general population mortality. ^a Further details are provided in Section 3.3.5.

Footnotes: ^aPer-cycle probabilities of death were capped by a lower limit based on GPM, to ensure that modelled mortality would not fall below general population norms.

Abbreviations: 1L/2L/3L: 1st/2nd/3rd line; AMR: annual mortality rate; FF: failure-free; HR: hazard ratio; KM: Kaplan-Meier; PF: progression-free; PFS: progression-free survival; PPS: post-progression survival; TTF: time to failure; TTP: time to progression.

3.3.1 *FF 1L to Death (pre-failure mortality on 1L treatment)*

Data source informing FF 1L to Death transition probability

Transitions from the FF 1L to the Death health state in patients receiving either the ibrutinib or ASCT regimen were informed by pre-failure mortality data from the ibrutinib and ASCT arms of TRIANGLE, respectively.³⁰ Pre-failure mortality was defined as death from any cause following randomisation prior to failure on 1L treatment.

The number of pre-failure mortality events as of the latest data cut of TRIANGLE (CCO: 09 May 2024) were limited across both arms (11/268 [4.1%] patients for the ibrutinib regimen and 22/269 [8.2%] patients for the ASCT regimen, respectively).⁶³ As such, standard parametric extrapolation was not used to extrapolate time to pre-failure mortality from TRIANGLE in the model. Instead, a pre-failure annual mortality rate (AMR) was derived for each arm.

Specifically, the pre-failure AMR was calculated by dividing the number of pre-failure mortality events observed by the number of person-years of follow-up in TRIANGLE for each arm.³⁰ The annual rate derived was then converted to a per-cycle probability (i.e., a 21-day rate), by assuming that the risk of death was spread equally across cycles. The pre-failure AMR was capped by a lower limit based on general population mortality (based on 2022–2024 life tables) to ensure that modelled mortality did not fall below that of the UK general population. The resulting per cycle probability for the ibrutinib regimen and ASCT regimen, respectively, is provided in Table 33.

Table 33: Pre-failure AMR and per-cycle probability

Treatment	Ibrutinib regimen	ASCT regimen
Pre-failure mortality events	11/268	22/269
Total number of FFS person-years	■	■
Pre-failure AMR	■	■
Per cycle (21-day) probability	■	■

Abbreviations: AMR: annual mortality rate; ASCT: autologous stem cell transplant; FFS: failure-free survival.

3.3.2 *FF 1L to PF 2L (failure on 1L treatment)*

Data source informing FF 1L to PF 2L transition probability

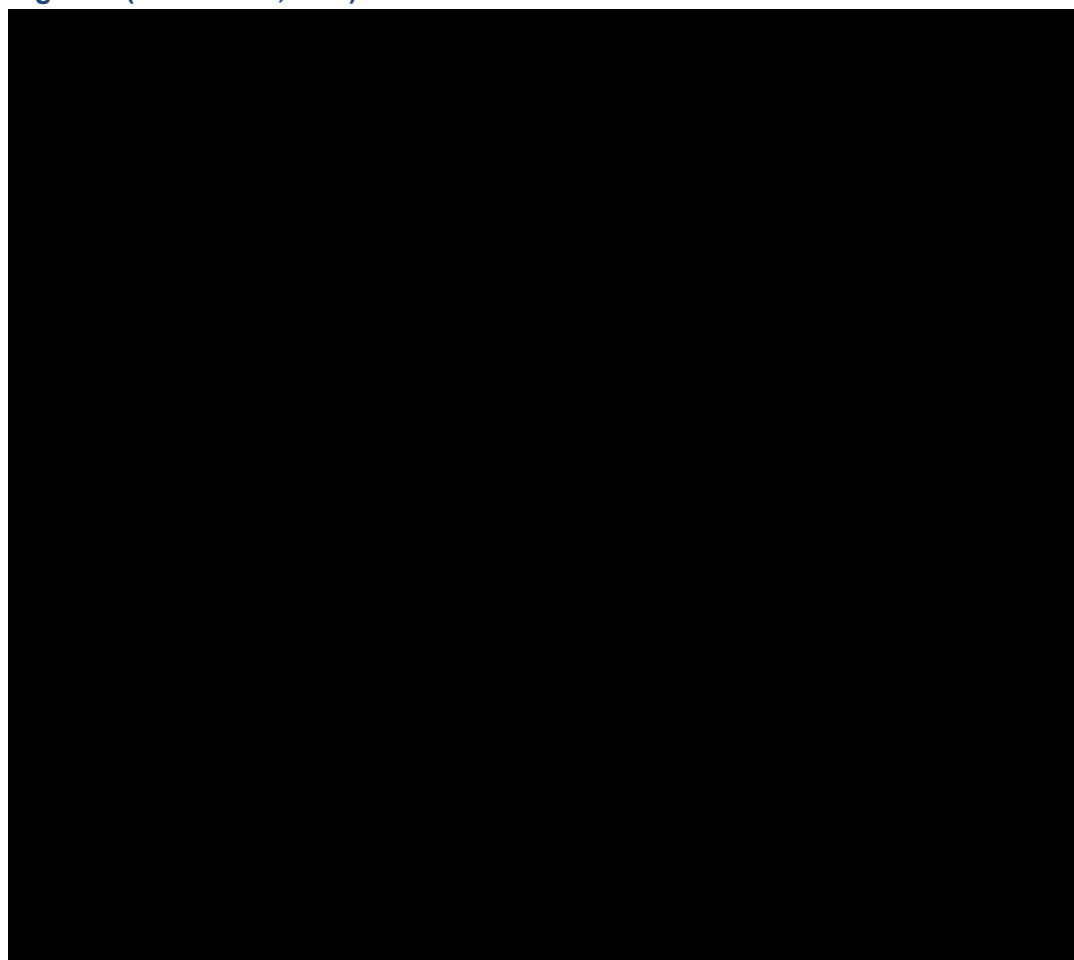
Transitions from the FF 1L health state in patients receiving the ibrutinib or ASCT regimen to the PF 2L health state were modelled using time to treatment failure (TTF) data from the ASCT (A) arm and ibrutinib (I) arm of TRIANGLE, respectively.³⁰ TTF was defined as time from randomisation to stable disease at the end of induction immunochemotherapy, or progressive Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

disease, whichever came first. As such, TTF represents a narrower definition of FFS; patients who experienced a pre-failure mortality event were censored in TTF. Pre-failure deaths were separately captured in the FF 1L to Death transition (see Section 3.3.1).

Of note, patients alive without failure at the latest contact were censored at the latest tumour assessment date, whilst patients without any lymphoma restaging during or at the end of induction were censored at the date of randomisation. Patients experiencing death events were also censored at time of death. Censoring for pre-failure deaths in the transition from FF 1L to PF 2L, and subsequently capturing pre-failure deaths separately as part of FF 1L to Death transition (as described in Section 3.3.1 above) addresses previous criticism of a prior four-state semi-Markov model for ibrutinib in chronic lymphocytic leukaemia (CLL [TA891]).⁸⁸

The KM TTF data from TRIANGLE (CCO 09 May 2024) for both the ibrutinib regimen and the ASCT regimen is presented in Figure 14.³⁰ As shown, at the May 2024 CCO, TTF for ibrutinib lay above the ASCT arm across the entire time horizon. While the curves appear to move closer together toward the end of the KM data, it is important to contextualise this within the greater degree of patient censoring from month 66 onwards and therefore the small patient numbers informing the tails of the curves. As the median time on study for TRIANGLE (54.9 months) was shorter than the model time horizon (43 years), TTF KM data were extrapolated via a parametric function to inform transitions in subsequent years.³⁰

Figure 14: Observed TTF Kaplan-Meier data for the ibrutinib regimen and the ASCT regimen (TRIANGLE, FAS)



Abbreviations: A: ASCT; ASCT: autologous stem cell transplant; FAS: final analysis set; I: ibrutinib; TTF: time to treatment failure.

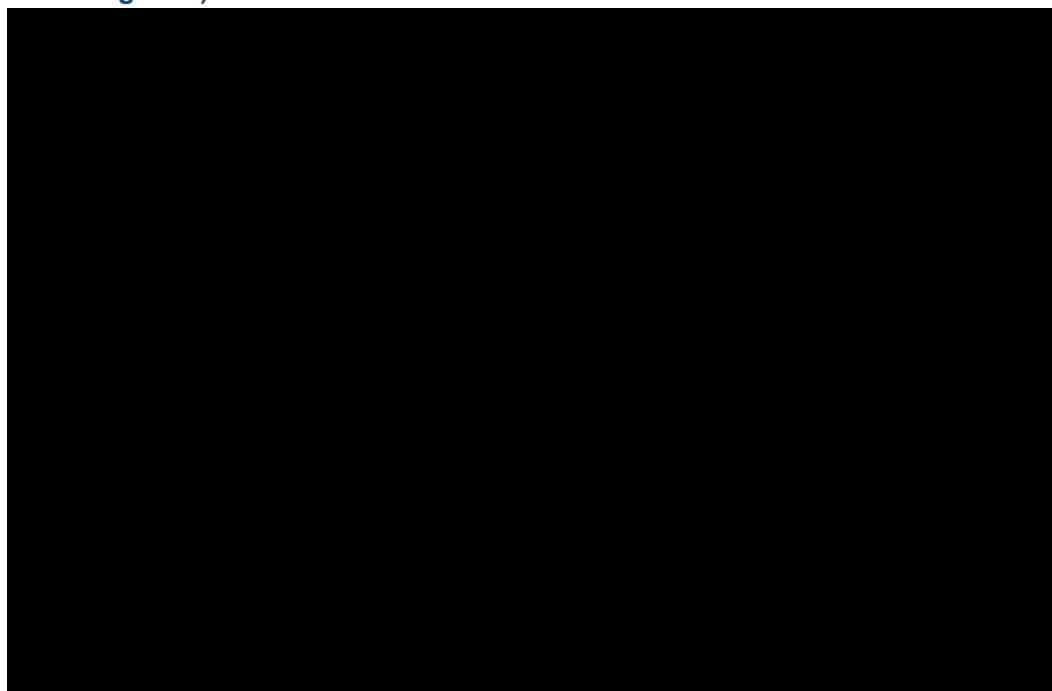
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PH testing

Formal diagnostic tests (including log-cumulative hazard plots, Schoenfeld residuals and quantile-quantile plots) were conducted to assess the proportionality of hazards between treatment arms as well as the suitability of proportional hazards (PH) or accelerated failure time models. The assessment of PHs was conducted visually using log-cumulative hazard plots and Schoenfeld residual plots; the assessment of the accelerated failure time assumption was conducted visually using log-survival odds and normal quantiles vs. log-time.

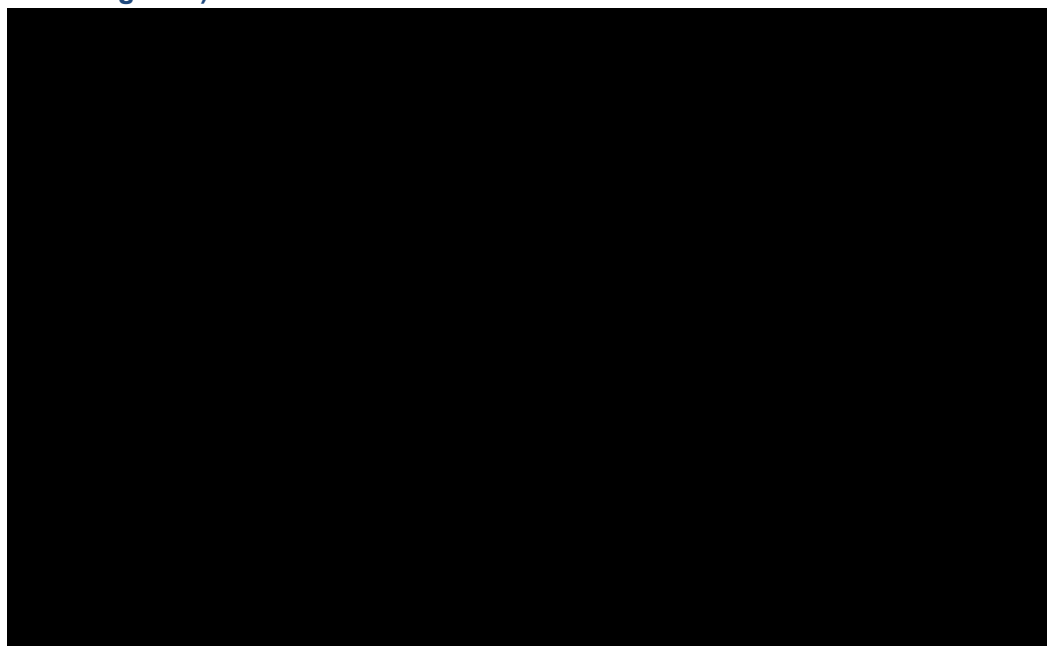
The log-cumulative hazard diagnostic plots (Figure 15) showed relatively parallel lines from approximately 6 to 54 months, but started to converge after month 54, indicating that the PH assumption appears to be violated after this timepoint. Assessment of the Schoenfeld residual plot (Figure 16) further confirmed that the PH assumption was violated, given the Schoenfeld residuals follow a non-zero trajectory, and the Schoenfeld p-value is significant (p-value <0.05; Schoenfeld statistics: p=██████). As such, the PH assumption was found to be violated and thus, in line with NICE TSD 14, individual fits were used to extrapolate the curves for the FF 1L to PF 2L transition probability (i.e., parametric curves were individually fitted to TTF data for the ibrutinib regimen and the ASCT regimen).⁹⁸

Figure 15: Log cumulative hazards plot for TTF in TRIANGLE (the ibrutinib regimen vs. the ASCT regimen)



Abbreviations: ASCT: autologous stem cell transplant; TTF: time to treatment failure.

Figure 16: Global Schoenfeld test for TTF in TRIANGLE (the ibrutinib regimen vs. the ASCT regimen)



Abbreviations: ASCT: autologous stem cell transplant; TTF: time to treatment failure.

Internal validity

Statistical fit

Table 34 presents a summary of the goodness-of-fit statistics for the TTF endpoint from TRIANGLE for the ibrutinib and ASCT regimen curves, respectively. The exponential distribution provided the best statistical fit based on both AIC and BIC for the ibrutinib regimen, whilst the log-normal represented the best fitting curve for the ASCT regimen based on both AIC and BIC.

Table 34: Goodness-of-fit statistics (AIC/BIC) for individually fitted parametric models fitted for TTF

	Ibrutinib regimen				ASCT regimen			
Distribution	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank
Exponential	■	1	■	1	■	7	■	6
Weibull	■	3	■	3	■	5	■	4
Gompertz	■	2	■	2	■	2	■	2
Log-logistic	■	6	■	6	■	4	■	3
Log-normal	■	5	■	5	■	1	■	1
Gamma	■	4	■	4	■	6	■	5
Generalised Gamma	■	7	■	7	■	3	■	7

Footnotes: The extrapolation with the best statistical fit is highlighted in **bold**.

Abbreviations: AIC: Akaike information criterion; ASCT: autologous stem cell transplant; BIC: Bayesian information criterion.

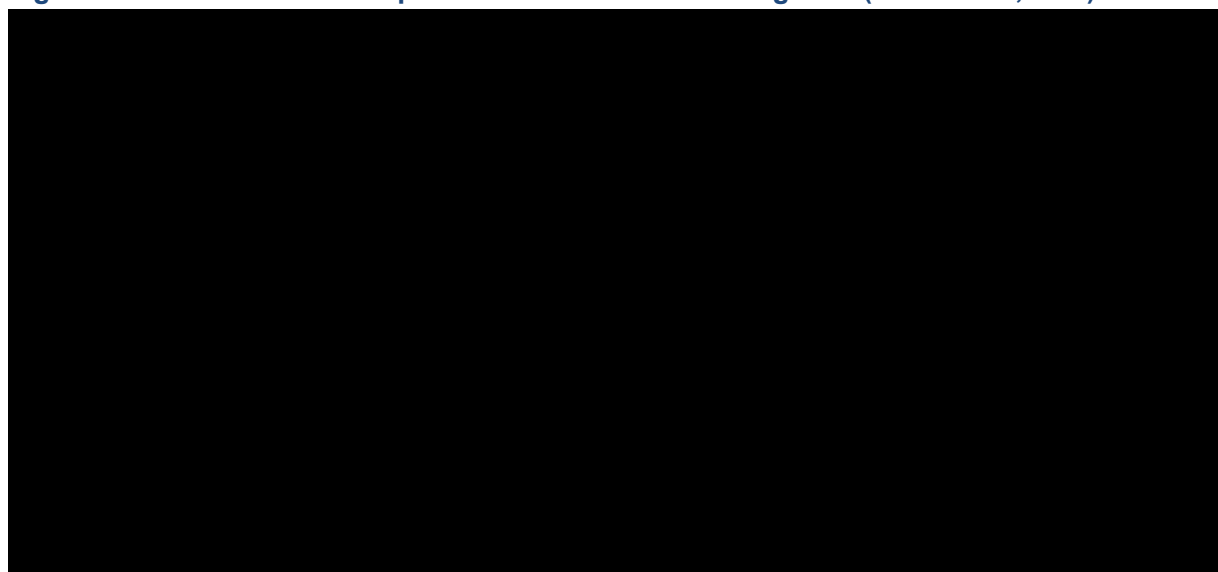
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Visual fit

Figure 17 and Figure 18 present the individually parametric extrapolations highlighting the visual fit to the observed TRIANGLE KM TTF data (CCO: 09 May 2024), for the ibrutinib regimen and the ASCT regimen, respectively.³⁰ Table 35 presents the TTF estimates for each parametric distribution. The TTF extrapolations are not capped by GPM; as detailed in Section 3.3.1, the pre-failure AMR used to model the transition from FF 1L to Death was capped by GPM, thus ensuring that the resulting reconstructed FFS survival curves for the ibrutinib and ASCT regimen (see Table 36) did not exceed that of the UK general population.

As shown in Figure 17, all extrapolations for the ibrutinib regimen TTF provide reasonable visual fit to the observed TTF KM data. For the ASCT regimen, all extrapolations apart from the exponential reasonably fit the KM data from TRIANGLE (see Figure 18).

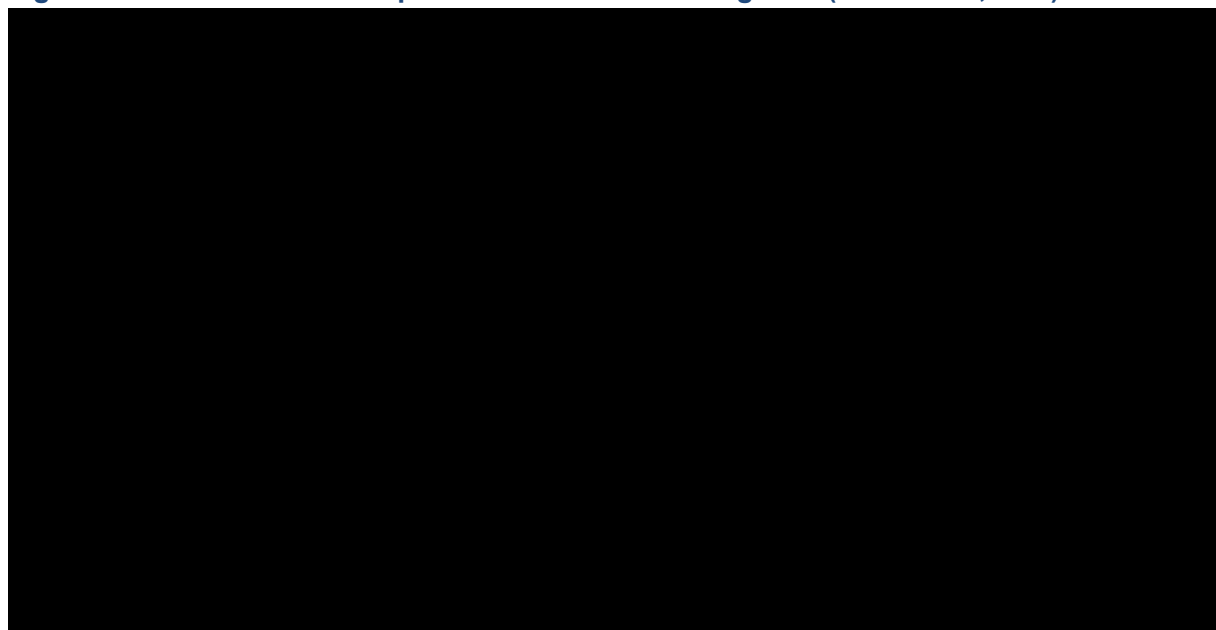
Figure 17: TTF: observed vs. predicted for the ibrutinib regimen (TRIANGLE, FAS)



Footnotes: TTF was derived from FFS data, censored for pre-failure mortality, to avoid double-counting.

Abbreviations: FAS: final analysis set; TTF: time to treatment failure

Figure 18: TTF: observed vs. predicted for the ASCT regimen (TRIANGLE, FAS)



Footnotes: TTF was derived from FFS data, censored for pre-progression mortality, to avoid double-counting.
Abbreviations: ASCT: autologous stem cell transplant; FAS: final analysis set; TTF: time to treatment failure

Table 35: Landmark estimates for the TTF extrapolations

	Ibrutinib regimen				ASCT regimen			
Distribution	Median TTF (years)	10 year (%)	15 year (%)	20 year (%)	Median TTF (years)	10 year (%)	15 year (%)	20 year (%)
Extrapolations								
Exponential	■	■	■	■	■	■	■	■
Weibull	■	■	■	■	■	■	■	■
Gompertz	■	■	■	■	■	■	■	■
Log-logistic	■	■	■	■	■	■	■	■
Log-normal	■	■	■	■	■	■	■	■
Gamma	■	■	■	■	■	■	■	■
Generalised Gamma	■	■	■	■	■	■	■	■

Abbreviations: ASCT: autologous stem cell transplant; TTF: time to treatment failure.

External validity

Given that, at the May 2024 CCO of TRIANGLE, the majority of patients were alive and failure free (see Section 2.6); see Figure 14), the majority of curves provided reasonable statistical and visual fit to the observed TTF KM data from TRIANGLE. However, for both regimens, the range of predicted long-term TTF estimates across the extrapolations was considerable (Table 35). As such, the clinical plausibility of the long-term TTF predictions for each regimen (informed by the external validity of the reconstructed FFS curve [see details below]) was considered the primary consideration to selecting the appropriate base case curve choices for each regimen.⁶³

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As part of the November 2025 advisory board, UK clinical experts provided most likely landmark estimates of FFS for the ibrutinib regimen and the ASCT regimen.⁴² Clinical experts' landmark FFS estimates for the ibrutinib regimen and the ASCT regimen are presented in Table 36, alongside the reconstructed FFS extrapolation landmark estimates.⁴² Specifically, the reconstructed FFS extrapolations in Table 36 incorporate the pre-failure AMR derived in Section 3.3.1 with the selected TTF standard parametric model, given FFS comprises both failure on 1L treatment and pre-failure mortality on 1L treatment.

Using the exponential to extrapolate TTF for the ibrutinib regimen resulted in FFS landmark estimates that are most closely aligned to clinical expert estimates at all three timepoints (10 year: ■% vs 57.0%; 15 year: ■% vs 42.0%; 20 year: ■% vs 28.0%).⁶³ The exponential was also the best statistically fitting extrapolation to the observed TTF ibrutinib regimen KM data. Using the log-logistic curve for the ibrutinib regimen resulted in the second most clinically plausible landmark estimates.

In relation to the ASCT regimen, the log-normal, Gompertz and log-logistic extrapolations for TTF (which were the three best statistically fitting curves; see Table 36) all resulted in reconstructed FFS curves that notably overestimated FFS for the ASCT regimen, with modelled estimates >■% higher than the clinical expert estimates of survival at 20 years. The Gamma and Weibull extrapolations for TTF resulted in the most clinically plausible FFS landmark estimates vs. the clinical expert estimates, although notably, for both these curves, FFS estimates remained slightly overestimated (compared with clinical expert estimates) at all three landmarks.

Table 36: Clinical expert and landmark estimates for the reconstructed FFS extrapolations

	Ibrutinib regimen			ASCT regimen		
Distribution	10 year (%)	15 year (%)	20 year (%)	10 year (%)	15 year (%)	20 year (%)
Clinical expert estimates						
Clinical expert estimates (FFS) ^a	57.0	42.0	28.0	44.6	33.6	22.0
Extrapolations^b						
Exponential	■	■	■	■	■	■
Weibull	■	■	■	■	■	■
Gompertz	■	■	■	■	■	■
Log-logistic	■	■	■	■	■	■
Log-normal	■	■	■	■	■	■
Gamma	■	■	■	■	■	■
Generalised Gamma	■	■	■	■	■	■

Footnotes: ^a The mean of the clinical experts' most likely value. ^b The reconstructed FFS extrapolations incorporate TTF (in which the standard parametric model informing the extrapolation of TTF data from TRIANGLE is varied) and the pre-failure AMR detailed in Section 3.3.1.

Abbreviations: ASCT: autologous stem cell transplant; FFS: failure-free survival; TTF: time to treatment failure.

Base case selection

As detailed above, the majority of curve choices provided a similar level of statistical and visual fit to the observed TTF KM data from TRIANGLE. As such, and given the relative immaturity of TRIANGLE TTF data, clinical plausibility of the reconstructed FFS extrapolations was the primary consideration in selecting the base case curves for the transition from FF 1L to PF 2L.

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For the ibrutinib regimen, selecting the exponential extrapolation to inform transitions from FF 1L to PF 2L (TTF) resulted in FFS estimates for the reconstructed FFS curves that were most closely aligned with the UK clinical expert estimates of FFS.⁴² The exponential was also the best statistically fitting curve to the observed TRIANGLE TTF KM data. As such, the exponential was selected as the base case curve to model the ibrutinib regimen FF 1L to PF 2L transition. The log-logistic, which provided the second most clinically plausible estimates of FFS was explored in a scenario analysis.

Regarding the ASCT regimen, the Gamma was selected to model the transition from FF 1L to PF 2L, given it predicted reconstructed landmark FFS estimates that were most closely aligned with UK clinical expert estimates. The Weibull, as the second most clinically plausible curve, was explored in a scenario analysis.

3.3.3 PF 2L to Death (pre-progression mortality on 2L treatment)

Data source informing PF 2L to Death transition probability

As detailed in Section 3.3.1 and Section 3.3.2 above, TRIANGLE data were used to inform first-line treatment efficacy (i.e., FF 1L to PF 2L) and mortality (i.e., FF 1L to Death) within the model.³⁰ However, given the focus of TRIANGLE was on the first-line treatment setting, and the majority of patients remained alive and failure-free as of the latest data cut of TRIANGLE (CCO: 09 May 2024), use of post-failure data in TRIANGLE to inform later line transitions in the model would be associated with notable limitations, as validated by feedback received from UK clinical experts.⁴² As such, given a Markov model structure permits external data to be incorporated and data specific to each line of treatment to be leveraged, alternative sources with more mature PFS and post-progression data were explored to inform transitions on later treatment lines (i.e., transitions from the 2L and PD states).

In UK clinical practice, as detailed in Section 1.3.4, 2L treatment options comprise BTKis (ibrutinib or zanubrutinib) and rituximab-based immunochemotherapy. Feedback received from UK clinical experts at the November 2025 advisory board indicated that as BTKis are associated with superior efficacy to rituximab-based immunochemotherapies, BTKis are the most commonly used subsequent treatment option in r/r MCL following failure on 1L treatment.^{11, 51}

As such, the RAY-3001 trial, which was the principal trial that led to the positive recommendation of ibrutinib as a 2L treatment option for patients with treating r/r MCL, was identified as a suitable source of literature to inform the transition probability from PF 2L to death, PF 2L to PD (see Section 3.3.4) and PD to Death (see Section 3.3.5) in the economic model.^{11, 85} Specifically, the subgroup of patients in the ibrutinib arm of RAY-3001 with r/r MCL who had received one prior line of therapy.⁸⁵ An overview of the baseline characteristics of the ibrutinib arm for this RAY-3001 subgroup is presented in Appendix K.1. When consulted at the November 2025 advisory board, UK clinical experts agreed that the RAY-3001 trial was an appropriate data source to inform these transition probabilities. Further details on RAY-3001 are provided in Table 37 below.⁴²

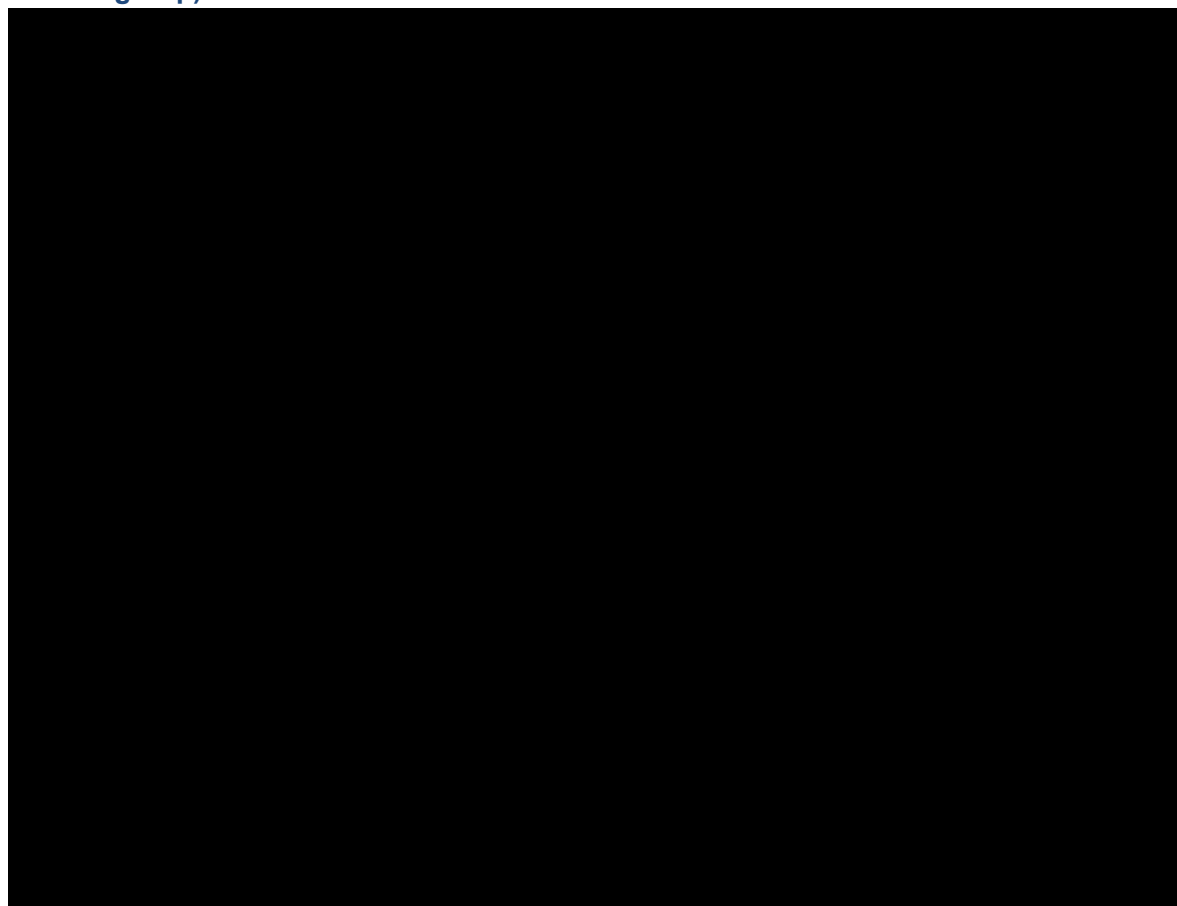
Table 37: Overview of RAY-3001

RAY-3001 (NCT01646021)⁸⁵

Study design	Randomised, open-label, multicentre, Phase III clinical trial
Population	Overall population: Patients with relapsed or refractory (R/R) MCL
	Subgroup 1: Patients with R/R MCL who have received 1 prior line of therapy
Overall population eligibility criteria	Key inclusion criteria: Patients with relapsed or refractory MCL who had received at least one previous rituximab-containing chemotherapy regimen, documented relapse, or disease progression after the last anti-mantle-cell lymphoma treatment, measurable disease, an ECOG performance status of 0 or 1 and at least one measurable site of disease. Key exclusion criteria: Use of chemotherapy, radiation, or other investigational drugs within 3 weeks, antibody treatment or immunoconjugates within 4 and 10 weeks, respectively, and previous treatment with mTOR or BTKis.
Intervention	Ibrutinib (560 mg administered orally once daily until treatment progression or unacceptable toxicity); n=139 Subgroup 1; n=57
Comparator	Temsirolimus (alternating doses of 175 mg/75 mg IV until treatment progression or unacceptable toxicity); n=141 Subgroup 1; n=50
Primary endpoint	PFS
Secondary endpoints	ORR, OS, DoR, TTNT, safety and pre-specified PROs
Median follow-up	38.7 months ⁹⁹

Abbreviations: 2L: 2nd line; BTK: Bruton tyrosine kinase; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; MCL: mantle cell lymphoma; mTOR: mammalian target of rapamycin; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PRO: patient-reported outcome; R/R: relapsed or refractory; TTNT: time to next treatment.

Figure 19: Observed PFS Kaplan-Meier data from the ibrutinib arm of RAY-3001 (one prior line subgroup)



Abbreviations: Ibr: ibrutinib; PFS: progression-free survival.

Transitions from the PF 2L to the Death state were informed by pre-progression mortality data from the ibrutinib arm of RAY-3001 (one prior line subgroup). At the November 2025 advisory board, all clinical experts agreed that the RAY-3001 trial was an appropriate evidence source to inform pre-progression mortality in the model given that RAY-3001 one prior line subgroup data are specific to 2L pre-progression patients receiving a BTKi and therefore are directly applicable to the PF 2L to Death transition in the model.⁴²

In line with the approach used for the transition from the FF 1L to Death state (see Section 3.3.1), the transition from the PF 2L to the Death state was informed by an AMR-based approach, rather than standard parametric extrapolations. Specifically, a pre-progression AMR was calculated by dividing the number of deaths in PFS observed by the number of person-years of follow-up in the ibrutinib arm of RAY-3001 (one prior line subgroup). The annual rate derived was then converted to a per-cycle probability (i.e., a 21-day rate), by assuming that the risk of death was spread equally across cycles. As with the pre-failure AMR described in Section 3.3.1, the pre-progression AMR was capped by a lower limit based on general population mortality (based on 2022–2024 life tables) to ensure that modelled mortality did not fall below that of the UK general population. The resulting per cycle probability of pre-progression death, which was applied to all patients receiving second-line treatment (regardless of first-line treatment), is provided in Table 38 below.

Table 38: Pre-progression AMR and pre-cycle probability

Treatment	Ibrutinib arm of RAY-3001 (one prior line subgroup)
Total number of PFS person-years	■
Number of deaths in PFS	I
AMR	■
Per-cycle (21-day) probability	■

Abbreviations: AMR: annualised mortality ratio; PFS: progression-free survival.

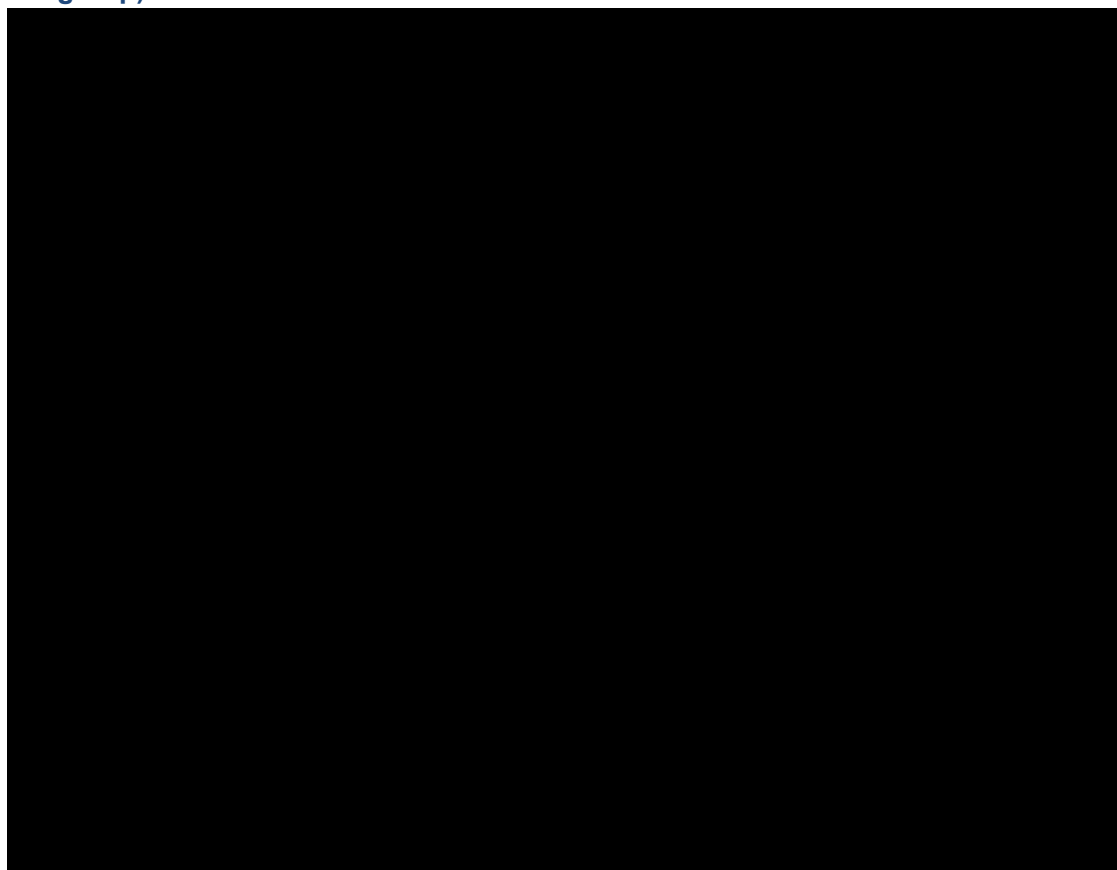
3.3.4 PF 2L to PD (progression on 2L treatment)

Data source informing PF 2L to PD transition probability

Transitions from the PF 2L to the PD health state for patients receiving 2L treatment with ibrutinib (regardless of 1L treatment) were derived from time to progression (TTP) data from the ibrutinib arm of the one prior line subgroup of RAY-3001.¹⁰ This was validated by UK clinical experts as a suitable source to inform this transition probability at the November 2025 advisory board.⁴²

TTP was derived from PFS data, censored for pre-progression mortality, to avoid double-counting. Pre-progression deaths were separately captured in the PF 2L to Death transition (see Section 3.3.3). The KM TTP data from the ibrutinib arm of RAY-3001 (one prior line subgroup) is presented in Figure 20. As the median follow-up of RAY-3001 (38.7 months) is shorter than the modelled time horizon (43 years), KM TTP data from the ibrutinib arm of RAY-3001 (one prior line subgroup) required extrapolation via a parametric function to inform transitions across the modelled time horizon.^{85, 99}

Figure 20: Observed TTP Kaplan-Meier data for the ibrutinib arm (RAY-3001, one prior line subgroup)



Abbreviations: Ibr: ibrutinib; TTP: time to progression.

Patients in the ibrutinib arm of RAY-3001 (one prior line subgroup) all received ibrutinib as a second-line treatment. As such, RAY-3001 (ibrutinib arm; one prior line subgroup) TTP data were suitable to inform the extrapolations of TTP for patients receiving BTKis in the second-line setting, hereafter referred to as the 'reference' TTP curve. Whilst clinical experts at the November 2025 advisory board confirmed that BTKis such as ibrutinib are anticipated to be used as the predominant treatment in the second-line setting following initial treatment with either the ASCT or ibrutinib regimen in UK clinical practice, a small proportion of patients are also expected to receive treatment with alternative therapies such as rituximab-based immunochemotherapies.⁴² As such, to account for the differential efficacy of second-line treatment options received by patients following first-line treatment with the ibrutinib or ASCT regimen, weighted average HRs based on the anticipated subsequent treatment distributions after each regimen were applied to the 'reference' TTP curve to form respective TTP curves for the ASCT regimen and the ibrutinib regimen, respectively.

Derivation and application of the weighted average hazard ratios for the ibrutinib and ASCT regimens respectively

As noted above, as the risk of progressing on second-line treatment is influenced by the treatment received at second line, the model accounted for differential second-line efficacy depending on the subsequent treatment regimens received following first-line treatment with the ASCT regimen and the ibrutinib regimen, respectively. Based on feedback received from UK clinical experts, almost all patients were assumed to receive active second-line treatment (ibrutinib, zanubrutinib and rituximab-based immunochemotherapies such as R-BAC), with a small minority (~1%) modelled Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

to receive best supportive care (BSC).⁴² The distribution of 2L treatments for patients receiving first-line treatment with the ibrutinib regimen and the ASCT regimen, respectively were obtained from feedback from UK clinical experts and are provided in Table 39.⁴²

At the November 2025 advisory board, clinical experts confirmed that an assumption of equal efficacy between the BTKis (ibrutinib and zanubrutinib) received in the second-line treatment setting was appropriate.⁴² However, patients receiving rituximab-based immunochemotherapy options in the second-line setting would experience an increased risk of disease progression, compared to patients receiving a BTKi. To reflect this, a PFS HR of 1.26 was derived from the MANTLE-FIRST study, which provides direct evidence on the relative efficacy of ibrutinib vs. R-BAC in patients (n=126) with first r/r MCL following first-line treatment with intensive regimens including R-HDAC.¹⁰⁰ UK clinical experts highlighted the MANTLE-FIRST study and validated that it represents the best available evidence to inform the differential efficacy between BTKis and rituximab-based chemotherapy, given it was a head-to-head trial in a relevant patient population who were treated with relevant therapies.⁴² In the absence of alternative data, BSC was assumed to be associated with equal efficacy to rituximab-based chemotherapy (Table 40).

Consequently, weighted average HRs were derived for the ibrutinib and ASCT model arms, based on their respective subsequent treatment distributions (Table 39) of the proportion of patients receiving subsequent treatment with ibrutinib or zanubrutinib, who were assigned a HR of 1, and the proportion of patients receiving R-BAC, BR or BSC, who were assigned a HR of 1.26 (Table 40). The resulting weighted average HRs for the ibrutinib arm and ASCT arm of the model, respectively are presented in Table 41 and indicate that fewer second-line progression events are experienced in the model for the ASCT arm compared with the ibrutinib arm. The weighted average HRs were subsequently applied to the chosen TTP curve (the 'reference' TTP curve), thus deriving adjusted TTP curves for both the ibrutinib and ASCT model arms, based on the subsequent treatment distributions modelled for each group.

For clarity, the selected 'reference' TTP curve, as well as the resultant TTP curves for both the ibrutinib and ASCT regimens, following application of the weighted average HRs, are presented in Figure 22 at the end of this section.

Table 39: Distribution of subsequent treatment use in 2L

1L treatment	2L treatment				
	Ibrutinib	Zanubrutinib	R-BAC	BR	BSC
Ibrutinib	-	57.6%	31.3%	10.0%	1.1%
ASCT	10.0%	84.8%	2.4%	2.0%	0.8%

Abbreviations: 1/2L: first/second line; ASCT: autologous stem-cell transplantation; BR: bendamustine and rituximab; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 40: Summary of PFS HRs for the subsequent treatments used in second-line MCL

Comparison	PFS HR	Source
Zanubrutinib vs ibrutinib	1.00	Assumption of equal efficacy, based on UK clinical expert feedback ⁴²
R-BAC vs ibrutinib	1.26	MANTLE-FIRST ¹⁰⁰
BR vs ibrutinib	1.26	MANTLE-FIRST ¹⁰⁰

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BSC vs ibrutinib	1.26	Assumption of equal efficacy with rituximab-based chemotherapy

Abbreviations: ASCT: autologous stem-cell transplantation; BR: bendamustine and rituximab; BSC: best supportive care; HR: hazard ratio; MCL: mantle cell lymphoma; PFS: progression-free survival; R-BAC: rituximab, bendamustine and cytarabine.

Table 41: Summary of weighted average HRs per model arm based on subsequent treatment distributions

	Ibrutinib regimen	ASCT regimen
Weighted average HR based on subsequent treatment distributions	1.103	1.012

Abbreviations: ASCT: autologous stem cell transplant; HR: hazard ratio.

Base case selection of the 'reference' TTP curve

Extrapolation methods

Standard parametric survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma) were fitted to the observed TTP data from the ibrutinib arm of RAY-3001 (one prior line subgroup). Selection of the most appropriate parametric model was assessed via both internal validity (using goodness-of-fit statistics and assessment of visual fit) and external validity. The following section details how the 'reference' TTP curve was selected.

Internal validity

Statistical fit

Table 42 presents a summary of the goodness-of-fit statistics to the observed TTP KM data for the ibrutinib arm in RAY-3001 (one prior line subgroup).⁸⁵ Assessment of statistical fit indicated that the exponential provided the best statistical fit based on both AIC and BIC. Overall, however, all curves provided a reasonably comparable statistical fit to the observed data.

Table 42: Goodness-of-fit statistics (AIC/BIC) for ibrutinib parametric models fitted for TTP (RAY-3001; one prior line subgroup)

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	■	1	■	1
Weibull	■	3	■	3
Gompertz	■	4	■	4
Log-logistic	■	7	■	6
Log-normal	■	5	■	5
Gamma	■	2	■	2
Generalised Gamma	■	6	■	7

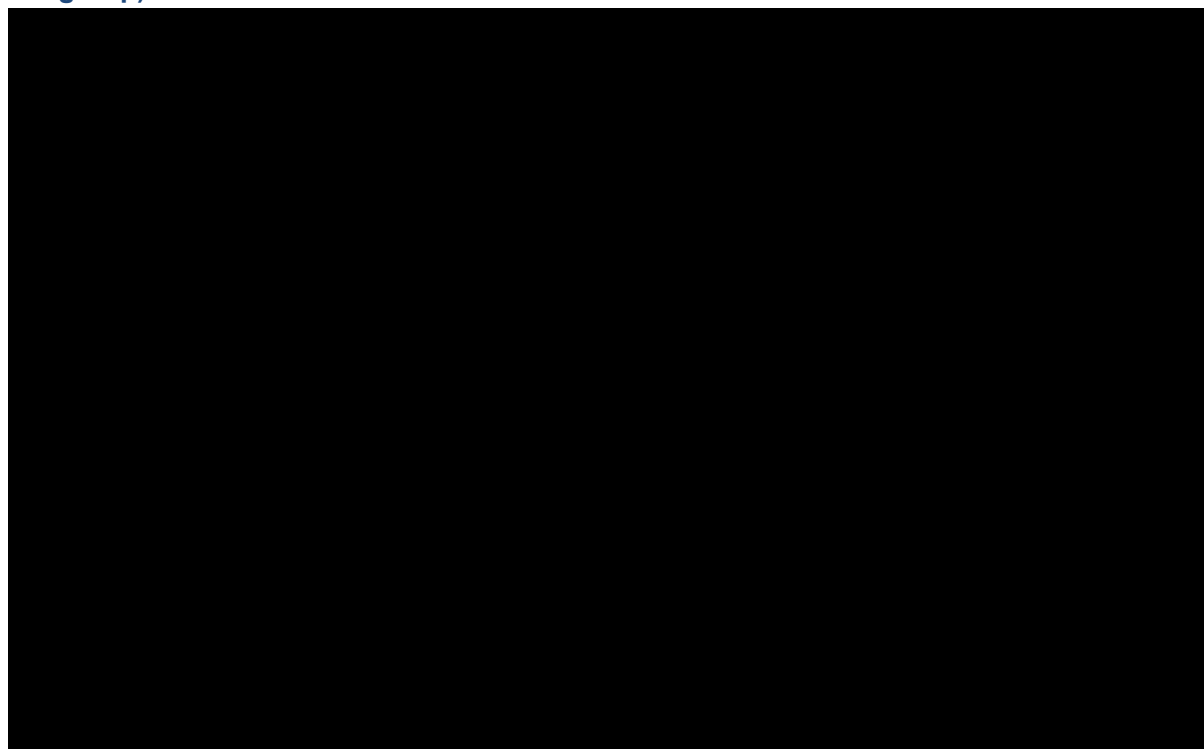
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

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Visual fit

Figure 21 presents parametric extrapolations highlighting the visual fit to the observed KM data of the one prior line of therapy subgroup of the ibrutinib arm in RAY-3001. As shown, whilst all curves provided comparable visual fit to the first 24 months of KM data, the visual fit of the extrapolations to the tail end of the KM data was weaker, likely due to the low numbers of patients at risk at this time (Figure 20). As such, as not one curve provided notably better fit to the data than the others, no clear conclusions were able to be drawn regarding the visual fit of the parametric functions to the observed TTP data for the ibrutinib arm of RAY-3001 (one prior line subgroup).

Figure 21: TTP observed vs. predicted for the ibrutinib arm (RAY-3001, one prior line subgroup)



Footnotes: TTP was derived from PFS data, censored for pre-progression mortality, to avoid double-counting.

Abbreviations: KM: Kaplan-Meier; TTP: time to progression.

Table 43: Landmark estimates for the reference curve TTP extrapolations (RAY-3001; one prior line subgroup)

Distribution	Median TTP (months)	5 year (%)	10 year (%)	15 year (%)	20 year (%)
Extrapolations					
Exponential	■	■	■	■	■
Weibull	■	■	■	■	■
Log-normal	■	■	■	■	■
Log-logistic	■	■	■	■	■
Gompertz	■	■	■	■	■
Gamma	■	■	■	■	■
Generalised Gamma	■	■	■	■	■

Abbreviations: TTP: time to progression.

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External validity

As detailed above, the majority of the extrapolation functions for the 'reference' TTP curve provided similar statistical fit to the observed TTP KM data from the ibrutinib arm of RAY-3001 (one prior line subgroup), and it was challenging to draw any clear conclusions regarding the visual fit.

As such, the clinical plausibility of the extrapolations was the primary consideration in selecting the base case extrapolation for TTP in patients who received ibrutinib at second line (the 'reference' TTP curve). However, in the absence of external sources of UK-based estimates for TTP specifically in this indication, the clinical experts most likely estimates of OS elicited as part of the November 2025 advisory board were used to aid selection of the most appropriate extrapolation to inform the PF 2L to PD transition.⁴² In order to do this, the reconstructed OS curves (see details below) derived when only the standard parametric model informing transitions from the PF 2L to PD health state was varied were generated.

Specifically regarding the reconstructed OS curves, in the semi-Markov model, OS was informed via a combination of multiple transitions, and thus on the base case curves/AMRs selected for the below transitions:

- Pre-failure mortality on second line treatment (FF 1L to Death; see Section 3.3.1)
- Failure on 1L treatment (FF 1L to PF 2L; Section 3.3.2)
- Pre-progression mortality on 2L treatment (PF 2L to Death; Section 3.3.3)
- PD to Death transition (PD to Death; Section 3.3.5)

As noted above, when generating the reconstructed OS curves, in addition to the use of the base case standard parametric models/AMRs informing the other modelled transitions, the standard parametric model informing the 'reference' curve for the PF 2L>PD transition was varied to generate landmark survival estimates from several potential reconstructed OS curves. It should be noted that for each standard parametric model informing the reference curve for the PF 2L>PD transition, the weighted average HR derived for the ibrutinib and ASCT regimen, respectively (as detailed in Table 41) was applied to each reference curve to generate separate reconstructed OS curves for the ibrutinib and ASCT arms of the model, respectively. The resulting landmark survival (OS) estimates at 10, 15 and 20 years from the resulting potential reconstructed OS curves for the ibrutinib and ASCT regimen are presented in Table 44. These estimates were subsequently compared against the clinicians most likely estimates for OS at the corresponding time points to determine which standard parametric model informing the reference curve for the PF 2L to PD transition (TTP) resulted in the most clinically plausible reconstructed OS curve.

For both regimens, selection of the log-logistic or the log-normal as the 'reference' TTP curve (in combination with the base case approach to modelling each transition probability within the 1L, 2L and PD health states) resulted in OS landmark estimates that were best aligned with clinical expert estimates of OS at 15 and 20 years.⁴² The Gompertz resulted in OS landmark estimates for the reconstructed OS curve that were most closely aligned with clinical expert estimates of OS at 10 years.⁴² The selection of the generalised gamma to model the 'reference' TTP (in combination with the other base case transition probabilities) resulted in OS landmark estimates for the reconstructed OS curve that were considerably lower than the clinical expert estimates at 15 and 20 years.⁴²

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Table 44: Clinical expert and landmark estimates for the reconstructed OS extrapolations

	Ibrutinib regimen ^c			ASCT regimen ^d		
Distribution	10 year (%)	15 year (%)	20 year (%)	10 year (%)	15 year (%)	20 year (%)
Clinical expert estimates						
Clinical expert estimates (OS) ^a	67.0	53.0	37.0	56.0	44.4	30.4
Extrapolations^b						
Exponential	67.8	50.4	35.6	56.4	40.6	29.0
Weibull	68.0	50.7	35.9	56.7	40.9	29.3
Gompertz	67.5	50.0	35.3	56.0	40.2	28.7
Log-logistic	69.2	52.5	37.8	58.3	43.0	31.4
Log-normal	69.2	52.6	38.0	58.4	43.2	31.5
Gamma	68.0	50.6	35.8	56.7	40.8	29.2
Generalised Gamma	66.5	49.1	34.7	54.6	39.2	28.1

Footnotes: ^aThe mean of the clinical experts' most likely values. ^bStandard parametric model informing the 'reference' curve for TTP. ^cLandmark survival estimates for OS at 10, 15 and 20 years for the ibrutinib arm of the model based on the reconstructed OS curve when only the standard parametric model informing TTP was varied and all other standard parametric models/AMRs informing transition probabilities in the model were fixed on their base case settings, as detailed throughout Section 3.3. It should be noted that the reconstructed OS curve for the ibrutinib arm of the model includes the application of a HR of 1.103 to the 'reference' curve for TTP in order to account for the differential risk of progression amongst the second-line treatments patients receive following the ibrutinib regimen (see Table 41). ^dLandmark survival estimates for OS at 10, 15 and 20 years for the ASCT arm of the model based on the reconstructed OS curve when only the standard parametric model informing TTP was varied and all other standard parametric models/AMRs informing transition probabilities in the model were fixed on their base case settings, as detailed throughout Section 3.3. It should be noted that the reconstructed OS curve for the ASCT arm of the model includes the application of a HR of 1.012 to the 'reference' curve for TTP in order to account for the differential risk of progression amongst the second-line treatments patients receive following the ASCT regimen (see Table 41).

Abbreviations: 1L/2L/3L: first/second/third line; ASCT: autologous stem cell transplant; OS: overall survival; PD: progressed disease; PF: progression-free; TTP: time-to-progression.

Conclusion

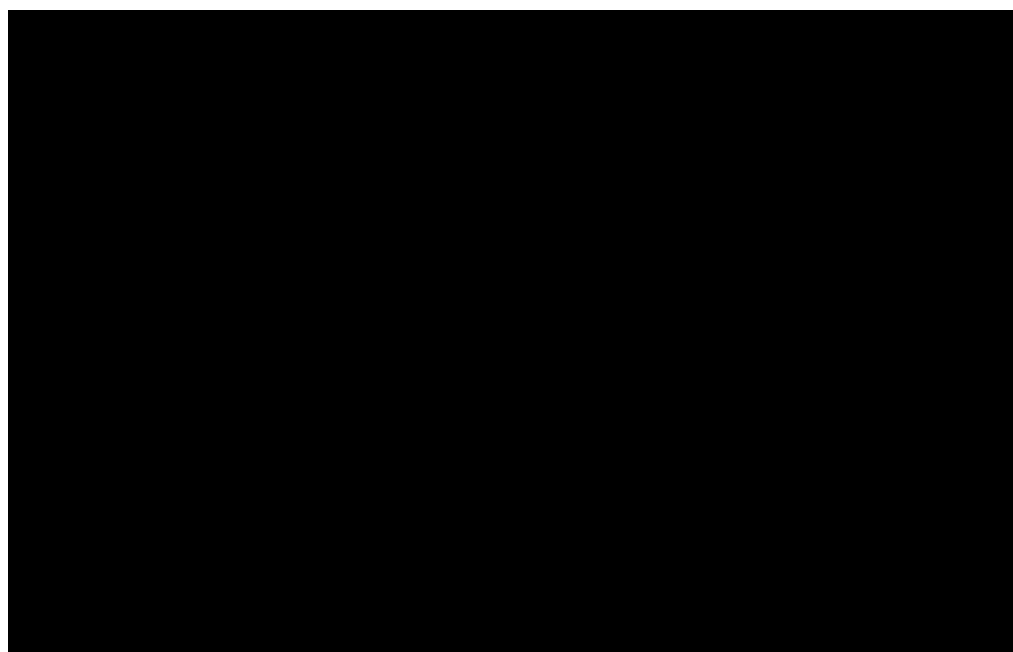
Clinical plausibility of the resulting reconstructed OS extrapolations (when only the standard parametric model informing the 'reference' TTP curve for the PF 2L to PD transition was varied and all other transition probabilities/AMRs were based on their base case settings) was the primary consideration for selecting the base case curve for TTP for patients who received ibrutinib at second line (the 'reference' TTP curve).

When the log-logistic extrapolation was used as the 'reference' TTP curve, the resulting OS estimates for the corresponding reconstructed OS curve were most closely aligned with the expert estimates of OS at all timepoints (including the closest aligned at 20 years; ibrutinib regimen: 10 year: 69.2% vs 67.0%; 15 year: 52.5% vs 53.0%; 20 year: 37.8% vs 37.0%; ASCT regimen: 10 year: 58.3% vs 56.0%; 15 year: 43.0% vs 44.4%; 20 year: 31.4% vs 30.4%), and therefore the log-logistic model was selected to inform the 'reference' curve for TTP in the base case economic analysis.⁴² The exponential, which was the best statistically fitting curve in terms of both AIC and BIC (see Table 42), was explored in a scenario analysis.

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For clarity, Figure 22 presents the selected 'reference' curve informing TTP in the base case economic analysis, alongside the resulting adjusted TTP curves for the ASCT regimen and the ibrutinib regimen, when the average weighted HRs from Table 41 have been applied to the 'reference' TTP curve to account for the differential risk of progression associated with second-line treatments in UK clinical practice. The presented TTP curves for the ibrutinib and ASCT regimen, respectively were used to inform transitions from the PF 2L to the PD health state for the ibrutinib and ASCT arms of the model respectively.

Figure 22: Base case 'reference' TTP curve and adjusted TTP curves for both the ibrutinib and ASCT model arms



Footnotes: TTP was derived from PFS data, censored for pre-progression mortality, to avoid double-counting. To derive the adjusted TTP curves, weighted average HRs (Table 41; which were based on the subsequent treatment distributions provided in Section 3.5.2, and data/assumptions around the relative efficacy between subsequent treatments) are applied to the 'reference' TTP curve (the log-logistic) for the PF 2L to PD transition. **Abbreviations:** ASCT: autologous stem cell transplant; TTP: time to progression.

3.3.5 *PD to Death (mortality on 3L treatment)*

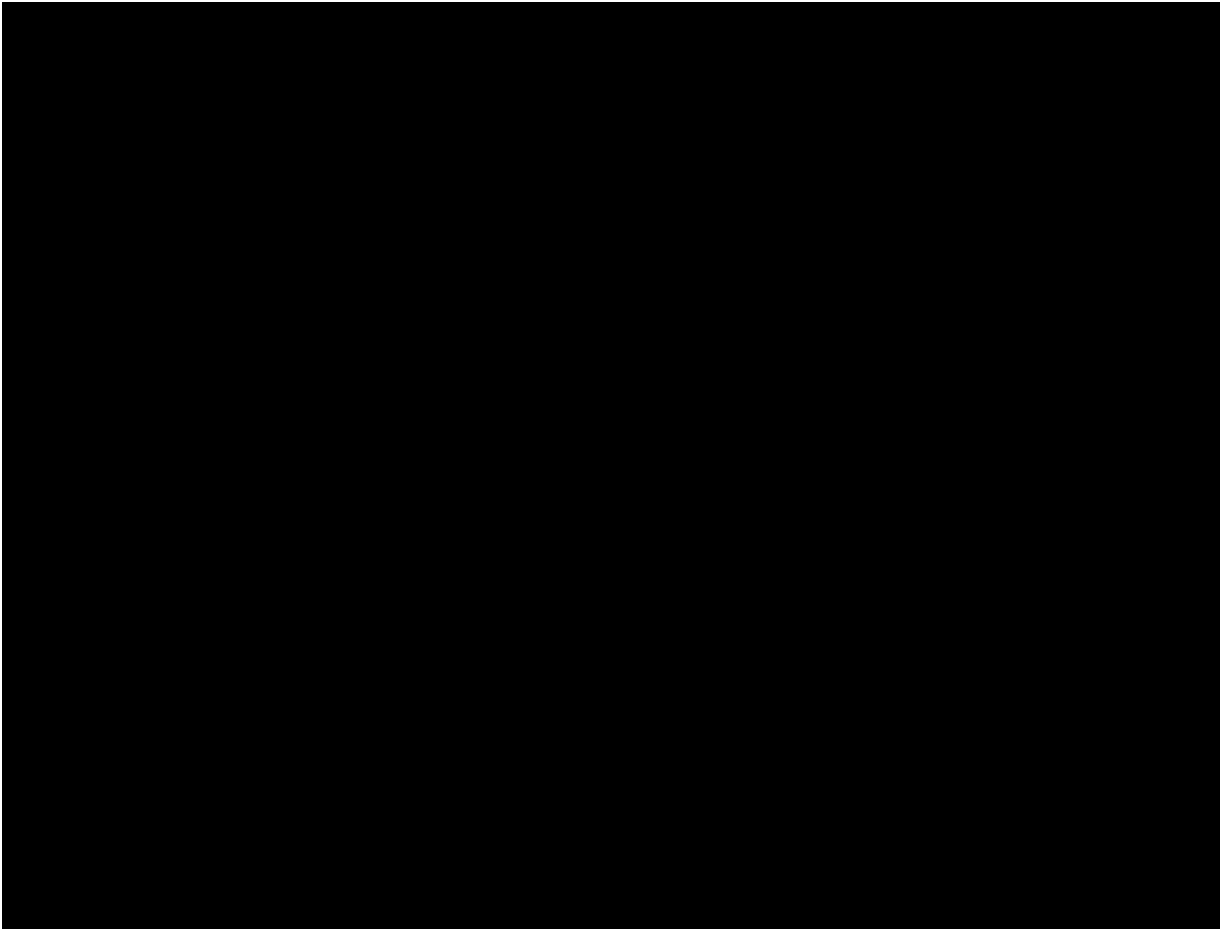
Data source informing PD to Death transition probability

In line with the approach to quantifying transition probabilities from PF 2L to Death (see Section 3.3.3) and PF to PD (see 3.3.4); transitions from PD to Death were informed by RAY-3001 given the limitations associated with subsequent treatment efficacy data in TRIANGLE discussed in Section 3.3 above. Specifically, post-progression survival (PPS) data from the ibrutinib arm of RAY-3001 (one prior line subgroup) were used to inform the PD to Death transition.

The KM PPS data from the ibrutinib arm of RAY-3001 (one prior line subgroup) is presented in Figure 23. The observed PPS data are mature, with the majority of events having occurred within the first 12 months of the observed period. As the median follow-up of RAY-3001 (38.7 months) is shorter than the modelled time horizon (43 years), KM PPS data from the ibrutinib arm of RAY-3001 (one prior line subgroup) required extrapolation via a parametric function to inform transitions from the PD state to the Death state in patients receiving 3L treatment across the modelled time horizon.^{85, 99}

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Figure 23: Observed PPS Kaplan-Meier data for the ibrutinib arm (RAY-3001, one prior line subgroup)



Abbreviations: PPS: post-progression survival.

Extrapolation methods

Standard parametric survival distributions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) were fitted to the observed PPS data from RAY-3001 (one prior line subgroup), and selection of the most appropriate parametric model was assessed using goodness-of-fit statistics and visual comparison with KM curves. Of note, the PPS extrapolations were capped by general population mortality (based on 2022–2024 life tables) to ensure that survival did not exceed that of the UK general population.

Internal validity

Statistical fit

A summary of the goodness-of-fit statistics for the PPS data from the ibrutinib arm of RAY-3001 (one prior line subgroup) is provided in Table 45. Assessment of statistical fit indicated that the Gompertz and exponential distributions were the best two fitting curves based on AIC and BIC.

Table 45: Goodness-of-fit statistics (AIC/BIC) for all parametric models fitted to PPS data (RAY-3001; one prior line subgroup)

Distribution	AIC	AIC rank	BIC	BIC rank

Exponential	■	2	■	1
Weibull	■	3	■	3
Gompertz	■	1	■	2
Log-logistic	■	5	■	5
Log-normal	■	6	■	6
Gamma	■	4	■	4
Generalised Gamma	■	7	■	7

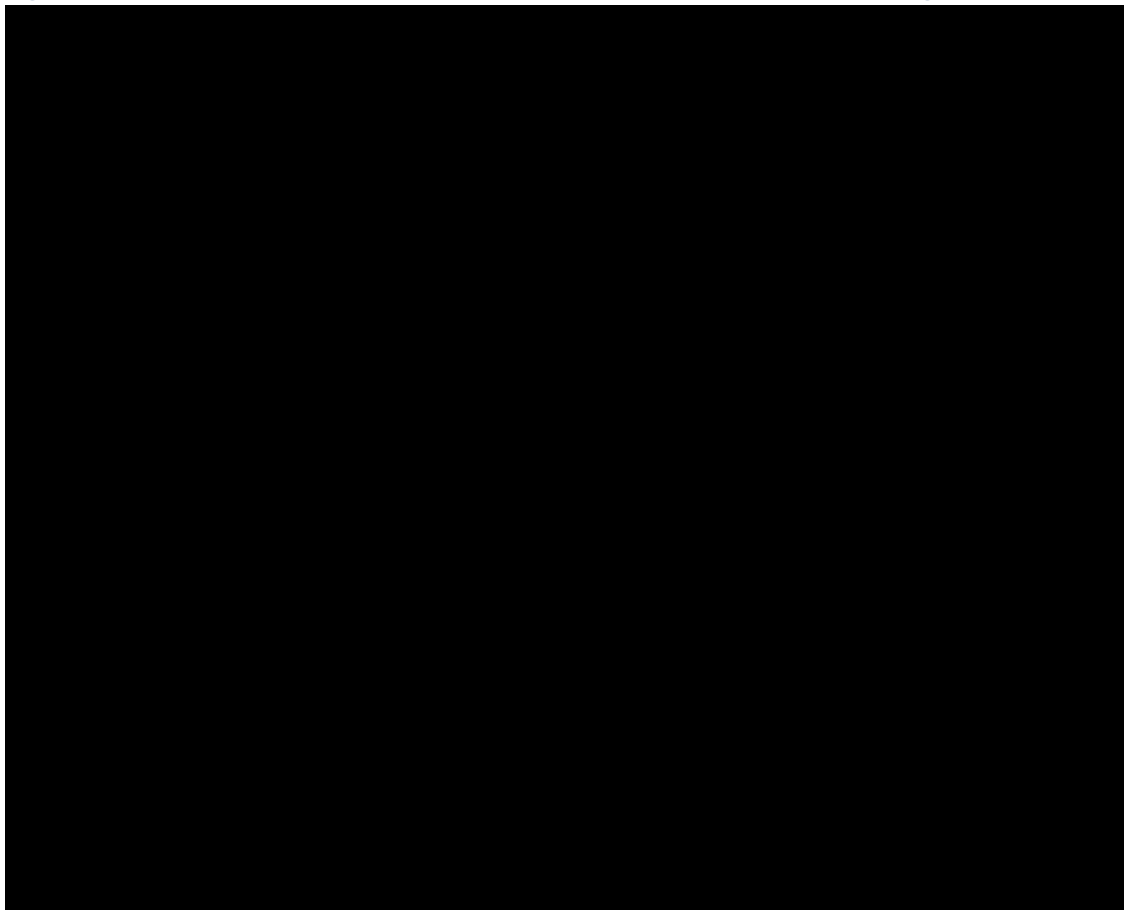
The extrapolation with the best statistical fit is highlighted in **bold**.

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; post-progression survival.

Visual fit

Figure 24 presents the parametric extrapolations highlighting the visual fit to the observed PPS KM data from the ibrutinib arm of RAY-3001 (one prior line subgroup). As expected given the maturity of the PPS data from RAY-3001, the curves provide good visual fit to the first 12 months of KM data. Poorer fit is seen towards the tail end of the KM data, likely due to the low numbers of patients at risk at this time.

Figure 24: PPS: observed vs. predicted (RAY-3001; one prior line subgroup)



Abbreviations: ASCT: autologous stem cell transplant; PPS: post-progression survival.

External validity

Table 46 presents the landmark estimates for PPS predicted by each of the standard parametric curves. All curves predicted 20-year PPS that is less than ■%, except for the Gompertz which

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predicted considerably higher PPS at █%. As such, despite being one of the best statistically fitting curves (see Table 45) the Gompertz was not considered a clinically plausible extrapolation to model long-term PPS in this setting, given that it implies implausibly low long-term mortality rates given the incurable nature of MCL

Table 46: Landmark estimates for PPS data (RAY-3001; one prior line subgroup) extrapolations

Distribution	5-year (%)	10-year (%)	15-year (%)	20-year (%)
Exponential	█	█	█	█
Weibull	█	█	█	█
Log-normal	█	█	█	█
Log-logistic	█	█	█	█
Gompertz	█	█	█	█
Gamma	█	█	█	█
Generalised Gamma	█	█	█	█

Abbreviations: PPS: post-progression survival.

Base case selection

The selection of the PPS curve was based primarily on internal validity given the maturity of the RAY-3001 (one prior line subgroup) PPS data. Based on statistical fit and visual fit, the exponential was selected as the base case curve to model PPS, given it was one of the two best statistically fitting curves (alongside the Gompertz), and the Gompertz provided clearly clinically implausible long-term PPS estimates. The next best statistically fitting curve (Weibull), was explored in a scenario analysis.

3.3.6 Summary of transition probabilities

A summary of the base-case modelling approach for each of the transition probabilities informing the cost-effectiveness model is provided in Table 47.

Table 47: Summary of transition probabilities (base case)

Transition probability	Ibrutinib regimen	ASCT regimen
FF 1L to Death (pre-failure mortality on 1L treatment)	Per-cycle probability of death from Arm I TRIANGLE (capped by GPM): ^a █	Per-cycle probability of death from Arm A of TRIANGLE (capped by GPM): ^a █
FF 1L to PF 2L (failure on 1L treatment)	TTF data from Arm I of TRIANGLE: exponential	TTF data from Arm A of TRIANGLE: Gamma
PF 2L to Death (pre-progression mortality on 2L treatment)	Per-cycle probability of death from the ibrutinib arm of RAY-3001 (one prior line subgroup; capped by GPM): ^a █	
PF 2L to PD (progression on 2L treatment)	Reference curve: PFS data from the ibrutinib arm of RAY-3001 (one prior line subgroup): log-logistic ^b	
PD to Death (mortality on 3L treatment)	PPS data from the ibrutinib arm of RAY-3001 (one prior line subgroup; capped by GPM): exponential	

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Footnotes: ^a Per-cycle probabilities of death were capped by a lower limit based on GPM, to ensure that modelled mortality would not fall below general population norms. ^b Differential weighted HRs were applied to this 'reference' TTP curve to derive the final modelled TTP curves for each regimen. These weighted HRs were based on the subsequent treatment distributions provided in Section 3.5.2, and data/assumptions around the relative efficacy between subsequent treatments. Further details are provided in Section 3.3.4.

Abbreviations: 1L/2L/3L: first/second/third line; ASCT: autologous stem cell transplant; GPM: general population mortality; PD: progressed disease; PF: progression-free; PFS: progression-free survival; TTF: time-to-failure.

3.3.7 Adverse events

In order to capture the potential toxicity associated with first-line treatment, a proportion of patients in the FF 1L health state in the model were assumed to experience AEs during treatment, with rates informed by Arm I and Arm A of TRIANGLE (CCO 09 May 2024; FAS) for the ibrutinib and ASCT regimen, respectively.^{30, 63} AEs considered in the model included treatment-emergent Grade ≥ 3 AEs with an incidence $\geq 5\%$ in at least one of the treatment arms in the model (i.e., the ibrutinib regimen or the ASCT regimen).^{30, 63} The inclusion rule that events must have occurred in at least 5% of patients in either arm was selected in order to capture AEs that would impact patients consistently enough to have validity in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting. Additionally, the inclusion of Grade ≥ 3 AEs ensures that the AEs that are most anticipated to impact patient HRQoL, and have associated costs, are captured within the model. The AE incidence rates included in the economic model are presented in Table 48.

The associated utility decrement and costs associated with each AE are presented in Section 3.4.4 and Section 3.5.4, respectively.

Table 48: Incidence of Grade ≥ 3 AEs included in the model

Adverse event	Ibrutinib regimen	ASCT regimen
Neutropenia	39.2%	38.8%
Anaemia	21.5%	34.3%
Thrombocytopenia	34.7%	42.5%
Febrile neutropenia	14.0%	26.5%
Leukopenia	9.4%	11.2%
Platelet count decreased	29.4%	33.2%
Neutrophil count decreased	24.2%	23.1%
White blood cell count decreased	6.4%	13.4%
Lymphocyte count decreased	4.5%	5.6%
Pneumonia	5.3%	4.1%
Stomatitis	1.5%	7.8%
Nausea	4.2%	7.8%
Diarrhoea	5.3%	6.0%
Mucosal inflammation	1.9%	13.1%
Hypokalaemia	6.4%	4.5%

Abbreviations: AE: adverse event; ASCT: autologous stem-cell transplant.

Source: EMA. Assessment Report: Imbruvica (2025).⁶³

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3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from clinical trials

As described in Section 2.3, TRIANGLE was an investigator-led trial and HRQoL data were not routinely collected.⁶³

3.4.2 Health-related quality-of-life studies

An SLR was conducted to identify all relevant utilities in adult patients with untreated MCL. The original SLR was performed in December 2023, with the first update performed in May 2025 and the second update performed in October 2025. In total, nine publications from seven unique studies were identified. Full details of the SLR search strategy, study selection process and the results of the included studies are reported in Appendix F.

HSUV for FF 1L health state

The humanistic SLR did not identify any studies reporting EuroQol five dimensions (EQ-5D) data in previously untreated, transplant-eligible patients with MCL. In the absence of data in the transplant-eligible population, clinical experts consulted indicated that utility data from a transplant-ineligible population would be more relevant than data from patients with other lymphomas (such as diffuse large B-cell lymphoma).⁶ The SLR identified two unique studies collecting EQ-5D data in transplant-ineligible patients with MCL: the SHINE study and the 2015 NICE appraisal for VR-CAP (TA370).^{86, 94} The study by Witzens-Harig et al. (2009) was additionally identified however given that it collected EQ-5D data in a broader non-Hodgkins lymphoma patient population and therefore was not specific to patients with MCL, it wasn't considered relevant, in line with the above clinician feedback.¹⁰¹

The data reported in TA370 were published over 10 years ago and the treatments available at the time were not representative of current clinical practice; these data were therefore considered outdated. Furthermore, feedback received from UK clinical experts indicated that the EQ-5D data from the SHINE trial were more appropriate given that utility data from SHINE were collected in patients receiving ibrutinib in combination with immunochemotherapy which is also applicable to the TRIANGLE trial (Arm I).⁹⁴ SHINE is a multicentre, randomised double-blind Phase III study comparing ibrutinib in combination with bendamustine plus rituximab (BR) and rituximab maintenance to placebo + BR and rituximab maintenance in patients aged ≥65 years with previously untreated stage II, III, or IV MCL who were ineligible for ASCT.⁸⁶ Furthermore, access to IPD from SHINE allowed for the possibility of adjusting the utility data to align more closely with the TRIANGLE population. The availability of IPD was therefore a key strength of the SHINE data given the paucity of available evidence in the untreated ASCT-eligible setting.⁸⁶ As such, the EQ-5D data from the SHINE trial were deemed most suitable to inform the health-state utility value (HSUV) in the FF 1L health state of the model. Details of how the data were incorporated into the model, including the adjustment process to align the HSUVs more closely with the TRIANGLE population is provided in Section 3.4.6.

HRQoL data, including EQ-5D-5L data, were collected every 12 weeks for the first 12 months, then every 16 weeks of the SHINE trial.⁸⁶ Utility data were derived from progression free patients receiving ibrutinib in combination with immunochemotherapy at first line (in line with the regimen used in Arm I of TRIANGLE). A summary of the SHINE trial is presented in Table 49 below.

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Table 49: Overview of the SHINE trial

SHINE (NCT01776840)	
Study design	Randomised, double-blind, international, Phase III clinical trial
Population	Patients (≥65 years) with untreated MCL
Overall population eligibility criteria	Key inclusion criteria: Patients ≥65 years with a centrally confirmed diagnosis of MCL with cyclin C1 overexpression or translocation breakpoints at t(11;14); previously untreated, documented stage II–IV disease, ≥1 measurable site of disease, an ECOG PS of 0 or 1, and adequate organ function Key exclusion criteria: Planned ASCT or known CNS involvement, history of stroke or intracranial haemorrhage ≤6 months before randomisation, anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A inhibitors, or clinically significant cardiovascular disease ≤6 months before screening
Intervention	Ibrutinib arm (560 mg administered orally once daily) in combination with BR ^a
Comparator	Matching placebo arm in combination with BR administered ^a
Primary endpoint	PFS
Secondary and exploratory endpoints	CR, OS, TTNT, ORR, DoR, MRD, lymphoma symptoms assessed via FACT-Lym, EQ-5D, safety and PK
Median follow-up	84.7 months

^aAll subjects received up to 6 cycles of BR background therapy. CR/PR patients received rituximab maintenance every two cycles for up to 12 additional doses. If CR/PR occurred after Cycle 30, the blinded study drug (ibrutinib/placebo) continued until progression, unacceptable toxicity, or study end. Subjects with stable disease after initial BR+ibrutinib/placebo immunochemotherapy continued ibrutinib/placebo until progression, toxicity, or study end. Progressive disease required discontinuation of all study treatment.

Abbreviations: ASCT: autologous stem-cell transplantation; BR: bendamustine and rituximab; CNS: central nervous system; CR: complete response; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; EQ-5D: EuroQol five-dimension; FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma; MCL: mantle cell lymphoma; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; PR: partial response; PS: performance status; TTNT: time to next treatment;

Source: Wang (2022).⁸⁶

HSUV for PF 2L and PD health states

HSUVs were also required to inform the PF 2L and PD health states in the economic model in patients receiving second and third line treatments.

As discussed in Section 1.3.4, and validated by feedback received from UK clinical experts, following 1L treatment, patients with MCL commonly receive BTKis in UK clinical practice.⁴² It was therefore considered most appropriate to use utility values elicited from patients with MCL receiving BTKis at 2L to inform these health states. As such, the HSUVs for PF 2L and PD for the two BTKis recommended by NICE in the 2L setting (ibrutinib [TA502] and zanubrutinib [TA1081]) were chosen.^{11, 51} These utility values were accepted as appropriate for decision making by the NICE committee in both appraisals.^{11, 51} These values were originally elicited using pooled EQ-5D data from patients with r/r MCL in the ibrutinib arms of the RAY-3001 and SPARK

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trials.^{85, 87} The RAY-3001 trial is a randomised, open-label, multicentre, Phase III trial comparing ibrutinib vs. temsirolimus in patients with r/r MCL who had received one or more rituximab-containing treatment.⁸⁵ The SPARK trial is a single arm, open-label, multicentre, Phase II trial investigating the impact of ibrutinib in patients with r/r MCL who had received prior rituximab-containing chemotherapy and who had progressed after bortezomib therapy.^{87 85, 87} EQ-5D estimates were collected as an exploratory endpoint in both trials.

3.4.3 Mapping

The utility value identified to inform FF 1L was mapped to inform an appropriate HSUV, in line with the NICE reference case. Pooled EQ-5D-five level (5L) scores collected in the SHINE trial were cross-walked to the EQ-5D-three level (EQ-3D-3L) utility index scored using the mapping function presented in Hernandez Alava et al. 2023, based on UK weights published in Dolan et al. 1997.^{102, 103} The resulting utility values for each of the health states are presented in Section 3.4.5. The health state utility values for PF 2L and PD were elicited directly from TA502.¹¹

3.4.4 Adverse reactions

To account for the HRQoL impact resulting from the toxicity of 1L treatments, a one-off disutility was applied to patients in each arm in the first model cycle. This utility decrement was derived from the AEs observed in TRIANGLE Arm I for patients receiving the ibrutinib regimen and Arm A for patients receiving the ASCT regimen. For each AE, a disutility was applied to the proportion of patients who experienced AEs in TRIANGLE (see Section 3.3.7, Table 48), based on the duration of AEs. Given that AE disutility data were not available from TRIANGLE, AE disutilities and duration were informed by published literature, as reported in Table 50. The resulting aggregated AE disutility in patients receiving the ibrutinib and the ASCT regimen, is provided in Table 51.

Table 50: AE utility decrement values

Adverse event	Disutility	Duration (days)	QALY lost per event	Source
Neutropenia	-0.160	15	-0.00661	NICE TA891 as per NICE TA487 ⁸⁸
Anaemia	-0.090	23	-0.00572	NICE TA891 as per NICE TA487 ⁸⁸
Thrombocytopenia	-0.110	23	-0.00699	NICE TA891 as per NICE TA487 ⁸⁸
Febrile neutropenia	-0.160	15	-0.00661	NICE TA891. ⁸⁸ Assumed to be the same as Neutropenia
Leukopenia	-0.160	15	-0.00661	NICE TA891. ⁸⁸ Assumed to be the same as Neutropenia
Platelet count decreased	-0.110	23	-0.00699	NICE TA891. ⁸⁸ Assumed to be the same as Thrombocytopenia
Neutrophil count decreased	-0.160	15	-0.00661	NICE TA891. ⁸⁸ Assumed to be the same as Neutropenia
White blood cell count decreased	-0.160	15	-0.00661	NICE TA891. ⁸⁸ Assumed to be the same as Neutropenia
Lymphocyte count decreased	-0.160	15	-0.00661	NICE TA891. ⁸⁸ Assumed to be the same as Neutropenia

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Pneumonia	-0.195	18	-0.00972	Tolley K et al. 2013; ¹⁰⁴ Used in NICE TA 891; ⁸⁸ Duration derived from NICE TA359 ¹⁰⁵
Stomatitis	-0.151	21	-0.00868	NICE TA779 as per Lloyd et al. 2006 ⁹⁷
Nausea	-0.061	11	-0.00175	Swinburn et al. 2012 ¹⁰⁶ ; Duration derived from TA789 ¹⁰⁷
Diarrhoea	-0.103	21	-0.00592	NICE TA779 as per Lloyd et al. 2006 ⁹⁷
Mucosal inflammation	-0.151	21	-0.00868	NICE TA779. Assumed to be equal to stomatitis
Hypokalaemia	-0.160	15	-0.00661	Assumed to be the same as Neutropenia

Abbreviations: AE: adverse event; NICE: National Institute of Health and Care Excellence; QALY: quality-adjusted life year; TA: technology assessment.

Table 51: Aggregated QALY loss

	Ibrutinib regimen	ASCT regimen
Disutility	-0.0138	-0.0181

Abbreviations: ASCT: autologous stem-cell transplantation; QALY: quality adjusted life year.

3.4.5 Additional utility decrements

In line with the approach taken in TA343 (obinutuzumab in combination with chlorambucil for untreated CLL), a utility decrement associated with IV administration was modelled for treatments requiring IV administration.⁸⁸ The decrement of 0.04 was applied per infusion visit, with the assumption that only one visit would be required on days where multiple components of a treatment regimen are administered. No disutility was modelled for administration of either oral or subcutaneous treatments. The utility decrements associated with treatment administration are summarised in Table 52.

Table 52: Summary of utility change due to treatment administration

	Utility value: mean (SE)	Justification
Utility decrement due to IV treatment	-0.04 (0.01)	NICE TA343 ¹⁰⁸
Utility decrement due to oral treatment	0.00 (0.00)	Assumption
Utility decrement due to SC treatment	0.00 (0.00)	Assumption

Abbreviations: ASCT: autologous stem cell transplantation; IV: intravenous; R-DHAP: rituximab, dexamethasone, high-dose cytarabine, and cisplatin; SC: subcutaneous; SE: standard error.

3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

For all three alive health states in the semi-Markov model (FF 1L, PF 2L and PD), treatment-independent utility values were applied to each health state to capture quality of life impacts of

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disease progression. The data sources and methods for deriving these utility values are summarised in Table 53 and described in detail in the sections below.

HSUV for FF 1L health state

As described in Section 3.4.2, EQ-5D-5L data from the SHINE trial were used to estimate the utility value for the FF 1L health state in the TRIANGLE cost-effectiveness model. Specifically, EQ-5D-5L data were obtained from patients in the ibrutinib + BR arm who were progression-free (data cut-off [DCO]: June 2021; median follow-up: 84.7 months), as these patients were most similar to patients in the FF 1L health state. Use of PFS data was deemed a suitable proxy for FFS given that the number of events with stable disease at the end of induction therapy in the TRIANGLE trial was limited (Arm I: n=1 (1%); Arm A: n=1 (1%)),³⁰ and hence FFS does not differ drastically from PFS. It is acknowledged that use of a less stringent endpoint than FFS may mean utility in the FF 1L state is slightly underestimated, but the impact is likely to be minimal and in favour of the ASCT arm who spend less time in the FF 1L health state.

The EQ-5D-5L data from the ibrutinib + BR arm in progression-free patients in SHINE were subsequently cross-walked to the EQ-3D-3L utility index scores using the mapping function presented in Hernandez Alava et al. 2023 (see Section 3.4.3 for further details).^{102, 103}

To account for the differences in population between the SHINE and TRIANGLE patient populations, a mixed-model repeated measures (MMRM) analysis was then applied to the data from progression-free patients in the ibrutinib arm of the SHINE trial. The model predicted EQ-5D scores considering the following key covariates identified via UK clinical experts: sex; presence of adverse events during the EQ-5D measurement (none, AE Grade 1 or 2, AE Grade ≥3); latest available ECOG performance status (0, 1, ≥2); baseline disease stage (II, III, IV); presence of B-symptoms (yes/no); creatinine clearance below 30 ml/min (yes/no); and bone marrow involvement (yes/no). Coefficients for each of these variables were estimated using the MMRM. Subsequently, the baseline characteristics of Arm I of the TRIANGLE trial were applied to these coefficients to estimate the utility value for the FF 1L health state. This approach ensured that the utility value reflected the characteristics of the TRIANGLE population, where available covariates allowed.

The resulting utility (mean utility value: 0.75; SE: 0.02; Table 53) was applied to both patients receiving the ibrutinib and ASCT regimen in the FF 1L health state. It should be noted that use of a treatment-independent utility in the FF 1L health state means that the impact of toxic HDT as well as ASCT with a median hospital duration of 30 days, including the resulting patient isolation from hospitalisation experienced by patients receiving the ASCT regimen first-line (further described in Section 1.3.5), are not accounted for within the base case economic analysis.^{43, 55}

HSUV for PF 2L and PD health states

In the base case analysis the HSUVs for PF 2L and PD were informed by pooled data from the RAY-3001 and SPARK trials (Table 53); in line with the accepted values informing the equivalent health states in TA502 and TA1081, which were deemed suitable for UK decision making by the NICE committee.^{11, 51} A mixed model analysis was carried out to determine the mean QoL pre and post progression for patients in the ibrutinib arm of the two trials.¹¹

To align the sources informing the HSUVs to that informing efficacy (transition probabilities) in these health states, HSUVs for PF 2L and PD derived from the RAY-3001 trial alone, were additionally explored as a scenario. This scenario however required HSUVs to be assumed to be Company evidence submission for ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

equal across the PF 2L and PD health states and therefore was associated with reduced clinical validity vs. the base case approach.

Utility values applied in the model

A summary of the utility values included in the cost-effectiveness model in the base case analysis presented in Table 53. When consulted at the November 2025 advisory board, clinical experts considered that the decrements between the health states to be reflective of the utility decrement patients would experience upon progression.⁴²

Table 53: Summary of base case utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	Source
FF 1L		SHINE (DCO: June 2021) ibrutinib arm EQ-5D-5L data were cross-walked to EQ-5D-3L based on the Hernandez Alava et al. 2023 mapping algorithm. ^{30, 102} TRIANGLE ibrutinib (I) arm mean utility estimated by using an MMRM model fit to the cross-walked SHINE data
PF 2L	0.780 (0.010)	Aligned with the HSUVs used in TA502 ¹¹ and TA1081. ⁵¹ These values were originally elicited using pooled EQ-5D data from patients with r/r MCL in the ibrutinib arms of the RAY-3001 and SPARK trials. ^{85, 87}
PD	0.680 (0.024)	

Abbreviations: 1/2L: first, second-line; ASCT: autologous stem cell transplantation; CI: confidence interval; DCO: data cut-off; EQ-5d-3L: EuroQol 5-Dimension 3-Level; EQ-5D-5L: EuroQol 5-Dimension 5-Level; FF: failure-free; HS: health state; HSUV: health state utility value; IV: intravenous; MMRM: mixed-model repeated measures; R-DHAP: rituximab, dexamethasone, high-dose cytarabine, and cisplatin; SC: subcutaneous; SE: standard error; TA: technology assessment.

A summary of the utility values included in the cost-effectiveness model in the HSUV scenario analysis presented in Table 54.

Table 54: Summary of scenario utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	Source
FF 1L		SHINE (DCO: June 2021) ibrutinib arm EQ-5D-5L data were cross-walked to EQ-5D-3L based on the Hernandez Alava et al. 2023 mapping algorithm. ^{30, 102} TRIANGLE ibrutinib (I) arm mean utility estimated by using an MMRM model fit to the cross-walked SHINE data
PF 2L		RAY-3001 patients treated with ibrutinib monotherapy regardless of progression status. ⁸⁵ A single MMRM was applied to cross-walked EQ-3D-3L scores to estimate overall utility while including all-follow-up visits from ibrutinib patients in the RAY-3001 study. EQ-5D-5L results were mapped to EQ-5D-3L based on Hernández et al. 2023 ¹⁰²
PD		

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Abbreviations: 1/2L: first, second-line; ASCT: autologous stem cell transplantation; CI: confidence interval; DCO: data cut-off; EQ-5d-3L: EuroQol 5-Dimension 3-Level; EQ-5D-5L: EuroQol 5-Dimension 5-Level; FF: failure-free; HS: health state; HSUV: health state utility value; IV: intravenous; MMRM: mixed-model repeated measures; R-DHAP: rituximab, dexamethasone, high-dose cytarabine, and cisplatin; SC: subcutaneous; SE: standard error; TA: technology assessment.

Age-based utility decrements

The model accounted for the expected decrease over time in quality of life associated with aging. The utility estimates for each model cycle were adjusted based on the difference between patients' age during the current cycle and the age at the start of the model. The starting age of the modelled population is 57 years (derived from the median age of TRIANGLE). The age-adjusted utilities were implemented using the mean EQ-5D-3L values by age estimated from the latest available wave of the Health Survey England (HSE) that included the EQ-5D-3L (published in 2014).¹⁰⁹

3.5 Cost and healthcare resource use identification, measurement and valuation

An economic SLR was also conducted to identify cost and resource use studies associated with treatment of adult patients with untreated MCL. The original SLR was conducted in December 2023, with the first update performed in May 2025 and the second update performed in October 2025. In total, 13 publications from 13 unique studies were identified. However, only one study reported on transplant-eligible patients with MCL, the population of interest in this appraisal, and the study did not report on relevant UK costs. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

The health economic analysis was conducted from the perspective of the NHS in England and therefore included only costs that would be incurred by the health system. Appropriate sources of unit costs, such as NHS Reference Costs 2024/25,¹¹⁰ British National Formulary (BNF)⁹¹ and drugs and pharmaceutical electronic market information tool (eMIT)⁹² were used for cost inputs in the model.

Specifically, the following cost components were considered in the model:

- Drug acquisition costs for the intervention and comparator (Section 3.5.1)
- Drug administration costs (Section 3.5.1)
- Subsequent treatment costs (Section 3.5.2)
- Medical resource use costs for routine care and monitoring (Section 3.5.3)
- Costs associated with the management of AEs and ASCT complications (Section 3.5.4)
- Costs associated with treatment failure (Section 3.5.5)
- Costs of terminal care (Section 3.5.5)

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3.5.1 Intervention and comparators' costs and resource use

Dosing regimens

The dosing regimens and dose intensities for first-line treatment options, the ibrutinib regimen and the ASCT regimen, are presented in Table 55 and are based on the TRIANGLE protocol and the licensed dosing regimens for each treatment.^{71, 82}

Where possible, the percentage of patients receiving each component of the regimen and the dose intensity were derived from TRIANGLE.³⁰ However, to align with UK clinical practice, an 80%:20% split between the Nordic regimen (alternating R-Maxi-CHOP and R-cytarabine) and alternating R-CHOP and R-DHAP (or R-DHAOx) as induction chemotherapy regimens prior to ASCT was included in the economic model, based on clinical expert feedback that the majority of patients would receive the Nordic regimen in UK clinical practice.⁴² Clinical experts indicated that the different chemotherapy induction regimens are considered to have equivalent efficacy in patients with untreated MCL, as supported by BSH guidelines, so only cost differences were reflected between the different regimens.^{4, 42}

In both arms, the TRIANGLE protocol allowed patients to receive either R-DHAP or R-DHAOx in combination with R-CHOP, which is aligned with the license for ibrutinib.¹ Based on UK clinical expert feedback, 85% of patients were assumed to receive R-DHAOx over R-DHAP. UK clinical experts noted that R-DHAOx is favoured over R-DHAP owing to its more tolerable safety profile and convenient outpatient administration compared to R-DHAP, which requires inpatient administration.⁴²

As discussed in Section 1.3.4, in UK clinical practice the duration of rituximab maintenance treatment varies between two and three years. In the model, the duration of rituximab maintenance treatment was assumed to be two years for the majority of patients (90%), with the remaining proportion of patients assumed to receive rituximab maintenance for three years (10%), in line with NICE guidelines and feedback received from UK clinical experts who noted that the majority of patients receive rituximab maintenance for two-years in UK clinical practice.⁴² The total costs for the ibrutinib regimen and the ASCT regimen are presented in Table 61.

Drug wastage was not considered in the cost-effectiveness analysis and therefore drug costs were calculated based on the dose required per cycle for each component within the dosing regimen.

Table 55: Dosing regimens of first-line treatments

Component	Patients receiving, %	Dosing regimen	Dose intensity	Treatment duration
ASCT Regimen				
<i>R-CHOP alternating with R-DHAP or R-DHAOx (20% of patients)</i>				
R-CHOP	100%	IV rituximab 375 mg/m ² on Day 0 or 1, IV cyclophosphamide 750 mg/m ² on Day 1, IV doxorubicin 50 mg/m ² on Day 1, IV vincristine 1.4 mg/m ² on Day 1, and oral prednisone 100 mg on Days 1-5	100%	Cycles 1, 3, 5
R-DHAP	15%	IV rituximab 375 mg/m ² on Day 0 or 1, IV or oral dexamethasone 40 mg	100%	Cycles 2, 4, 6

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		on Days 1-4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on Day 2, and IV cisplatin 100 mg/m ² over 24 h on Day 1 ^a		
R-DHAOx	85%	IV rituximab 375 mg/m ² on Day 0 or 1, IV or oral dexamethasone 40 mg on Days 1-4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on Day 2, and IV oxaliplatin 130 mg/m ² on Day 1 ^a	100%	Cycles 2, 4, 6
<i>NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine) (80% of patients)</i>				
Maxi-CHOP	100%	IV rituximab 375 mg/m ² on Day 1, IV cyclophosphamide 1,200 mg/m ² on Day 1, IV doxorubicin 75 mg/m ² on Day 1 and IV vincristine 1.4 mg/m ² (maximum dose 2 mg) on Day 1 ^a	100%	Cycles 1, 3, 5
R-cytarabine	100%	IV rituximab 375 mg/m ² on Day 1, IV cytarabine 3g/m ² every 12 hours (total 4 doses) on Days 1 and 2 ^a	100%	Cycles 2, 4, 6
ASCT				
Stem-cell apheresis	87%	NA	NA	Cycle 4
HDT	87%	BEAM or THAM regimens: ^b BEAM: carmustine 300 mg/m ² (Day -7) + etoposide 2 x 100 mg/m ² (Day -6 to Day -3) + cytarabine 2 x 200 mg/m ² (Day -6 to Day -3) + melphalan 140 mg/m ² (Day -2) THAM: TBI 10 Gy (Day -7 to -5) + cytarabine 2 x 1.5 g/m ² (Day -4 and -3 every 12 hours) + melphalan 140 mg/m ² (Day -2)	NA	Cycle 6
ASCT	87%	Transplant	NA	Cycle 7
Maintenance				
Maintenance	■	Rituximab 375 mg/m ²	100%	Once every 2 months for 2–3 years after transplant ^c
Ibrutinib regimen				
<i>R-CHOP alternating with R-DHAP or R-DHAOx</i>				
R-CHOP in combination with ibrutinib	100%	IV rituximab 375 mg/m ² on Day 0 or 1, IV cyclophosphamide 750 mg/m ² on Day 1, IV doxorubicin 50 mg/m ² on Day 1, IV vincristine 1.4 mg/m ² on Day 1, and oral prednisone 100 mg on Days 1-5 in combination with ibrutinib 560 mg on Days 1–19	R-CHOP: 100% Ibrutinib: 95.2%	Cycles 1, 3, 5
R-DHAP	15%	IV rituximab 375 mg/m ² on Day 0 or 1, IV or oral dexamethasone 40 mg on days 1-4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on Day 2, and IV	100%	Cycles 2, 4, 6

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		cisplatin 100 mg/m ² over 24 h on Day 1 ^a		
R-DHAOx	85%	IV rituximab 375 mg/m ² on Day 0 or 1, IV or oral dexamethasone 40 mg on Days 1-4, IV cytarabine 2 × 2 g/m ² for 3 h every 12 h on Day 2, and IV oxaliplatin 130 mg/m ² on Day 1 ^a	100%	Cycles 2, 4, 6
<i>Maintenance</i>				
Maintenance	■	Rituximab 375 mg/m ²	100%	Once every 2 months for 2–3 years after transplant ^c
	■	Ibrutinib 560 mg	92.9%	Daily for 2 years after transplant

Footnotes: ^aPegfilgrastim was assumed to be given once at Day 6. ^bDay refers to the day of the transplant. ^c 90% of patients receiving rituximab maintenance were assumed to receive treatment for two years; 10% of patients were assumed to receive treatment for three years.

Abbreviations: ASCT: autologous stem cell transplantation; BEAM: carmustine, cytarabine, etoposide and melphalan; G-CSF: granulocyte colony-stimulating factor; h: hour; HDT: high-dose chemotherapy; IV: intravenous; NA: not applicable; Q12h: every 12 hours; R-: rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin; THAM: total body irradiation, cytarabine and melphalan; WBC: white blood cell count.

Source: EMA. Assessment Report: Imbruvica (2025),⁶³ European MCL Network (2023) TRIANGLE Protocol,⁷¹ J&J IM Data on File. November 2025 Advisory Board.⁴²

Unit costs

The ibrutinib and the ASCT regimens detailed in Table 55 are composed of several individual treatments, with the unit costs of each component detailed in Table 56. The unit cost of ibrutinib includes a PAS discount of ■%, in line with the existing PAS discount associated with ibrutinib.

Table 56: Unit costs for each treatment in a first-line regimen

Treatment	Cost per pack (£)	PAS discount	Discounted cost per pack (£)	Tablet/capsule/vial size	Pack size	Administration route	Source
Ibrutinib	£5,723.20	████	██████	560 mg	28	Oral	BNF 2025 ⁹¹ (Imbruvica 560mg tablets; pack size: 28)
	£4,292.40	████	██████	420 mg	28	Oral	BNF 2025 ⁹¹ (Imbruvica 420mg tablets; pack size: 28)
	£2,861.60	████	██████	280 mg	28	Oral	BNF 2025 ⁹¹ (Imbruvica 280mg tablets; pack size: 28)
	£1,430.80	████	██████	140 mg	28	Oral	BNF 2025 ⁹¹ (Imbruvica 140mg tablets; pack size: 28)
Doxorubicin	£19.56	NA	NA	200 mg	1	IV	eMIT 2025 ⁹² (Doxorubicin 200mg/100ml solution for infusion vials / pack size 1)
Vincristine	£10.61	NA	NA	2 mg	1	IV	eMIT 2025 ⁹² (Vincristine 2mg/2ml solution for injection vials / pack size 1)
Prednisone	£0.31	NA	NA	5 mg	28	Oral	eMIT 2025 ⁹² (Prednisolone 5mg tablets / pack size 28)
Dexamethasone	£3.25	NA	NA	3.3 mg	10	IV	eMIT 2025 ⁹² (Dexamethasone 3.3mg/1ml solution for injection ampoules / pack size 10)
Cytarabine	£49.59	NA	NA	500 mg	5	IV	eMIT 2025 ⁹² (Cytarabine 500mg/5ml solution for injection vials / pack size 5)
Cisplatin	£16.76	NA	NA	50 mg	1	IV	eMIT 2025 ⁹² (Cisplatin 50mg/50ml solution for infusion vials / pack size 1)
Pegfilgrastim	£411.83	NA	NA	6 mg	1	SC	BNF 2025 ⁹¹ (Pelmeg 6mg/0.6ml solution for injection pre-filled syringes; Napp Pharmaceuticals Ltd)

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Rituximab	£785.84	NA	NA	10 mg/mL	50 mL	IV	BNF 2025 ⁹¹ (Ruxience 500mg/50ml concentrate for solution for infusion vials; Pfizer Ltd)
	£157.17	NA	NA	10 mg/mL	100 mL	IV	BNF 2025 ⁹¹ (Ruxience 100mg/10ml concentrate for solution for infusion vials; Pfizer Ltd)
Cyclophosphamide	£25.32	NA	NA	2,000 mg	1	IV	eMIT 2025 ⁹² (Cyclophosphamide 2g powder for solution for injection vials / pack size 1)
	£12.60	NA	NA	1,000 mg	1	IV	eMIT 2025 ⁹² (Cyclophosphamide 1g powder for solution for injection vials / pack size 1)
	£10.00	NA	NA	500 mg	1	IV	eMIT 2025 ⁹² (Cyclophosphamide 500mg powder for solution for injection vials / pack size 1)
Carmustine	£325.54	NA	NA	100 mg	1	IV	eMIT 2025 ⁹² (Carmustine 100mg powder and solvent for solution for injection vials / pack size 1)
Etoposide	£7.22	NA	NA	100 mg	1	IV	eMIT 2025 ⁹² (Etoposide 100mg/5ml solution for injection vials / pack size 1)
Melphalan	£20.22	NA	NA	50 mg	1	IV	eMIT 2025 ⁹² (Melphalan 50mg powder and solvent for solution for injection vials / pack size 1)
Oxaliplatin	£87.03	NA	NA	200 mg	1	IV	eMIT 2025 ⁹² (Oxaliplatin 200mg/40ml solution for infusion vials / pack size 1)

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; G-CSF: granulocyte colony-stimulating factor; IV: intravenous; NA: not applicable; PAS: patient access scheme.

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Acquisition cost per administration

The unit costs detailed above are then used to calculate the cost per dose of first-line treatments, presented in Table 57 below. The costs per dose of first-line treatments are applied at the end of each model cycle, in line with the ibrutinib and the ASCT regimens detailed in Table 54 above.

Table 57: Cost per dose of first-line treatments (drug acquisition costs)

Component	Patients receiving, %	Dose per administration		Acquisition cost (per administration)
ASCT Regimen				
R-CHOP alternating with R-DHAP or R-DHAOx (20% of patients)				
R-CHOP	100%	Rituximab	742.5 mg	£1,257.35
		Cyclophosphamide	1,485.0 mg	£22.60
		Doxorubicin	99.0 mg	£19.56
		Vincristine	2.8 mg	£21.23
		Prednisone	100.0 mg	£0.22
R-DHAP	15%	Rituximab	742.5 mg	£1,257.35
		Dexamethasone	40.0 mg	£4.22
		Cytarabine	3,960.0 mg	£79.34
		Cisplatin	198.0 mg	£67.03
		Pegfilgrastim	6.0 mg	£411.83
R-DHAOx	85%	Rituximab	742.5 mg	£1,257.35
		Dexamethasone	40.0 mg	£4.22
		Cytarabine	3,960.0 mg	£79.34
		Oxaliplatin	257.4 mg	£174.06
		Pegfilgrastim	6.0 mg	£411.83
NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine) (80% of patients)				
Maxi-CHOP	100%	Rituximab	742.5 mg	£1,257.35
		Cyclophosphamide	2,376.0 mg	£35.32
		Doxorubicin	148.5 mg	£19.56
		Vincristine	2.8 mg	£21.23
		Prednisone	100.0 mg	£0.22
		Pegfilgrastim	6.0 mg	£411.83
R-cytarabine	100%	Rituximab	742.5 mg	£1,257.35
		Cytarabine	5,940.0 mg	£119.01
		Pegfilgrastim	6.0 mg	£411.83
ASCT				
Stem-cell apheresis	87%	NA		£6,386.86
HDT	87%	NA		£2,150.32
ASCT	87%	Transplant		£42,040.84
Maintenance				
Maintenance	87%	Rituximab	742.5 mg	£1,257.35

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Ibrutinib regimen				
R-CHOP alternating with R-DHAP or R-DHAOx				
R-CHOP in combination with ibrutinib	100%	Rituximab	742.5 mg	£1,257.35
		Cyclophosphamide	1,485.0 mg	£22.60
		Doxorubicin	99.0 mg	£19.56
		Vincristine	2.8 mg	£21.23
		Prednisone	100.0 mg	£0.22
		Ibrutinib	560.0 mg	
R-DHAP	15%	Rituximab	742.5 mg	£1,257.35
		Dexamethasone	40.0 mg	£4.22
		Cytarabine	3,960.0 mg	£79.34
		Cisplatin	198.0 mg	£67.03
		Pegfilgrastim	6.0 mg	£411.83
R-DHAOx	85%	Rituximab	742.5 mg	£1,257.35
		Dexamethasone	40.0 mg	£4.22
		Cytarabine	3,960.0 mg	£79.34
		Oxaliplatin	257.4 mg	£174.06
		Pegfilgrastim	6.0 mg	£411.83
Maintenance				
Maintenance		Rituximab	742.5 mg	£1,257.35
		Ibrutinib	560.0 mg	

Abbreviations: ASCT: autologous stem cell transplantation; HDT: high-dose chemotherapy; NA: not applicable; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin.

Source: BNF 2025,⁹¹ EMA. Assessment Report: Imbruvica (2025),⁶³ eMIT 2025,⁹² European MCL Network (2023) TRIANGLE Protocol,⁷¹ J&J IM Data on File. November 2025 Advisory Board.⁴²

Stem-cell apheresis and transplant costs

Costs for the ASCT procedure were split between stem-cell apheresis and ASCT, with NHS reference costs used to inform the cost of apheresis and NICE NG52 guidance (inflated to 2024 values) used to inform ASCT. The cost of ASCT is aligned with that used in a recent prior NICE appraisal (TA1048) which was considered appropriate for UK decision making.¹¹¹ The costs associated with stem-cell apheresis and ASCT used in the economic model are provided in Table 58 below.

These costs were applied as a one-off cost in the corresponding model cycle. For example, a cost of £6,386.86 was incurred by patients experiencing stem-cell apheresis in Cycle 4 as per the dosing regimen defined in Table 58. In addition, a cost of £42,040.84 was incurred by patients receiving ASCT in Cycle 7 as per the dosing regimen defined in Table 58.

Table 58: Summary of procedural costs

Resource	Inpatient Admission Cost	Source
Stem-cell apheresis	£6,386.86	NHS Reference Costs 2024/25 - NHS trusts and NHS foundation trusts - Weighted average inpatient: SA34Z ¹¹⁰

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ASCT	£42,040.84	NICE NG52 (guidelines Non-Hodgkin's lymphoma, 2016, Appendix A) ASCT cost of £34,000, inflated to 2024 prices using the PSSRU 2024 (inflation index factor of 1.2364954) ²⁴

Abbreviations: ASCT: autologous stem-cell transplantation; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NG: NICE guidance; PSSRU: Personal Social Services Research Unit.

Administration costs

Administration costs of £256.03 and £129.86 were applied per administration of IV and SC treatments, respectively, based on unit costs from the NHS Reference Costs 2024/25 (see Table 59).¹¹⁰ Orally administered drugs were assumed not to incur any administration costs.

Table 59: Summary of administration costs

Category	Administration cost	Source
IV administration	£256.03	NHS Reference Costs 2024/25 - NHS trusts and NHS foundation trusts - Total HRGs: Outpatient Procedures: SB12Z ¹¹⁰
Oral administration	£0.00	Assumption
SC administration	£129.86	NHS Reference Costs 2024/25 - N10AF - Specialist Nursing, Cancer Related, Adult, Face to face ¹¹⁰

Abbreviations: IV: intravenous; HDT: high-dose chemotherapy; NA: not applicable; NHS: National Health Service; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin; SC: subcutaneous.

Costs for treatments administered in an inpatient setting

R-DHAP and R-cytarabine are typically administered in an inpatient setting in UK clinical practice.^{111, 112} For these regimens, an additional inpatient admission cost was applied in addition to the drug acquisition and administration costs for each regimen, as detailed in Table 60 below. The inpatient duration of 2 days, respectively, was based on the dosing regimen for each treatment. For treatments administered in an inpatient setting, no additional administration costs are applied to avoid the potential for double counting.

High dose chemotherapy is also administered in an inpatient setting; however, the inpatient costs are assumed to be captured as part of the cost for ASCT previously detailed in Table 58.

Table 60: Summary of inpatient cost

Resource	Number of inpatient days required	Total costs	Source
R-DHAP / R-Cytarabine	2	£2,002	Weighted cost of SA31F Year 2024/25 - Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's ¹¹⁰

Abbreviations: ASCT: autologous stem cell transplant; BEAM: carmustine, cytarabine, etoposide and melphalan; HDT: high-dose chemotherapy; NHS: National Health Service; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin; THAM: total body irradiation, cytarabine and melphalan.

Summary of acquisition and administration costs

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All costs detailed in this section, including unit costs, procedural costs (stem-cell apheresis and transplant) and administration costs (including costs associated with treatments requiring inpatient admission) associated with the induction, consolidation and maintenance components of each regimen, all contribute to the overall costs of the ibrutinib regimen and the ASCT regimen. For each regimen, the total undiscounted drug acquisition and administration costs, in line with the dosing regimens described in Table 55, have been calculated across the entire model time horizon, to generate a total cost per regimen, presented in Table 61.

Table 61: Total cost of the ibrutinib regimen and the ASCT regimen

	Total acquisition cost per regimen	Total administration cost per regimen	Total cost per regimen
ASCT regimen	£70,137.60	£4,520.12	£74,657.72
Ibrutinib regimen (with PAS discount)	████████	████████	████████

Abbreviations: ASCT: autologous stem-cell transplantation; PAS: patient access scheme.

3.5.2 Subsequent treatment costs

The subsequent treatments and their associated distributions included in the model were informed by leading UK clinical experts. This approach was deemed appropriate given the model does not utilise post-failure on first-line treatment data from TRIANGLE and therefore trial-derived subsequent treatment data were considered less relevant.⁴² The model includes the following treatments, in line with the treatment pathway for patients with MCL in the UK (see Section 1.3.4):

- At 2L, patients with MCL receive either ibrutinib, zanubrutinib, R-BAC, BR or BSC
- At 3L, patients with MCL receive either R-BAC, less intensive R-based chemotherapy (including R-CHOP and BR) or BSC

Subsequent treatment distributions

The distribution of treatments received following failure on 1L treatment was dependent on the 1L treatment received, with the split informed by feedback received from UK clinical experts during the November 2025 advisory board.⁴² Four UK clinical experts provided their individual estimates, these were subsequently aggregated and the mean of these estimates was presented and unanimously validated as appropriate by all four clinical experts. These aggregated values are presented in Table 62.

Similarly, the distribution of treatments received following disease progression on 2L treatment were dependent on the 2L treatment received. These were also informed by feedback received from UK clinical experts during the November 2025 advisory board and are summarised in Table 63 below, based on 1L treatment received (see Appendix L.1.2 for further details).⁴² The experts indicated patients could receive a range of alternative less intensive, rituximab-based immunochemotherapy regimens in the 3L setting – as a simplifying assumption, BR was used as a proxy for the efficacy and costs of these regimens in the economic model.⁴²

Table 62: Distribution of subsequent treatment use in 2L

	2L treatment				
1L treatment	Ibrutinib	Zanubrutinib	R-BAC	BR	BSC

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Ibrutinib	-	57.6%	31.3%	10.0%	1.1%
ASCT	10.0%	84.8%	2.4%	2.0%	0.8%

Abbreviations: 1/2L: first/second line; ASCT: autologous stem-cell transplantation; BR: bendamustine and rituximab; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 63: Distribution of subsequent treatment use in 3L

	3L treatment		
1L treatment	R-BAC	BR	BSC
Ibrutinib	41.9%	33.3%	24.8%
ASCT	67.4%	16.2%	16.4%

Abbreviations: 2/3L: second/third line; BR: bendamustine and rituximab; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Subsequent treatment dosing regimens

The dosing regimens of subsequent treatments are presented in Table 64. For treat-to-progression drugs (e.g., ibrutinib and zanubrutinib), patients were assumed to be on treatment in 2L if they were alive and progression-free. For fixed-duration regimens (e.g., R-BAC), patients were assumed to be on treatment if they were alive and progression free, but were capped by the maximum treatment duration (6 x 28-day cycles). As a simplifying assumption, subsequent treatments were assumed to have a dosing intensity of 100%.

Table 64: Dosing regimens of subsequent treatments

Treatment	Component	Regimen	Administration route	Duration	Source
Ibrutinib	Ibrutinib	Daily 560 mg	Oral	Until disease progression	BNF 2025 ⁹¹ (Imbruvica 560mg tablets; pack size: 28)
Zanubrutinib	Zanubrutinib	Twice daily 160 mg	Oral	Until disease progression	BNF 2025 ⁹¹ (Brukinsa 80mg capsules; pack size 120; BeOne Medicines UK Ltd)
R-BAC	Rituximab	375 mg/m ² – Day 1 every 28 days	IV	6 x 28-day cycles	Rummel et al. 2016 ¹¹³
	Bendamustine	70 mg/m ² – Day 2, 3 every 28 days	IV	6 x 28-day cycles	
	Cytarabine	800 mg/m ² - Day 2, 3, 4 every 28 days	IV	6 x 28-day cycles	
BR	Rituximab	375 mg/m ² – Day 1 every 28 days	IV	6 x 28-day cycles	Rummel et al. 2016 ¹¹³
	Bendamustine	90 mg/m ² – Day 2, 3 every 28 days	IV	6 x 28-day cycles	

Abbreviations: BNF: British National Formulary; BR: bendamustine and rituximab; IV: intravenous; R-BAC: rituximab, bendamustine and cytarabine.

Subsequent treatment unit costs

The unit costs for ibrutinib (with and without PAS), zanubrutinib, and the components of R-BAC and BR are detailed in Table 65.

Table 65: Unit costs for each subsequent treatment

Treatment	Cost per pack (£)	PAS discount	Discounted cost per pack (£)	Tablet/capsule/vial size	Number of units per pack	Source
Ibrutinib	£5,723.20	■	■	560 mg	28	BNF 2025 ⁹¹ (Imbruvica 560mg tablets; pack size: 28)

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	£4,292.40	■■■■	■■■■■	420 mg	28	BNF 2025 ⁹¹ (Imbruvica 420mg tablets; pack size: 28)
	£2,861.60	■■■■	■■■■■	280 mg	28	BNF 2025 ⁹¹ (Imbruvica 280mg tablets; pack size: 28)
	£1,430.80	■■■■	■■■■■	140 mg	28	BNF 2025 ⁹¹ (Imbruvica 140mg tablets; pack size: 28)
Zanubrutinib	£4,928.65	NA	NA	80 mg	120	BNF 2025 ⁹¹ (Brukinsa 80mg capsules; pack size 120; BeOne Medicines UK Ltd)
Bendamustine	£44.85	NA	NA	25 mg	5	eMIT 2025 ⁹² (Bendamustine 25mg powder for solution for infusion vials / pack size 5)
Cytarabine	£49.59	NA	NA	500 mg	5	eMIT 2025 ⁹² (Cytarabine 500mg/5ml solution for injection vials / pack size 5)
Rituximab	£785.84	NA	NA	10 mg/mL	500 mL	BNF 2025 ⁹¹ (Ruxience 500mg/50ml concentrate for solution for infusion vials; Pfizer Ltd)
	£157.17	NA	NA	10 mg/mL	100 mL	BNF 2025 ⁹¹ (Ruxience 100mg/10ml concentrate for solution for infusion vials; Pfizer Ltd)

Abbreviations: BNF: British National Formulary; eMIT: electronic market information tool; PAS: patient access scheme.

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Administration costs of subsequent treatments

Administration costs for subsequent treatments were the same as those applied for first-line treatments (see Section 3.5.1, Table 59).

Summary of acquisition and administration costs for subsequent treatments

The total cost per cycle for each 2L and 3L treatment option is comprised of acquisition and administration costs. A summary of each subsequent treatment option is provided in Table 66.

Table 66: Total subsequent treatment costs

Treatment		Dose per administration	Acquisition cost (per administration)	Administration cost (per administration)	Administrations per cycle	Cost per cycle
Ibrutinib (with PAS discount)		560.0 mg	██████	£0.00	21	██████
Zanubrutinib		160.0 mg	£82.14	£0.00	42	£3,450.06
R-BAC	Rituximab	742.5 mg	£1,257.35	£256.03	Cycles 1–3 and 5–7: 1	£2,724.49
	Bendamustine	138.6 mg	£53.82	£256.03	Cycles 1–3 and 5–7: 2	
	Cytarabine	1,584.0 mg	£39.67	£256.03	Cycles 1–3 and 5–7: 2	
BR	Rituximab	742.5 mg	£1,257.35	£256.03	Cycles 1–3 and 5–7: 1	£2,168.96
	Bendamustine	178.2 mg	£71.76	£256.03	Cycles 1–3 and 5–7: 2	

Abbreviations: PAS: patient access scheme; R-BAC: rituximab, bendamustine and cytarabine.

3.5.3 Health-state unit costs and resource use

Resource use costs

Resource use costs (monitoring and follow-up) were estimated via the following approach: each category of resources was itemised and estimated by UK clinical experts, multiplied by a corresponding unit cost, and the results summed to produce a per cycle resource use estimate for the model.⁶ For the FF 1L health state, the resource use was determined for each treatment (the ibrutinib regimen and the ASCT treatment) separately, with the approach detailed below. For the PF 2L and PD health states, resource use was treatment independent. The model base-case presented includes resource use for first, second and third-line treatments.

FF 1L health state

The time patients spend in the FF 1L health state is split across induction, consolidation, maintenance, and either on or off-active frontline treatment. Annual resource utilisation was modelled to vary across the individual phases. Resource use for each of these individual phases was derived from the ESMO 2017 treatment guidelines for patients with MCL and validated through feedback received from UK clinical experts in March 2025.^{6, 95} These resource use frequencies are summarised in Table 67. The aggregated medical resource use costs were then

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calculated as a product of the unit cost for each resource, listed in Table 68. The aggregated resource use cost per cycle stratified by first-line treatment is summarised in Table 69.

As a simplifying assumption, medical resource use during the induction phase was not considered as it was assumed to be identical between treatment arms, as validated by feedback received from UK clinical experts.⁶ Similarly, as a simplifying assumption, patients off-active treatment were assumed to incur the same resource use, regardless of prior active treatment received.

As the consolidation phase is only relevant to the ASCT regimen, where patients are hospitalised during high-dose chemotherapy and ASCT, only resource use estimates for the ASCT-regimen are provided for this phase. Given inpatient cost associated with the consolidation phase for ASCT were accounted for as part of the administration costs detailed in Section 3.5.1, Table 58, to avoid double-counting inpatient resource use for the consolidation phase of the ASCT regimen were not reconsidered here. Outpatient haematologist visits at one month and three months post-ASCT as well as a CT or positron emission tomography (PET) scan at three months post-ASCT were however considered for patients in the consolidation phase receiving ASCT based on feedback from UK clinical experts.⁶

Finally, resource use associated with the maintenance phase in the FF 1L health state was treatment-dependent with resource use frequencies based on feedback received from UK clinical experts.⁶

Table 67: Per year frequency of medical resource use in FF 1L health state stratified by treatment

	On active treatment					Off active treatment	
Resource	Induction ^a	Consolidation		Maintenance		ASCT regimen	Ibrutinib regimen
		High-dose chemotherapy + ASCT	Ibrutinib regimen	ASCT regimen	Ibrutinib regimen		
Full-blood count	0.00	0.00	NA	6.00	6.00	0.00	0.00
Imaging	0.00	0.00	NA	0.00	0.00	0.00	0.00
Biopsy	0.00	0.00	NA	0.00	0.00	0.00	0.00
Haematologist visit	0.00	2.00	NA	0.00	0.00	4.00	4.00
CT scan	0.00	1.60	NA	0.00	0.00	1.00	1.00
PET scan	0.00	0.00	NA	0.00	0.00	0.06	0.06
Infection prophylaxis	0.00	0.00	NA	2.25	2.25	0.00	0.00
Duration	Cycle 1 to 6 for all treatments	Cycle 6 for arm A only	NA	Cycle 7 to Cycle 52	Cycle 6 to Cycle 52	Cycle 53 to failure	Cycle 53 to failure

^a Not considered as assumed to be identical between treatment arms.

Abbreviations: 1L: first-line; ASCT: autologous stem-cell transplantation; CT: computerised tomography; FF: failure-free; NA: not applicable; PET: positron emission tomography.

Source: J&J IM. Data on File. Advisory Board MCL (March 2025).⁶

Table 68: Summary of unit costs of medical resources

Resource	Unit Cost	Source
Full-blood count	£2.78	National Schedule of NHS Costs Year 2024/25 ¹¹⁰ - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: PATH05
Imaging	£45.30	National Schedule of NHS Costs Year 2024/25 ¹¹⁰ - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: PF
Biopsy	£1,676.68	National Schedule of NHS Costs Year 2024/25 ¹¹⁰ - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: WH54A-B (weighted average of daycare costs)
Haematologist visit	£323.87	National Schedule of NHS Costs Year 2024/25 ¹¹⁰ - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: WF01B (Non-Admitted Face-to-Face Attendance, First)
CT scan	£171.15	National Schedule of NHS Costs Year 2024/25 ¹¹⁰ - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: RD22Z (Service code: 812)
PET scan	£405.82	National Schedule of NHS Costs Year 2024/25 - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: RN07A (Service code: 812)
Infection prophylaxis	£45.00	PSSRU 2024 ⁹³ - Table 9.4.2; Unit costs for a GP - Per surgery consultation lasting 10 minutes

Abbreviations: CT: computerised tomography; GP: general practitioner; NHS: National Health Service; PET: positron emission tomography; PSSRU: Personal Social Services Research Unit.

Table 69: Summary of routine care costs per cycle in FF 1L stratified by treatment

	On active treatment				Off active treatment
	Consolidation, mean (SE)		Maintenance, mean (SE)		
	ASCT regimen	Ibrutinib regimen	ASCT regimen	Ibrutinib regimen	
Cost	£52.99 (5.30)	NA	£6.78 (0.68)	£6.78 (0.68)	£107.66 (10.77)

Abbreviations: 1L: first-line; ASCT: autologous stem cell transplant; FF: failure free; SE: standard error.

PF 2L and PD health state

For the PF 2L and PD health states, resource use was assumed to remain the same regardless of second- or third-line treatment received. Nevertheless, a similar approach to identifying resource use costs for each health state as that presented for FF 1L was undertaken. The

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frequency of each resource use was determined by UK clinical experts during a March 2025 advisory board,⁶ summarised in Table 70, and was then multiplied by the unit cost of each resource (previously described in Table 68), to generate a mean routine care cost for each health state, presented in Table 71.

Table 70: Per year and per cycle frequency of medical resource use in PF 2L and PD health state not stratified by treatment

Resource	Frequency in PF 2L		Frequency in PD	
	Per year	Per cycle	Per year	Per cycle
Full-blood count	0.00	0.00	0.00	0.00
Imaging	0.00	0.00	0.00	0.00
Biopsy	0.00	0.00	0.00	0.00
Haematologist visit	4.00	0.23	4.00	0.23
CT scan	1.00	0.06	1.00	0.06
PET scan	1.00	0.06	1.00	0.06
Infection prophylaxis	0.00	0.00	0.00	0.00

Abbreviations: 2: second-line; CT: computerised tomography; PD: progressed disease; PET: positron emission tomography; PF: progression-free.

Source: J&J IM. Data on File. Advisory Board MCL (March 2025).⁶

Table 71: Summary of routine care costs per cycle in PF 2L and PD not stratified by treatment

	PF 2L, mean (SE)	PD, mean (SE)
Cost	£107.66 (10.77)	£107.66 (10.77)

Abbreviations: 2L: second-line; PD: progressed disease; PF: progression-free; SE: standard error.

3.5.4 Adverse reaction unit costs and transplant complication cost

As noted in Section 3.3.7, to account for the resource use associated with the significant AEs observed in first-line treatment of MCL, Grade ≥ 3 AEs occurring in over 5% of patients in either treatment arm of TRIANGLE were included in the FF 1L health state of the model, with proportions presented in Section 3.3.7, Table 48. The associated unit costs for each AE included are presented in Table 72.

Table 72: Summary of AE unit costs

Adverse event	Unit cost	Source
Neutropenia	£734.61	NHS Reference Costs 2024/25. ¹¹⁰ SA35A-E - Agranulocytosis; Weighted average of non-elective short-stay

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Anaemia	£710.90	NHS Reference Costs 2024/25. ¹¹⁰ SA09G-J, L - Other red blood cell disorders; Weighted average of non-elective short-stay
Thrombocytopenia	£734.61	NHS Reference Costs 2024/25. ¹¹⁰ SA35A-E - Agranulocytosis; Weighted average of non-elective short-stay
Febrile neutropenia	£734.61	NHS Reference Costs 2024/25. ¹¹⁰ SA35A-E - Agranulocytosis; Weighted average of non-elective short-stay
Leukopenia	£602.04	NHS Reference Costs 2024/25. ¹¹⁰ SA08G, H, J - Other Haematological or Splenic Disorders; Weighted average of non-elective short-stay
Platelet count decreased	£750.35	NHS Reference Costs 2024/25. ¹¹⁰ SA12G, H, J, K - Thrombocytopenia; Weighted average of non-elective short-stay
Neutrophil count decreased	£734.61	NHS Reference Costs 2024/25. ¹¹⁰ SA35A-E - Agranulocytosis; Weighted average of non-elective short-stay
White blood cell count decreased	£602.04	Assumed to be the same as Leukopenia
Lymphocyte count decreased	£602.04	Assumed to be the same as Leukopenia
Pneumonia	£709.43	NHS Reference Costs 2024/25. ¹¹⁰ DZ11R-V - Lobar, Atypical or Viral Pneumonia (without interventions); Weighted average of non-elective short-stay
Stomatitis	£520.26	NHS Reference Costs 2024/25. ¹¹⁰ CB02A-F - Non-Malignant, Ear, Nose, Mouth, Throat, Head or Neck Disorders; Weighted average of non-elective short-stay
Nausea	£601.59	NHS Reference Costs 2024/25. ¹¹⁰ FD10A-H, J-M - Non-Malignant Gastrointestinal Tract Disorders; Weighted average of non-elective short-stay
Diarrhoea	£601.59	NHS Reference Costs 2024/25. ¹¹⁰ FD10A-H, J-M - Non-Malignant Gastrointestinal Tract Disorders; Weighted average of non-elective short-stay
Mucosal inflammation	£520.26	NHS Reference Costs 2024/25. ¹¹⁰ CB02A-F - Non-Malignant, Ear, Nose, Mouth, Throat, Head or Neck Disorders; Weighted average of non-elective short-stay
Hypokalaemia	£622.04	NHS Reference Costs 2024/25. ¹¹⁰ KC05G, J-N - Fluid or Electrolyte Disorders; Weighted average of non-elective short-stay

Abbreviations: AE: adverse events; NHS: National health Service.

Cost of ICU

In addition to AEs, the model accounts for a proportion of patients experiencing ICU events. As discussed in Section 1.3.3, due to the toxicity of the ASCT regimen and the fact that patients are immunocompromised for several weeks following the ASCT regimen, putting them at high risk of infections, some patients receiving the ASCT regimen require admission to the ICU.²⁶ It is reported in the literature that 1 in 20 (5%) patients undergoing the ASCT regimen require admission to the ICU.^{43, 44} As ICU stays are associated with substantial costs to the NHS,

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admissions to ICU (and their associated costs) were captured in the economic model. Specifically, in line with published literature, 5% of patients receiving the ASCT regimen in the FF 1L health state were modelled to require ICU admission.^{43, 44} Of note, this likely represents a conservative assumption given that feedback received from a UK clinical expert at the November 2025 advisory board indicated that, based on their clinical experience, 10% of patients require admission to ICU in UK clinical practice.⁴² As no ICU events were recorded in patients receiving the ibrutinib regimen at the latest CCO of the TRIANGLE trial, despite extensive follow-up (~4.5 years) no ICU events were modelled for this regimen.³⁰

In the model, the cost of an ICU event was incurred as a one-off cost of £2,405.64 per day. The percentage of patients anticipated to experience ICU events, the duration of an event and the total costs associated with ICU events associated with the ASCT arm of the model in the FF 1L health state are presented in Table 73.

Table 73: Cost of ICU associated with the ASCT regimen in FF 1L health state

	ASCT regimen	Source
Cost of ICU per day	£2,405.64	NHS Reference Costs 2024/25 ¹¹⁰ , XC01Z-07Z - Adult Critical Care, 0-6+ Organs Supported: weighted average - Per Day
Percentage of patients receiving ICU events	5.0%	Kerhuel et al. 2015 ⁴⁴
Duration, days	5	Borrega et al. 2023 ¹¹⁴
Total ICU costs associated with the ASCT regimen	£601.41	Calculation

Abbreviations: ASCT: autologous stem cell transplant; ICU; intensive care unit.

Total AE cost per treatment in FF 1L health state

An aggregated cost of AE management was subsequently applied to each treatment arm in the FF 1L health state. This aggregated cost, presented in Table 74, was based on a weighted average of the percentages of patients treated for AEs in the outpatient setting (see Section 3.3.7, Table 48) and the cost of treating each AE (see Table 72), and the cost of ICU events (see Table 73).

Table 74: Aggregated cost of AE management in FF 1L stratified by 1L treatment

	Ibrutinib regimen	ASCT regimen
Cost	£1,471.41	£2,486.62

Abbreviations: 1L: first-line; AE: adverse event; ASCT: autologous stem-cell transplantation; FF: failure-free.

3.5.5 Miscellaneous unit costs and resource use

Failure on first-line or progression on second-line treatment cost

In addition, given that feedback received from UK clinical experts indicated that when patients fail first-line and second-line treatment they require a full-blood count, imaging, and in some cases, a

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biopsy, in the base case analysis, patients were modelled to incur a one-time treatment failure cost when they failed on first-line treatment and when they progressed on second-line treatment. The total cost associated with failure on first-line or progression on second-line treatment was £886.42, with further details on the derivation of this cost presented in Table 75 below.

Table 75: Summary of disease progression costs

Resource	Unit cost	% of patients receiving ^a	Source (unit cost only)
Full-blood count	£2.78	100.0%	NHS Reference Costs 2024/25 - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: PATH05 ¹¹⁰
Imaging	£45.30	100.0%	NHS Reference Costs 2024/25 - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: PF ¹¹⁰
Biopsy	£1,676.68	50.0%	NHS Reference Costs Year 2025/45 - NHS trusts and NHS foundation trusts - Haematology: Directly accessed pathology services: WH54A-B ¹¹⁰

Footnotes: ^a Elicited from UK clinical experts during the March 2025 advisory board.⁶

Abbreviations: NHS: National Health Service; UK: United Kingdom.

Terminal care costs

A one-off cost representing the cost of terminal care was applied in the model for the proportion of patients that died in each cycle. The cost applied in the model (£13,409.00) was derived from Personal Social Services Research Unit (PSSRU) 2024 costs.⁹³

3.6 Severity

N/A – This technology is not expected to meet the criteria for a severity modifier for this appraisal.

3.7 Uncertainty

Extensive validation was sought from both UK clinical and health economic experts in order to validate model inputs and inform assumptions.^{6, 42} This ensures that the model closely reflects UK clinical practice, and thus reduces any uncertainty associated with the inputs and assumptions. Remaining parameter uncertainty in the model was assessed via probabilistic (PSA) and deterministic sensitivity analyses (DSA), the results of which are presented in Section 3.11.1 and Section 3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.11.3.

3.8 Managed access proposal

N/A - This submission does not contain a proposal for managed access – the ibrutinib and ASCT data informing this submission are based on [REDACTED], the Company is not aware of any plans from the European MCL network for future data cuts in the ITT analysis to be made available during or shortly after this submission. Importantly, consistent with the derivation of the FAS (see Section 2.4.1), no further data cuts will be available for the purpose of HTA.

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3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of inputs used in the base case analysis is presented in Table 76.

Table 76: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Modelled patient population		
Median starting age, years	57	Table 28, Section 3.2.1
Proportion of female patients, %	21.97%	
Mean body weight, kg	████	
Mean BSA, m²	████	
Model settings		
Discount rate (costs and benefits)	3.5%	Section 3.2.2
Time horizon	Lifetime (43 years)	
Cycle length	21 days	
Efficacy settings		
FF 1L to PF 2L – (failure on 1L treatment) data source	TRIANGLE	Section 3.3.1
FF 1L to PF 2L – (failure on 1L treatment) – ibrutinib regimen extrapolation	Exponential	
FF 1L to PF 2L – (failure on 1L treatment) – ASCT regimen extrapolation	Gamma	
FF 1L to Death (pre-failure mortality on 1L treatment) data source	TRIANGLE	Section 3.3.1
FF 1L to Death (pre-failure mortality on 1L treatment) – ibrutinib regimen AMR (per cycle [21-day] probability)	████ (capped by GPM) ^a	
FF 1L to Death (pre-failure mortality on 1L treatment) – ASCT regimen AMR (per cycle [21-day] probability)	████ (capped by GPM) ^a	
PF 2L to PD (progression on 2L treatment) data source	RAY-3001 (ibrutinib one prior line subgroup)	Section 3.3.4
PF 2L to PD (progression on 2L treatment) extrapolation (ibrutinib and ASCT regimens)	Log-Logistic	
PF 2L to PD subsequent treatment HR (ibrutinib regimen)	1.103	
PF 2L to PD subsequent treatment HR (ASCT regimen)	1.012	
PF 2L to Death (pre-progression mortality on 2L treatment) – data source	RAY-3001 (ibrutinib one prior line subgroup)	Section 3.3.3
PF 2L to Death (pre-progression mortality on 2L treatment) – AMR (per cycle [21-day] probability)	████ (capped by GPM) ^a	

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PD to Death (mortality on 3L treatment) – data source	RAY-3001 (ibrutinib one prior line subgroup)		Section 3.3.5
PD to Death (mortality on 3L treatment) - extrapolation	Exponential (capped by GPM) ^a		
Adverse events			
Adverse event	Ibrutinib regimen	ASCT regimen	Source
Neutropenia	39.2%	38.8%	Table 48, Section 3.3.7
Anaemia	21.5%	34.3%	
Thrombocytopenia	34.7%	42.5%	
Febrile neutropenia	14.0%	26.5%	
Leukopenia	9.4%	11.2%	
Platelet count decreased	29.4%	33.2%	
Neutrophil count decreased	24.2%	23.1%	
White blood cell count decreased	6.4%	13.4%	
Lymphocyte count decreased	4.5%	5.6%	
Pneumonia	5.3%	4.1%	
Stomatitis	1.5%	7.8%	
Nausea	4.2%	7.8%	
Diarrhoea	5.3%	6.0%	
Mucosal inflammation	1.9%	13.1%	
Hypokalaemia	6.4%	4.5%	
Adverse event disutilities			
Adverse event	Disutility	Duration (days)	Source
Neutropenia	-0.160	15	Table 50, Section 3.4.4
Anaemia	-0.090	23	
Thrombocytopenia	-0.110	23	
Febrile neutropenia	-0.160	15	
Leukopenia	-0.160	15	
Platelet count decreased	-0.110	23	
Neutrophil count decreased	-0.160	15	
White blood cell count decreased	-0.160	15	
Lymphocyte count decreased	-0.160	15	
Pneumonia	-0.195	18	
Stomatitis	-0.151	21	
Nausea	-0.061	11	
Diarrhoea	-0.103	21	
Mucosal inflammation	-0.151	21	
Hypokalaemia	-0.160	15	
Health state utilities			
FF 1L	[REDACTED]		Table 53, Section 3.4.5
PF 2L	0.780 (0.010)		

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PD	0.680 (0.024)		
Utility decrements due to treatment administration			
Utility decrement due to IV treatment	-0.04 (0.01)	Table 52, Section 3.4.5	
Utility decrement due to oral treatment	0.00 (0.00)		
Utility decrement due to SC treatment	0.00 (0.00)		
Cost settings			
Ibrutinib regimen – 1L treatment breakdown			
Treatment	Proportion receiving	Source	
R-CHOP	100%	Table 55, Section 3.5.1	
R-DHAP	15%		
R-DHAOx	85%		
Ibrutinib induction	100%		
Ibrutinib maintenance	█%		
Rituximab maintenance	█%		
ASCT regimen – 1L treatment breakdown			
Treatment	Proportion receiving	Source	
R-CHOP	20%	Table 55, Section 3.5.1	
R-DHAP	3% ^b		
R-DHAOx	17% ^b		
NORDIC	80%		
Stem cell apheresis	87%		
High dose chemotherapy	87%		
BEAM	87%		
THAM	87%		
ASCT	87%		
Rituximab maintenance	█		
Treatment administration and procedural costs			
R-DHAP inpatient admission cost	£2,002.44	Section 3.5.1	
High dose chemotherapy inpatient admission cost	£2,150.32		
Stem-cell apheresis	£6,386.86		
ASCT	£42,040.84		
IV treatment administration cost	£256.03		
Subsequent treatment breakdown – 2L			
	Ibrutinib regimen	ASCT regimen	Source
Ibrutinib	-	10.0%	Section 3.5.2
Zanubrutinib	57.6%	84.8%	
R-BAC	31.3%	2.4%	
BR	10.0%	2.0%	
BSC	1.1%	0.8%	
Subsequent treatment breakdown – 3L			
	Ibrutinib regimen	ASCT regimen	Source

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R-BAC	41.9%	67.4%	Section 3.5.2
BR	33.3%	16.2%	
BSC	24.8%	16.4%	
Unit costs			
Ibrutinib 560 mg			Section 3.5.1
Bendamustine 25 mg	£44.85		
Doxorubicin 160 mg	£19.56		
Vincristine 2 mg	£10.61		
Prednisone 50 mg	£0.31		
Dexamethasone 3.3 mg	£3.25		
Cytarabine 500 mg	£49.59		
Cisplatin 50 mg	£16.76		
Pegfilgrastim 6 mg	£411.83		
Rituximab 10 mg/mL; 50 mL	£785.84		
Cyclophosphamide 2,000 mg	£25.32		
Zanubrutinib 80 mg	£4,928.65		
Carmustine 100 mg	£325.54		
Etoposide 100 mg	£7.22		
Melphalan 50 mg	£20.22		
Routine care costs			
FF 1L	Ibrutinib regimen	ASCT regimen	Source
On active treatment (consolidation; mean [SE])	NA	£52.99 (5.30)	Section 3.5.3
On active treatment (maintenance; mean [SE])	£6.78 (0.68)	£6.78 (0.68)	
Off active treatment	£107.66 (10.77)		
PF 2L; mean (SE)	£107.66 (10.77)		
PD; mean (SE)	£107.66 (10.77)		
Adverse event costs			
Neutropenia	£734.61		Table 72, Section 3.5.4
Anaemia	£710.90		
Thrombocytopenia	£734.61		
Febrile neutropenia	£734.61		
Leukopenia	£602.04		
Platelet count decreased	£750.35		
Neutrophil count decreased	£734.61		
White blood cell count decreased	£602.04		
Lymphocyte count decreased	£602.04		
Pneumonia	£709.43		
Stomatitis	£520.26		
Nausea	£601.59		
Diarrhoea	£601.59		

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Mucosal inflammation	£520.26	
Hypokalaemia	£622.04	
Cost of ICU	£2,405.64	Table 73, Section 3.5.4
Miscellaneous unit costs		
Disease progression costs	Unit cost	Proportion receiving
Full-blood count	£2.78	100.0%
Imaging	£45.30	100.0%
Biopsy	£1,676.68	50.0%
<i>Total</i>	£886.42	
Terminal care costs	£13,409.00	Section 3.5.5

Footnotes: ^aPer-cycle probabilities of death were capped by a lower limit based on GPM, to ensure that modelled mortality would not fall below general population norms. ^b20% of patients receiving the ASCT regimen received R-CHOP alternating with R-DHAP or R-DHAox. Of these, 15% received R-DHAP and 85% received R-DHAox, in line with proportions reported in Section 3.5.1.

Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; AMR: annual mortality rate; ASCT: autologous stem-cell transplant; BEAM: carmustine, cytarabine, etoposide and melphalan; BR: bendamustine and rituximab; BSA: body surface area; BSC: best supportive care; FF: failure-free; GPM: general population mortality; HR: hazard ratio; IV: intravenous; PD: progressed disease; PF: progression-free; R-BAC: rituximab, bendamustine and cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAox: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin; SC: subcutaneous; THAM: total body irradiation, cytarabine and melphalan.

3.9.2 Assumptions

A summary of the key assumptions utilised in the base case economic analysis are presented in Table 77.

Table 77: Summary of assumptions in the economic analysis

Parameter	Assumption	Justification
Efficacy assumptions		
FF 1L to Death	AMR derived from pre-failure mortality data from TRIANGLE (modelled separately for the ibrutinib regimen and the ASCT regimen from Arm I and Arm A, respectively)	The number of pre-failure mortality events as of the latest data cut of TRIANGLE (CCO: 09 May 2024) were limited across both arms (11/268 [4.1%] patients for the ibrutinib regimen and 22/269 [8.2%] patients for the ASCT regimen, respectively). ⁶³ As such, standard parametric extrapolation was not used to extrapolate time to pre-failure mortality from TRIANGLE in the model as any resulting extrapolations would be associated with substantial uncertainty. Instead, a pre-failure AMR was derived for each arm to model a constant per cycle probability of death for each regimen. The pre-failure AMR was capped by a lower limit based on GPM, to ensure that modelled mortality did not fall below that of the UK general population. This approach was deemed appropriate by feedback received from UK clinical and health economic experts consulted as part of the November 2025 advisory board. ⁴²
FF 1L to PF 2L	Standard parametric functions were fitted to observed TTF from TRIANGLE (modelled separately for the ibrutinib regimen and the ASCT regimen from Arm I and Arm A, respectively) In the base case analysis, the ibrutinib regimen was modelled by via independent extrapolation of Arm I via the exponential whilst the ASCT regimen was modelled via independent extrapolation of Arm A via the gamma extrapolation.	Transitions from the FF 1L health state in patients receiving the ibrutinib or ASCT regimen to the PF 2L health state were modelled using TTF data from Arm A and Arm I of TRIANGLE, respectively.³⁰ However, as the median time on study for TRIANGLE (54.9 months) was shorter than the model time horizon (43 years), Kaplan-Meier data were extrapolated via a parametric function to inform transitions in subsequent years. PH tests indicated that the PH assumption was violated and therefore parametric curves were individually fitted to TTF data for the ibrutinib regimen and the ASCT regimen, respectively. As the majority of curves provided reasonable statistical and visual fit to the observed TTF Kaplan-Meier data from TRIANGLE, the clinical plausibility of the long-term TTF predictions for each regimen was considered the primary consideration to select the appropriate base case curve choices for each regimen. Thus, the exponential extrapolation was selected as the base case

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		curve to model the ibrutinib regimen FF 1L to PF 2L transition and the gamma extrapolation was selected for the ASCT regimen.
PF 2L to Death	AMR derived from pre-progression mortality data from RAY-3001 (one prior line of therapy subgroup; ibrutinib arm)	RAY-3001, which was the principal evidence source for the clinical effectiveness of ibrutinib in the NICE appraisal of ibrutinib in the 2L MCL setting,¹¹ represents a source of more mature PFS and post-progression data than TRIANGLE, and thus given the flexibility of the Markov model structure to incorporate external data to inform transitions, data from RAY-3001 were leveraged to inform transitions beyond the first-line setting. Transitions from the PF 2L to the Death state were informed by pre-progression mortality data from the ibrutinib arm of RAY-3001 (one prior line subgroup). Specifically, an AMR-based approach was utilised and applied to all patients receiving second-line treatment (regardless of first-line treatment) to model a constant per cycle probability of death from the PF 2L health state. The pre-progression AMR was capped by a lower limited based on GPM to ensure that modelled mortality did not fall below that of the UK general population. This approach was considered appropriate by feedback received from UK clinical and health economic experts consulted as part of the November 2025 advisory board.⁴²
PF 2L to PD	Standard parametric functions were fitted to the TTP KM curve from RAY-3001, to act as a reference curve to inform TTP in the economic model. In the base case analysis, the log-logistic curve was used. Differential weighted HRs were then applied to this curve to derive the final modelled TTP curves for patients receiving the ibrutinib and ASCT regimen in the model, respectively. These weighted HRs were based on the subsequent treatment distributions provided in Section 3.5.2, and data/assumptions around the relative efficacy between subsequent treatment provided in Section 3.3.4.	Transitions from the PF 2L to the PD health state for patients receiving second-line treatment with ibrutinib (regardless of first-line treatment) were derived from TTP data from the ibrutinib arm of the one prior line subgroup of RAY-3001, given the limitations associated with subsequent treatment efficacy data in TRIANGLE (see Section 2.7). As detailed above, RAY-3001 provides more mature PFS and post-progression data to inform transitions on later treatment lines (i.e., transitions from the 2L and PD states), and was therefore deemed by UK clinical experts to be a more appropriate source to inform these transitions than TRIANGLE.⁴² The clinical plausibility of the available extrapolations (specifically the reconstructed OS curves) was considered the primary consideration in selecting the base case extrapolation for TTP for patients who received ibrutinib at second line (the 'reference' curve). Based on clinical plausibility of the reconstructed OS curve, the log-logistic curve was selected to model the transition from PF 2L to PD in the base case economic analysis.

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		Of note, the model accounted for differential second line efficacy depending on the subsequent treatment regimens received. As detailed in the 'Subsequent treatment efficacy' assumption below, a weighted average HR was applied to the 'reference' TTP curve (reflecting patients receiving ibrutinib at second line) to derive adjusted TTP curves for both the ibrutinib and ASCT model arms, based on the subsequent treatment distributions modelled for each group (see Section 3.5.2).
PD to Death	Standard parametric functions were fitted to observed PPS from RAY-3001 (one prior line of therapy subgroup; ibrutinib arm) to inform the reference curve. In the base case analysis the data were extrapolated via the exponential function.	Transitions from PD to Death were modelled using PPS data from the ibrutinib arm of RAY-3001 (one prior line subgroup) given the limitations associated with subsequent treatment efficacy data in TRIANGLE (see Section 2.7). Kaplan-Meier data were extrapolated via a parametric function to inform transitions over the modelled time horizon (43 years).^{85, 99} The PPS extrapolations were capped by GPM to ensure that survival did not exceed that of the UK general population. Based on statistical fit, visual fit and clinical plausibility, the exponential was selected as the base case curve to model PPS, given it was one of the two best statistically fitting curves (alongside the Gompertz), and the Gompertz provided clearly clinically implausible long-term PPS estimates.
Subsequent treatment efficacy	Differential subsequent treatment efficacy in the PF 2L to PD transition was captured via a HR-based approach. A weighted average HR was applied to the chosen reference curve to derive adjusted TTP curves for both the ibrutinib and ASCT regimens, based on the subsequent treatment distributions modelled for each group. The HR informing the relative efficacy of R-BAC versus a BTKi was informed by the MANTLE-FIRST study. ¹⁰⁰	As the risk of progressing on 2L treatment is influenced by the treatment received at 2L, as validated by feedback received from UK clinical experts, to improve accuracy, the model accounted for differential 2L efficacy depending on the subsequent treatment regimens received.⁴² As a simplifying assumption, the two BTKis (ibrutinib and zanubrutinib) were assumed to be associated with equal efficacy; this assumption was validated as appropriate by feedback received from five UK clinical experts at a November 2025 advisory board.⁴² Furthermore, feedback received from UK clinical experts at the same November 2025 advisory board indicated that the PFS HR of 1.26 from the MANTLE-FIRST study, represented the most appropriate HR to determine the relative efficacy of a BTKi versus R-BAC in this setting given that it is the only direct study comparing BTKis versus R-BAC in a relevant setting that they were aware of.^{42, 100} Justification for the modelled subsequent treatment distributions which were subsequently used to derive the weighted average HR for each arm is provided below.

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Subsequent treatment distributions	The distribution of subsequent treatments that patients received following failure on 1L treatment was informed by feedback received from UK clinical experts during the November 2025 advisory board as summarised in Table 62; Section 3.5.2. ⁴²	Given the lack of routine collection of subsequent treatment data in the investigator-initiated TRIANGLE trial, the proportion of patients receiving subsequent treatment were informed by feedback from five UK clinical experts consulted during a November 25 advisory board. ⁴² These estimates are anticipated to be most reflective of UK clinical practice and therefore, the most appropriate for UK decision making. ⁴²
Cost assumptions		
Resource use during the induction phase	Medical resource use associated with first-line treatment during the induction phase was not included in the economic model.	Given that patients receiving the ibrutinib and ASCT regimens receive the same treatments during the induction phase, feedback from UK clinical experts indicated that resource use is identical between first-line treatments in this phase. ⁶ As such, as a simplifying assumption, it was assumed that resource use is identical between treatment arms at this stage. This approach was considered appropriate by UK clinical experts. ⁶
Utility assumptions		
Treatment independent application of utility values	HSUVs are assumed to be treatment independent.	In the absence of utility data in patients with untreated MCL receiving the ASCT regimen, utility values in the FF 1L health state were applied in a treatment independent manner informed by the SHINE trial. This assumption ignores the impact of toxic high-dose chemotherapy as well as the impact on HRQoL of hospitalisation (median 30 days) and potential isolation following ASCT experienced by patients in Arm A during this treatment phase. ^{43, 55} Therefore, use of treatment independent HSUVs in this health state likely represents a conservative assumption given the increased toxicity of the ASCT regimen vs. the ibrutinib regimen (see Section 3.13). The potential disutility associated with the ASCT regimen is explored in a scenario analysis (see Section 3.11.3).
Utility decrement	It is assumed that there is no utility decrement associated with oral or SC treatments.	This is a simplifying assumption, considered appropriate given any utility decrement associated with these methods of administration would be minimal. This is a standard simplifying assumption used and accepted in many prior economic analyses submitted to NICE.
	A utility decrement of 0.04 associated with IV administration was assumed for treatments requiring IV administration	This assumption is in line with the approach taken in TA343. ⁸⁸

Abbreviations: 1/2L: first-/second-line; ASCT: autologous stem cell transplantation; FF: failure-free; GPM: general population mortality; HR: hazard ratio; HRQoL: health-related quality of life; HSUV: health-state utility value; IV: intravenous; MCL: mantle cell lymphoma; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PF: progression-free; PH: proportional hazard; SC: subcutaneous; UK: United Kingdom.

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3.10 Base-case results

3.10.1 Base-case incremental cost-effectiveness analysis results

The base case probabilistic and deterministic cost-effectiveness results for the ibrutinib regimen (with PAS) vs. the ASCT regimen are presented in Table 78 and Table 80, respectively, with results at the ibrutinib list price presented in Table 79 and Table 81. To note, following the upcoming change to the willingness-to-pay (WTP) threshold, INHB results will be updated accordingly. Details of the probabilistic analysis are presented in Section 3.11.1.

With the PAS price, the ibrutinib regimen was found to be a cost-effective use of NHS resources when compared with the ASCT regimen at a willingness-to-pay (WTP) threshold of £30,000/QALY in both the deterministic and probabilistic analyses. In all base case analyses, the ibrutinib regimen was associated with positive incremental LYGs (ranging from 1.35–1.37 LYG) and QALYs (ranging from [REDACTED]–[REDACTED]) vs. the ASCT regimen. These results highlight the improvements in both quality and length of life that the ibrutinib regimen may offer to patients in this setting. The ibrutinib regimen was also associated with reduced costs compared to the ASCT regimen, with cost-savings ranging from [REDACTED] to [REDACTED]. This means that the ibrutinib regimen was found to be dominant versus the ASCT regimen in the base case analyses.

A summary of the disaggregated cost outcomes in the model (with ibrutinib PAS) is provided in Table 82, and a summary of the disaggregated QALY outcomes is provided in Table 83.

Table 78: Probabilistic base-case results (ibrutinib PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	████████	12.13	████	-	-	-	-	-
ASCT regimen	£207,013.07	10.75	████	████████	1.37	████	Dominant	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 79: Probabilistic base-case results (ibrutinib list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	£248,330.75	12.13	████	-	-	-	-	-
ASCT regimen	£212,220.87	10.75	████	£36,109.87	1.37	████	████	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 80: Deterministic base-case results (ibrutinib PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	████████	12.11	████	-	-	-	-	-
ASCT regimen	£205,721.59	10.77	████	████████	1.35	████	Dominant	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 81: Deterministic base-case results (ibrutinib list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000

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Ibrutinib regimen	£247,376.14	12.11	■	-	-	-	-	-
ASCT regimen	£210,866.98	10.77	■	£36,509.16	1.35	■	■	■

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 82: Disaggregated costs for the ibrutinib and ASCT regimens (ibrutinib PAS price)

Health state	Costs (Ibrutinib Regimen)	Costs (ASCT Regimen)	Increment	Absolute increment	% absolute increment
FF 1L	■	£82,912.61	■	■	■
PF 2L	■	£107,620.86	■	■	■
PD	■	£4,083.52	■	■	■
Death	■	£8,617.98	■	■	■
AE Management	■	£2,486.62	■	■	■
Total	■	£205,721.59	■	■	■

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; FF: failure-free; PAS: patient access scheme; PD: progressed disease; PF: progression-free.

Table 83: Disaggregated QALYs for the ibrutinib and ASCT regimens (ibrutinib PAS price)

Health state	QALYs (Ibrutinib Regimen)	QALYs (ASCT Regimen)	Increment	Absolute increment	% absolute increment
FF 1L	■	■	■	■	■
PF 2L	■	■	■	■	■
PD	■	■	■	■	■
Administration Disutility	■	■	■	■	■
AE Disutility	■	■	■	■	■
Total	■	■	■	■	■

Abbreviations: AE: adverse event; ASCT: autologous stem cell transplant; FF: failure-free; PAS: patient access scheme; PD: progressed disease; PF: progression-free; QALY: quality adjusted life year.

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3.11 *Exploring uncertainty*

Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections 3.11.1 and 3.11.2, respectively. In addition, key assumptions in the model were explored in several probabilistic scenario analyses, the results of which are presented in Section 3.11.3. Overall, it is considered that all relevant uncertainties included in the analyses have been adequately accounted for, and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

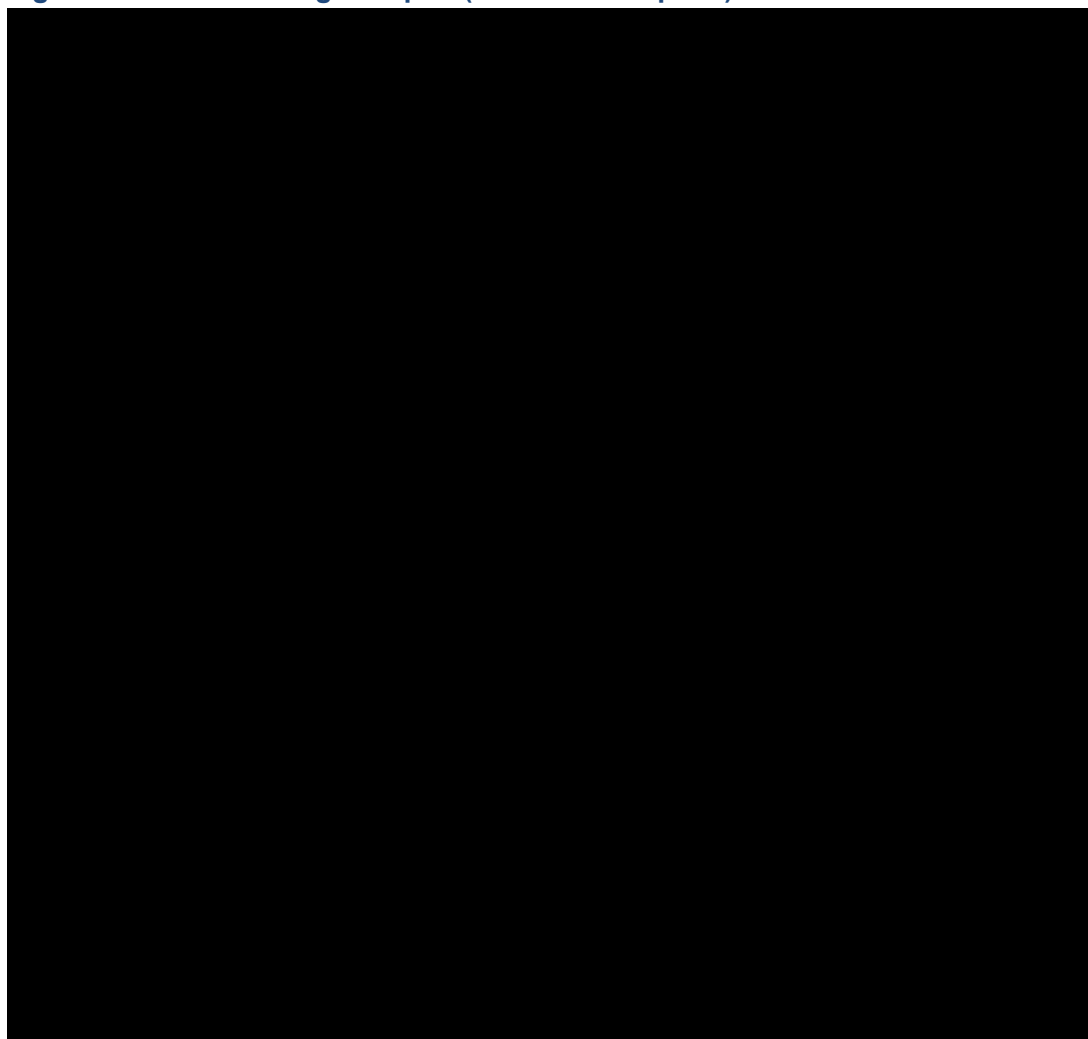
3.11.1 *Probabilistic sensitivity analysis*

A PSA was conducted in order to assess the simultaneous effect of uncertainty in the different model parameters and to demonstrate whether the model results are robust to those variations. The PSA was run with 500 iterations, with estimates of model parameters based on the uncertainty in the source data (where data availability permitted). The modelled time horizon, discount rates, unit costs for treatments and healthcare resource use and other structural choices related to data sources and assumptions on patient pathways were excluded from the PSA since they were not subject to parameter uncertainty.

Beta distributions were assumed for uncertain parameters bound by zero and one, including utilities, proportions, and probabilities. Log-normal distributions were assumed for hazard ratios. Gamma distributions were assumed for costs. Normal distributions were assumed for other uncertain parameters including resource use frequencies, with capping in place to ensure positivity for parameters which must be non-negative.

The ICER convergence plot is provided in Figure 25 and demonstrates that the ICER stabilised after approximately 300 iterations. As such the number of iterations run in the PSA are suitable for decision-making.

Figure 25: ICER convergence plot (ibrutinib PAS price)



Abbreviations: INHB: incremental net health benefit; PAS: patient access scheme.

The probabilistic cost-effectiveness planes for the ibrutinib regimen vs. the ASCT regimen are presented in Figure 26. The results indicate that the ibrutinib regimen increased QALYs in all iterations of the PSA, with the majority of iterations indicating that the ibrutinib regimen also reduced in cost savings compared to the ASCT regimen.

The cost-effectiveness acceptability curve is presented in Figure 27; the PSA found the probability of the ibrutinib regimen being a cost-effective use of NHS resources to be [REDACTED] and [REDACTED] at a WTP threshold of £20,000 and £30,000 per QALY gained, respectively.

Figure 26: Probabilistic cost-effectiveness plane for ibrutinib regimen vs. ASCT regimen (ibrutinib PAS price)



Abbreviations: ASCT: autologous stem cell transplant; PAS: patient access scheme; QALY: quality-adjusted life year.

Figure 27: Cost-effectiveness acceptability curve for ibrutinib regimen vs. ASCT regimen (ibrutinib PAS price)



Abbreviations: ASCT: autologous stem cell transplant; PAS: patient access scheme.

3.11.2 *Deterministic sensitivity analysis*

In order to assess the robustness of the base case cost-effectiveness results, a DSA was conducted by varying the input for each parameter in the model, whilst keeping all other inputs the same. Where possible, CIs or published ranges were used as alternative values. In the absence of CIs or published ranges, parameters were varied by 10% to estimate upper and lower bound inputs.

A tornado diagram showing the top 10 most influential parameters on the incremental net health benefit (INHB) for the ibrutinib regimen vs. the ASCT regimen is presented in Figure 28. None of the inputs were found to significantly impact the INHB when varied to their limits, with no changes to the overarching base case cost-effectiveness conclusions observed. The model was found to be most sensitive to the following parameters:

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- **The weighted average HR applied to derive second-line disease progression transition probability for the ibrutinib regimen:** In the base case, a weighted average HR of 1.103 was applied to the reference curve to derive the probability of second-line disease progression for the ibrutinib regimen, based on the subsequent treatment distribution (see Section 3.3.4). Varying this HR to its extreme bounds of uncertainty results in small changes to the INHB – however, a more realistic alternative scenario has been conducted in Section 3.11.3, which demonstrates that assuming equal efficacy between all subsequent treatments used in the second-line setting has a minimal impact on the ICER.
- **Relative dose intensity of ibrutinib in the maintenance phase:** The base case estimate of ibrutinib RDI of 95.2% was robustly derived using the mean RDI from TRIANGLE, which represents the best available source of evidence.³⁰
- **The AMR for the ASCT regimen in the 1L FF health state:** The AMR for patients in the 1L FF health state was derived from pre-failure mortality data from TRIANGLE, which represents the most robust evidence to inform this transition probability. This annual mortality is also capped by GPM, ensuring clinical plausibility of the modelled transition probability relative to the UK general population over the lifetime horizon of the model.

Figure 28: DSA tornado diagram for ibrutinib regimen vs. ASCT regimen; INHB (ibrutinib PAS price)



Abbreviations: AE: adverse event; AMR: annual mortality rate; ASCT: autologous stem cell transplant; FF: failure free; HR: hazard ratio; INHB: incremental net health benefit; IV: intravenous; PAS: patient access scheme; PD: progressed disease; PF: progression free.

3.11.3 Scenario analysis

Scenario analyses were conducted to explore the impact of structural assumptions and alternative inputs on the results of the cost-effectiveness model. A complete list of the scenario analyses explored along with the rationale for their selection is provided Table 84. Results of the scenario analysis are presented in Table 85.

Notably, none of the scenario analyses changed the cost-effectiveness conclusions of the base case analysis; the ibrutinib regimen remained cost-effective vs. the ASCT regimen in all analyses and the changes in ICER were minor, demonstrating that the base case results are associated with minimal uncertainty. The ibrutinib regimen remained dominant versus ASCT in most scenarios, and was associated with an ICER of <£10,000 across the remaining analyses - demonstrating that the results of the base case analysis are robust to uncertainty, and that the ibrutinib regimen remains a cost-effective use of NHS resources in this indication.

Table 84: Summary of scenario analyses

#	Scenario	Description of scenario	Rationale
1	1L TTF ibrutinib extrapolation: log-logistic	Extrapolation for ibrutinib 1L TTF changed from exponential to log-logistic.	As noted in Section 3.3.2, given the relative immaturity of TRIANGLE TTF data, clinical plausibility of the reconstructed FFS extrapolations was the primary consideration in selecting the most appropriate base case TTF extrapolation for the ibrutinib regimen. The log-logistic curve was the second most clinically plausible extrapolation for the ibrutinib regimen.
2	1L TTF ASCT extrapolation: Weibull	Extrapolation for ASCT 1L TTF changed from Gamma to Weibull	As noted in Section 3.3.2, given the relative immaturity of TRIANGLE TTF data, clinical plausibility of the reconstructed FFS extrapolations was the primary consideration in selecting the most appropriate base case TTF extrapolation for the ASCT regimen. The Weibull extrapolation was the second most clinically plausible extrapolation for the ASCT regimen.
3	1L TTF: both extrapolations	Extrapolation for ibrutinib 1L TTF changed from exponential to log-logistic. Extrapolation for ASCT 1L TTF changed from Gamma to Weibull	To investigate the cumulative impact of changing the choice of survival extrapolation in both treatment arms, a scenario analysis was conducted in which the survival extrapolations from Scenario 1 and Scenario 2 were applied to the ibrutinib regimen and the ASCT regimen, respectively at the same time.
4	2L TTP extrapolation: Exponential	Extrapolation for 2L TTP changed from log-logistic to exponential	The exponential extrapolation was less clinically plausible than the log-logistic extrapolation used in the base case analysis but represented the best statistically fitting extrapolation. Given the relative maturity of the TTP data from RAY-3001, statistical fit was also an important factor in curve selection for TTP.
5	3L PPS extrapolation: Weibull	Extrapolation for 3L PPS changed from exponential to Weibull	The Weibull extrapolation was the second best statistically fitting curve and predicted clinically plausible estimates. Given the relative maturity of the PPS data from RAY-3001, statistical fit was a key factor in curve selection for PPS.
6	HSUVs: RAY-3001 for 2L and 3L	HSUVs for PF 2L and PD changed to be informed by RAY-3001 alone as opposed to pooled RAY-3001/SPARK data. As a result, HSUVs for the PF 2L and PD health states are assumed to be equal	Alternative source of utility data to inform the PF 2L and PD health states which was aligned to the source informing efficacy evidence in these health states.
7	ASCT disutility scenario	All patients who receive ASCT are assumed to incur a long-term utility decrement of -0.04 for the remainder of the modelled time horizon.	ASCT is a highly toxic treatment option, which results in widespread and significantly life-altering impacts on patients and their caregivers. As previously detailed in Section 1.3.5, patients face a substantial physical and psychological burden during the receipt of the treatment regime, followed by potentially long-lasting impacts that can persist for years after receipt of treatment.

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#	Scenario	Description of scenario	Rationale
			However, in the base case economic analysis, no disutility is applied specifically for patients receiving ASCT, due to data paucity. This is likely to be a highly conservative assumption. As a scenario analysis, a disutility value of -0.04 is applied to all patients who receive ASCT for the remainder of the modelled time horizon. In the absence of data for MCL specifically, this disutility was derived from Brandt <i>et al.</i> (2010), which reported an average disutility of -0.04 for a population of patients with Hodgkin's lymphoma who received a peripheral blood stem cell transplant over a median follow-up of 11 years.
8	Exclusion of weighted 2L HRs	All subsequent treatments at 2L are assumed to have equal efficacy.	To assess the impact of modelling differential treatment efficacy for 2L treatments (Section 3.3.4), a scenario analysis assuming no difference in efficacy between these treatments was explored.
9	Time horizon of 20 years	Model time horizon changed from lifetime (43 years) to 20 years	Whilst a lifetime horizon is aligned with the NICE reference case, a scenario was explored over a shorter time horizon of 20 years.

Abbreviations: 1L/2L/3L: first-/second-/third-line; ASCT: autologous stem cell transplantation; HSUV: health state utility value; MCL: mantle cell lymphoma; PFS: progression-free survival; PPS: post-progression survival; TTF: time-to-treatment failure; TTP: time to progression.

Table 85: Summary of scenario analysis results – probabilistic (with ibrutinib PAS)

Scenario		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case		██████	██	Dominant	██	
1	1L TTF ibrutinib extrapolation: log-logistic	██████	██	Dominant	██	██
2	1L TTF ASCT extrapolation: Weibull	██████	██	Dominant	██	██
3	1L TTF: both extrapolations	██████	██	Dominant	██	██
4	2L TTP extrapolation: exponential	██████	██	£8,007	██	██
5	3L PPS extrapolation: Weibull	██████	██	Dominant	██	I
6	HSUVs: RAY-3001 for 2L PF and PD	██████	██	Dominant	██	I
7	ASCT disutility scenario	██████	██	Dominant	██	██
8	Exclusion of weighted 2L HRs	██████	██	Dominant	██	██
9	Time horizon of 20 years	██████	██	£1,759	██	██

Abbreviations: 1L/2L/3L: first-/second-/third-line; ASCT: autologous stem cell transplant; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; PFS: progression-free survival; PPS: post-progression survival; QALY: quality-adjusted life year; TTF: time-to-treatment failure; TTP: time to progression.

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3.12 Subgroup analysis

N/A – As noted in Section 1.1, no subgroup analyses are relevant for this appraisal and as such no subgroup analyses were included in the cost-effectiveness analysis.

3.13 Benefits not captured in the QALY calculation

Value of a more effective, more tolerable treatment option to patients

As detailed in Section 1.3.5, the ASCT regimen imposes a substantial burden beyond its toxicity profile. Patients routinely require up to a month in hospital during treatment, with engraftment taking 2–3 weeks and undergoing immunosuppression that raises the risk of infection.²⁶ The recovery process can extend for several months, with intensive monitoring, weekly follow-ups, and transfusions.²⁶ During this period, it is common for patients to see an increase in symptoms, such as fatigue and nearly half of patients (47%) experience treatment-related pain. Patients consulted as part of a patient research study conducted by the Company between July and October 2025 described the conditioning chemotherapy phase of the process as intense and overwhelming.²⁷ The impact of the resulting side effects from high-dose immunochemotherapy treatment were also described as being much worse than anticipated (see Section 1.3.5).²⁷

It can take patients up to six months to recover and return to normal day to day life (such as work).^{26, 55} This lengthy recovery results in a significant and long-lasting HRQoL impairment, as patients must physically and psychologically recover from their treatment. A lymphoma patient described the experience as the “lowest point of [their] life”, noting that it took them “two to five months to feel [they] were recovering”.¹¹⁵ This statement clearly demonstrate the significant additional burden existing first-line treatment in the UK has on patients’ lives, over and above the clinical burden of the disease. Despite this pronounced impact, there is no additional utility decrement applied in the FF 1L health state in patients receiving ASCT in the base case analysis.

Furthermore, given the HSUVs within the model are applied in a treatment independent manner, and not based on HRQoL data from TRIANGLE, the disutility resulting from ASCT is not formally captured within the model beyond the disutility associated with specific AEs. However, patient experience captured in a patient research study conducted by the Company between July and October 2025 describe mood changes, depression, severe fatigue, anxiety and feelings of isolation all stemming from treatment with the ASCT regimen (see Section 1.3.5).²⁷ The availability of ibrutinib would help ease this excessive burden as it is an orally administered treatment option with a more manageable tolerability profile. The ibrutinib regimen therefore enables patients to avoid the significant acute-toxicity burden associated with the ASCT regimen. Additionally, it would enable patients to avoid the long hospital stays required for ASCT, reducing disruption to their daily lives. The ability of ibrutinib to relieve this burden therefore represents a key benefit associated with the ibrutinib regimen that is not captured in the QALY in the base case analysis. The potential impact of this was explored in a scenario analysis, in which an additional utility decrement (to the existing AE decrement) was modelled for the ASCT regimen. The result of this scenario analysis is provided in Section 3.11.3 and resulted in additional incremental QALYs associated with the ibrutinib regimen compared to the ASCT regimen, thereby demonstrating that the base case analysis is conservative.

Value of a more effective, more tolerable treatment option to caregivers

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Additionally, the ASCT regimen has a significant impact on caregivers and/or relatives of patients receiving ASCT due to the care burden associated with the frequent hospital visits as well as the increased anxiety of a loved one undergoing a highly toxic treatment which is associated with increased mortality risk (as supported by the sharp initial drop in OS KM curves in Arm A compared with Arm I at 6 months, correlating to receipt of treatment with high-dose chemotherapy followed by ASCT in Arm A at that timepoint; See Section 2.6.4).³⁰ Caregivers interviewed in the patient research study conducted by the Company reported that caring for a loved one undergoing treatment with the ASCT regimen was associated with an increased emotional, logistical and financial burden (see Section 1.3.5).²⁷ The impact of improved HRQoL outcomes for caregivers and/or relatives of patients receiving the ibrutinib regimen is not considered within the economic analysis but is likely substantial.

Value to the NHS of a treatment option which does not require lengthy inpatient stays

Finally, the prolonged inpatient and post-discharge care associated with the ASCT regimen consumes NHS resources, particularly bed capacity, and contributes to a substantial and long-term burden on healthcare resource availability, not only in MCL but across all therapy areas that require inpatient admission.⁵⁷ As noted in Section 1.3.6, ≥ 23 hospitalisation days can be eliminated by omitting HDT-ASCT from the treatment pathway. As such, the resource use capacity savings associated with the ibrutinib regimen, which is orally administered and therefore does not require inpatient stays, is unlikely to be fully captured within the economic analysis.⁶² Furthermore, the model estimates that 5% of patients treated with the ASCT regimen would require admission to ICU, however a UK clinical expert noted that approximately 10% of patients receiving ASCT require admission to the ICU.⁴² These data combined indicate that the modelled total costs associated with the ASCT regimen are likely to be conservative and therefore the cost-savings and wider hospital resource implications associated with the ibrutinib regimen are likely underestimated.

Value of additional treatment choice

As an efficacious first-line treatment option for patients with MCL that provides deep and durable responses, the ibrutinib regimen would provide an additional treatment option that allows patients to avoid the toxicity associated with the ASCT regimen. In the context of NHS care and service delivery, enabling patients to choose among first-line regimens and allowing clinicians to tailor treatment to individual needs are fundamental aspects of care that enhance patients' sense of control over their disease. As noted in Section 1.3.5, patients with MCL have a strong desire for alternative treatment options in this setting.²⁷ The investigator-initiated nature of TRIANGLE underscores the clinical community's desire for an alternative treatment option to the ASCT-regimen in this setting. Additionally, as noted above, the OS results from TRIANGLE highlight that patients treated with the ibrutinib regimen are associated with extended survival and can avoid the increased mortality-risk experienced by patients treated with the ASCT regimen, thus decreasing the anxiety of patients and their caregivers associated with starting this treatment.³⁰ Patients' increased hope and reductions in anxiety resulting from the availability of the ibrutinib regimen as an additional treatment choice are not captured in the QALY calculation.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Face validity

Model validations were performed in alignment with best practices.¹¹⁶ The model structure, source data and key model inputs and assumptions were reviewed by external experts, including health economic and UK clinical experts in MCL and were confirmed to be appropriate.⁴² Where survival data required extrapolation, selection of the appropriate survival curves was conducted in alignment with NICE TSD 14.⁹⁸ This included face validity checks of the chosen survival curves in terms of visual inspection of fit and assessment of the proportionality of hazards between treatment arms; further information on this is presented in Section 3.3.

Internal validity

Quality-control procedures for verification of input data and coding were performed by health economists not involved in the model development. These procedures included validating the logical structure of the model, mathematical formulas, sequences of calculations, and the values of numbers supplied as model inputs. Unexpected model behaviour, implementation, and typing errors were checked for during this review.

The quality check process included checking the intermediate calculations for references (whether they are linked to the correct cells, etc.), implementation (whether correct signs for the parameters are used, etc.) and evaluation of the face validity of predicted results. The expected function of parameters was checked with extreme value sensitivity analysis. The process also involved checking the functionality of any built in VBA macros to ensure they functioned appropriately.

Additionally, the appropriateness of distributions used in the probabilistic analysis of the model were checked. Furthermore, given first-line transitions in the model were informed by TRIANGLE, the internal validity of the model survival predictions for FFS on first-line treatment were checked against the observed FFS KM data in TRIANGLE. The reconstructed FFS curves predicted by the model (for both regimens; based on the base case settings) are presented in Figure 29 alongside the observed FFS data from TRIANGLE. As shown, the model-predicted FFS curve is highly aligned with the observed FFS KM data from TRIANGLE, clearly demonstrating that the base case modelling approach produced clinical efficacy estimates that accurately reflect the empirical data informing the model.

Of note, as discussed in Section 3.11.3, the cost-effectiveness results were found to be robust across a range of alternative parametric models explored, thereby providing confidence in the validity of the base case results.

Figure 29: Reconstructed FFS curves vs observed TRIANGLE FFS KM

Abbreviations: FFS: failure-free survival; KM: Kaplan-Meier.

External validity

Clinical feedback was also used to validate key inputs and assumptions utilised in the model, including subsequent treatment distribution and monitoring frequencies. Where possible, UK

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sources were used for model inputs and similar inputs and approaches to those used in prior appraisal were adopted.^{11, 88} Model outcomes (FFS and OS for the ibrutinib and ASCT regimen, respectively) were also validated against estimates provided from UK clinical experts and other long-term studies and found to be clinically plausible and externally valid.⁴²

As discussed throughout Section 3.3, the clinical plausibility of the curve(s) for each transition, and thus the resulting reconstructed FFS and OS curves, was the primary consideration for the selection of the base case curves. This is reflected in the fact that clinical expert estimates and model-predicted estimates were closely aligned at all landmark estimates for both regimens for the reconstructed FFS curves (see Section 3.3.2) and reconstructed OS curves (see Section 3.3.4).

For clarity, the OS estimates predicted by the semi-Markov model (based on the base case modelling approach) are presented in Table 86 along with the clinical experts' most likely estimates of OS for each regimen at landmark timepoints.⁴² At Year 10 and Year 20, the model slightly but consistently overpredicted OS across both regimens (<2.5%), whereas at 15 years, the model slightly underpredicted OS across both regimens (<1.5%). Crucially, any difference between clinical expert estimates and model-predicted estimates remained less than <2.5% across all landmarks; at 20 years, the difference in estimates was 0.8% for the ibrutinib regimen and 1% for the ASCT regimen. These findings validate the modelling approaches for the transition probabilities, demonstrating that the long-term predictions of OS from the model align closely with expected outcomes in UK clinical practice.⁴²

Table 86: Clinical expert estimates and model-predicted landmark estimates for OS

Distribution	Median OS (years)	10 year (%)	15 year (%)	20 year (%)
Ibrutinib regimen				
Clinical expert estimates ^a	NA	67.0	53.0	37.0
Model predicted estimates ^b	15.8	69.2	52.5	37.8
ASCT regimen				
Clinical expert estimates ^a	NA	56.0	44.4	30.4
Model predicted estimates ^b	12.5	58.3	43.0	31.4

Footnotes: ^aThe mean of the clinical experts' most likely values. ^bLandmark survival estimates for OS at 10, 15 and 20 years based on the reconstructed OS curve when all standard parametric models/AMRs informing transition probabilities in the model were fixed on their base case settings, as detailed throughout Section 3.3.

Abbreviations: ASCT: autologous stem cell transplant; OS: overall survival.

Source: J&J IM Data on File. November 2025 Advisory Board.⁴²

Additionally, predicted OS estimates for the ASCT regimen were closely aligned to values reported in the literature for patients with untreated MCL. The predicted median OS of patients receiving the ASCT regimen in the model (12.5 years) is closely aligned with the landmark survival estimate of the MCL2 trial assessing the Nordic regimen (alternating cycles of maxi-CHOP and cytarabine), followed by ASCT in 159 patients with previously untreated MCL (median OS of the Nordic regimen: 12.7 years).²⁰ Similarly, the 7-year generated OS for those receiving the ASCT regimen within the model (70.0%) aligned closely with the landmark estimates of the 120 MCL patients receiving rituximab maintenance therapy following ASCT in the LyMA trial where the 7-year OS was 69.5%.^{49, 117}

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3.15 *Interpretation and conclusions of economic evidence*

Summary of the cost-effectiveness evidence

TRIANGLE demonstrated the efficacy and safety of the ibrutinib regimen in patients with untreated MCL. The ibrutinib regimen substantially prolonged FFS, PFS and OS vs. the ASCT regimen. In addition to improved survival, the ibrutinib regimen offers a more manageable tolerability profile that enables patients to avoid the significant acute-toxicity burden associated with ASCT as well as reduce the risk of adverse-event related mortality.³⁰ Overall, the results of TRIANGLE demonstrate that, if reimbursed, the ibrutinib regimen will address the significant unmet need in untreated MCL for a treatment option with improved efficacy and a more manageable safety profile vs. the highly toxic ASCT regimen.

These compelling efficacy results were reflected in the base case economic analysis, where at PAS price, the probabilistic results showed that the ibrutinib regimen was associated with 1.37 LYG and ■■■ QALYs gained vs. the ASCT regimen. The base case probabilistic results also demonstrated that the ibrutinib regimen was associated with a cost saving of £■■■ versus the ASCT regimen. As such, the ibrutinib regimen was shown to be dominant versus the ASCT regimen in the base case analyses.

It should be noted that these base case results omit important benefits that cannot be captured in the QALY, including a reduction in the long-term HRQoL burden associated with the ASCT regimen and the value to patients of an additional more effective treatment choice. This means that the base case results likely represent a conservative estimate of the true cost-effectiveness of the ibrutinib regimen vs. the ASCT regimen in UK clinical practice (see Section 3.13).

The PSA found the probability of the ibrutinib regimen being cost-effective to be ■■■ and ■■■ at a WTP threshold of £20,000 and £30,000 per QALY, respectively. The DSA highlighted that the INHB was most sensitive to the weighted average HR applied to the PF 2L to PD transition for the ibrutinib regimen, the RDI for ibrutinib (maintenance), and the AMR for the ASCT regimen in the FF 1L health state. However, overall, the base case results were found to be robust to uncertainty across all model parameters, as demonstrated by the close alignment of deterministic and probabilistic analyses. Scenario analyses additionally demonstrated that the model was robust to uncertainty – crucially, none of the scenario analyses resulted in meaningful changes to the cost-effectiveness conclusions of the base case analysis; the ibrutinib regimen remained cost-effective vs. the ASCT regimen at PAS price across all scenarios.

Strengths

Efficacy data for the first-line setting in the model were sourced from TRIANGLE, a high-quality, methodologically robust Phase III RCT in the patient population of interest to this evaluation, providing robust, direct comparative evidence on the efficacy and safety of the ibrutinib regimen and the only relevant comparator in UK clinical practice, the ASCT regimen. This eliminates the need for indirect treatment comparisons and minimises uncertainty within the analyses.

As detailed in Section 3.2.2, despite the extensive follow-up of the TRIANGLE study, with a median follow-up of ~4.5 years, up to a maximum of ■■■ years, uncertainty around long-term survival estimates over the full model time horizon of 43 years remained.⁶³ Use of the semi-Markov model structure allowed for external data from the RAY-3001 trial to be incorporated into the analyses, thereby providing flexibility in the approach to modelling long-term survival

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extrapolations. This reduced uncertainty in long-term survival extrapolations is a key strength of the modelling approach. Of note, the additional external data source utilised within the model (RAY-3001) was the key data source informing the reimbursement of ibrutinib in the 2L setting in MCL by NICE [TA502], during which it was deemed suitable for UK decision making.¹¹ The relevance of the trial to this appraisal was validated by five UK-based clinical experts during an November 2025 advisory board who agreed that given the paucity of data in this setting, RAY-3001 represents an appropriate source of data to inform transition probabilities in the second and third-line setting.⁴² Use of the semi-Markov approach is in line with precedent established by NICE in similar appraisals in B-cell lymphomas.^{11, 88}

Comprehensive clinical validation was sought to validate key model inputs and assumptions as well as long-term survival estimates, as discussed further below. UK clinical experts largely agreed that key model inputs and assumptions were aligned with UK clinical practice and reflective of the evidence base available. For example, the clinical experts reviewed the baseline characteristics of patients enrolled in TRIANGLE, and confirmed that they were broadly generalisable to ASCT-eligible patients with untreated MCL in the UK.⁴² In addition, the predicted long-term survival estimates for FFS and OS for the ibrutinib and ASCT regimen were aligned with UK clinical expert estimates for treatment with both the ibrutinib regimen and the ASCT regimen, reflecting that the long-term predictions of survival from the model align closely with expected outcomes in UK clinical practice.⁴² The results of the economic analysis are therefore considered highly relevant to UK decision-making.

Finally, the model closely aligns to the NICE reference case, adopting an NHS and PSS perspective as well as utilising a lifetime horizon of 43 years to ensure all costs and QALY gains associated with both interventions are fully captured and discounting costs and benefits at a rate of 3.5% per annum.

Limitations

As discussed in Section 3.7, long-term extrapolation of TTF data from TRIANGLE were still required when adopting a semi-Markov approach due to the median follow-up of TRIANGLE being shorter than the lifetime model time horizon, which is associated with inherent uncertainty. There were similar limitations with the TTP and PPS data from RAY-3001 trial. To address this limitation, as noted in Section 3.3, selection of the most appropriate parametric survival functions followed the recommendations outlined by the NICE DSU TSD 14.⁹⁸ Specifically, selection was informed by a combination of goodness-of-fit statistics, inspection of visual fit and feedback received from UK clinical experts, with the latter deemed the most important consideration to ensure the predicted outcomes were generalisable to UK clinical practice.⁴² This ensured that the selected base case extrapolations were associated with both high internal and external validity (see Section 3.14). Furthermore, uncertainty surrounding the long-term survival estimates used within the model were explored in scenario analyses, which demonstrated that the ibrutinib regimen remained cost-effective versus the ASCT-regimen across a range of alternative plausible assumptions (Section 3.11.3).

Conclusion

There remains a significant unmet need in patients with untreated MCL for an additional front-line treatment option which is associated with increased efficacy and more favourable tolerability profile and therefore is able to simultaneously improve survival outcomes and relieve the clinical burden and invasive nature of the current SoC. The substantial unmet need and therefore desire

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in the clinical community for an alternative treatment to the ASCT-regimen is underscored by the investigator-initiated nature of TRIANGLE. If recommended, the ibrutinib regimen would address the significant unmet need for patients with untreated MCL, by providing patients and their clinicians with an effective treatment option which can delay disease progression, and offer an improved safety profile compared to the highly toxic current SoC with the ASCT regimen. Overall, the probabilistic and deterministic base case ICERs demonstrated the ibrutinib regimen to be cost-effective use of NHS resources, associated with both QALY gains and cost-savings versus the ASCT regimen as a treatment for patients with untreated MCL. These findings were found to be robust to variations in key model inputs and assumptions as assessed via various sensitivity and scenario analyses. The ibrutinib regimen can therefore be considered a cost-effective use of NHS resources, whilst fulfilling the significant unmet need for patients with untreated MCL in the UK.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Summary of Information for Patients (SIP)

January 2026

File name	Version	Contains confidential information	Date
ID6596_Ibrutinib_NICE_SIP_NoCON	V2.0	No	25 th February 2026

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from National Institute for Health and Care Excellence (NICE) for their treatment to be sold to the National Health Service (NHS) for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: ibrutinib; brand name: Imbruvica®

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).

Please note: Further explanations for the words and phrases highlighted in **bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or documents are highlighted in **orange**.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

In August 2025, the **Medicines and Healthcare products Regulatory Agency (MHRA)** granted **marketing authorisation** for ibrutinib in combination with **R-CHOP** alternating with **R-DHAP** (or **R-DHAOx**) without ibrutinib, followed by ibrutinib with or without rituximab as a treatment for patients with previously untreated MCL who would be eligible for **ASCT**. For further information on the components within this regimen, please see **Section 3a**.

Further licensing information for ibrutinib can be found on the MHRA website, available [here](#).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Johnson & Johnson Innovative Medicine (J&J IM) provided the following support to relevant patient groups in the UK in the last 12 months.

As a member of the Association of the British Pharmaceutical Industry (ABPI), J&J IM must publish information annually about its relationships with patient advocacy groups, as presented in **Table 1** below. Any financial support provided is used in line with the request from the patient organisation, and does not require the patient organisation to purchase, use, recommend or arrange for the use of any product of J&J IM or any of its affiliates.

Table 1. Summary of J&J IM disclosures

Patient group:	Engagement/ activity:	Reason for engagement/ activity	Financial support provided
Anthony Nolan	J&J IM provided Anthony Nolan with a grant of £19,000 to support the implementation of a Cell Therapies Nurse Specialist – Year 2	Grant requested by patient organisation	£19,000
Anthony Nolan	Johnson & Johnson provided Anthony Nolan with a grant of £10,000 towards delivery of their Patient Information Services in 2026	Grant requested by patient organisation	£10,000
Blood Cancer UK	J&J IM covered travel costs of £371.50 for Blood Cancer UK's involvement in a J&J IM Haematology study day	Patient organisation attending J&J IM event to demonstrate resources available to HCP's and their patients	£371.50

Blood Cancer UK	J&J IM provided Blood Cancer UK with a grant of £45,910 towards the cost of delivering their National Blood Cancer Action Plan –Year 2	Grant requested by patient organisation	£45,910
Blood Cancer UK	Johnson & Johnson provided a grant of £45,000 to Blood Cancer UK supporting their Minimum Standard of Care Project	Grant requested by patient organisation	£45,000
Bood Cancer Alliance	Johnson & Johnson provided the Blood Cancer Alliance with a fee of £3,300 for five representatives to participate in a J&J workshop on early diagnosis in blood cancer	Invited to attend and contribute due to their expertise in this area	£3,300
Cancer 52	J&J IM provided sponsorship of £20,000 to Cancer 52 towards their activities to improve the lives of patients with less common cancers through their policy and campaigns work	Grant requested by patient organisation	£20,000
Leukaemia Care	J&J IM provided Leukaemia Care with a grant of £5000 to support the delivery of their core services including a helpline, support groups and hospital hubs	Grant requested by patient organisation	£5,000
Leukaemia UK	Johnson & Johnson provided Leukaemia UK with a grant of £9,500 to	Grant requested by patient organisation	£9,500

	support the development of a report on the analysis of Leukaemia diagnosis, treatment, and economic impact		
Lymphoma Action	J&J provided Lymphoma Action with a sponsorship of £5000 to support the delivery of their Lymphoma Management Conference Series	Sponsorship requested by patient Organisation	£5,000

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The main condition that the medicine will treat is mantle cell lymphoma (MCL)

What is MCL?

MCL is a rare type of **lymphoma** (a cancer of the **lymphatic system**, which supports the functions of the immune system).^{1,2} Lymphomas can be grouped as **Hodgkin lymphomas** or **non-Hodgkin lymphomas (NHL)**, depending on the types of cell they affect. MCL is a type of NHL that affects **white blood cells** called **B cells** (also known as **B lymphocytes**).¹ It is called 'mantle cell' lymphoma because it affects B cells in an area of the **lymph node** called the mantle zone.³

In healthy people, B cells play an important role in how the body fights off infection. B cells are made in the soft centre of bones (**bone marrow**). From there, they enter the blood and travel to other parts of the body, such as the **spleen** and lymph nodes, where they help to fight infection. In patients with MCL, B cells become abnormal, so they are unable to fight infection properly.¹ These **MCL cells** build up in the bone marrow, spleen and lymph nodes and sometimes in other organs such as the **gastrointestinal tract** and liver. This can stop these parts of the body from working properly.²

MCL can affect patients differently:

- In around 1 in 10 patients, MCL grows slowly and causes few or no symptoms. This is sometimes called '**indolent**' or 'low-**grade**' MCL. It may not affect **quality of life**, and patients might not need to start treatment for a long time, sometimes years.³
- More commonly, patients have fast-growing MCL, and treatment is needed straight away. This is known as '**aggressive MCL**' or 'high-grade MCL'.³ Aggressive MCL can reduce quality of life substantially.⁴

What are the symptoms of MCL?

Patients living with MCL may not show any symptoms of their disease.¹ However, the most common symptom of MCL is one or more painless swellings in the neck, armpit or groin. This happens when MCL cells build up in the lymph nodes.^{1, 2} Other common symptoms of MCL are shown in **Figure 1**.

Many patients also have MCL cells in their bone marrow when they are diagnosed. This might lead to some or all of the following:³

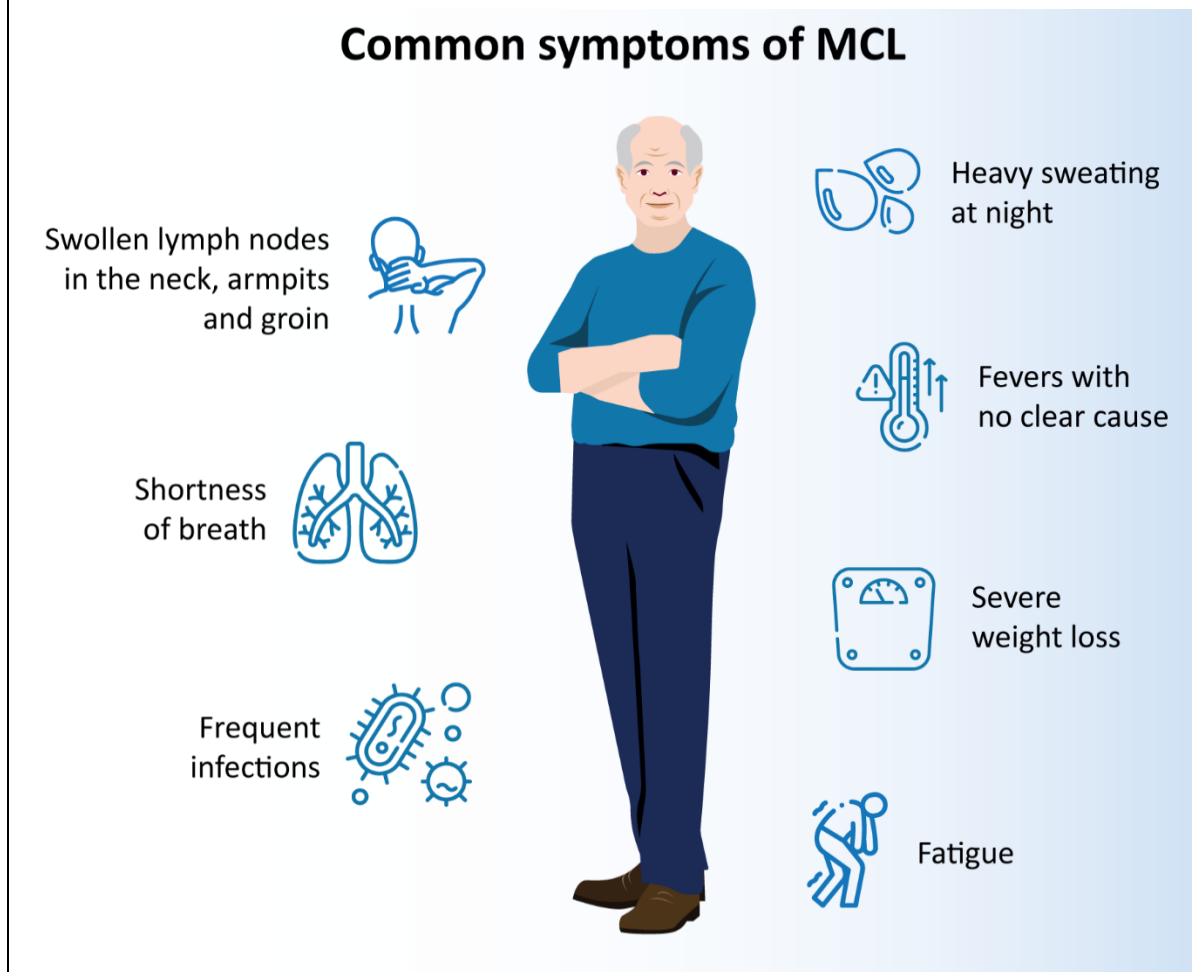
- A low number of **red blood cells**, which can cause tiredness and shortness of breath
- A low number of **platelets**, which makes patients more likely to bruise and bleed
- A low number of white blood cells, which makes patients more prone to infection

Some patients also have other symptoms called 'B symptoms. These include:³

- Heavy sweating at night
- Fevers that come and go with no obvious cause
- Losing a lot of weight without trying to (more than one tenth of a person's total weight – for example, a 70 kg person losing more than 7 kg of weight)²

As MCL can affect other organs, patients with MCL may also have a range of other symptoms. MCL can spread to the bowel and, in rare cases, to the stomach. If this happens, it can cause symptoms such as diarrhoea, tummy pain and sickness.^{2, 3} MCL can also spread to the spleen, which can cause tummy pain and back pain.²

Figure 1: Common symptoms of MCL^{1,3}



How many patients get MCL?

MCL is a rare form of cancer.¹ Each year in the UK, approximately 600 patients are diagnosed with MCL.⁵ MCL can affect anyone, but some factors can make a person more likely to develop MCL. For example, MCL is more common among men than women and usually occurs in older people, with most cases diagnosed in people over 70 years old.⁶

How long can someone with MCL expect to live?

MCL affects patients differently.⁴ However, MCL is generally considered an 'aggressive' form of cancer,⁷ which means that someone with MCL may have a shorter lifespan than a person without the disease or a person with a different type of cancer.⁸ In addition, patients with MCL are generally diagnosed with **advanced** disease, which results in shortened lifespan (additional information on stages of disease can be found in **Section 2b**).⁹ Certain factors (known as '**prognostic factors**') have been linked to a shorter survival rate for patients with MCL. These include:⁹

- Older age (over 50 years old)
- Lower level of fitness (sometimes called a lower **performance status**)
- High numbers of white blood cells in the blood

- High levels of a **protein** called **lactate dehydrogenase** in the blood

What is the cost of MCL for the patient, caregiver and society?

As MCL is a rare form of cancer, there is little information about the cost burden it causes to patients and society. However, there is information about the costs of other types of Non-Hodgkin lymphomas (NHL) to patients and society,^{10, 11} which are likely to be similar to MCL. Usually, patients with aggressive MCL have a greater disease burden than patients with indolent MCL.¹²

Cost for the patient and caregiver

Patients with MCL may need a lot of medical care to treat their condition and manage their symptoms.¹³ This can involve going to hospital to receive MCL treatment or to manage side effects.¹⁴ Also, many patients with MCL **relapse** after their first treatment.³ This means that patients often need multiple types of treatment for their MCL over the course of their lifetime.¹² It can take time and money for patients and their caregivers to travel to and from appointments to receive MCL treatment.^{10, 15}

If patients with MCL are employed, they may need to take time off work because of their symptoms or to receive treatment. Likewise, caregivers may need to take time off work to take patients to hospital appointments or to care for them. Some patients and their caregivers might need to stop work altogether.^{11, 16} Additionally, as described in **Section 2c**, the available treatment for MCL (ASCT) requires patients to spend up to a month in hospital to receive treatment. Following this, patients are required to attend weekly follow-up visits for monitoring and **blood transfusions** likely preventing them and their caregiver from working.³ This can mean they lose some or all of their income, which might be very stressful and worrying for patients and their loved ones.^{16, 17}

Cost for society

MCL can be costly for the healthcare system and to employers.¹¹ As discussed above, there is little information about the burden MCL causes to society, but it is likely to be similar to that for other types of NHL given the need for ongoing patient care to address the symptoms faced by patients.^{10, 11} As described in **Section 2c** below, the current available treatment for patients with MCL is very costly to society, and particularly the NHS, as patients need to stay overnight in hospital for up to a month to receive treatment.¹⁶

What is the emotional impact of MCL on patients and their caregivers?

Impact on patients

The emotional impact of MCL varies among patients, but often being diagnosed with MCL can be very difficult. As with other types of lymphoma, patients with MCL may experience emotions that can be hard to cope with, such as shock, anger and helplessness.¹⁸ Many patients may be worried about how the condition will affect their future.¹⁸ MCL is a rare

type of cancer, so there is sometimes a lack of awareness and understanding about the condition. This might mean patients with MCL feel alone.¹⁹

If symptoms like extreme tiredness develop, it can be difficult for patients with MCL to do everyday tasks and take care of themselves.¹⁶ It can also be hard for them to maintain relationships because of their symptoms or emotions.²⁰ This can further isolate patients with MCL and lead to feelings of loneliness. Patients also experience an additional burden due to the impact of currently available treatment options (see **Section 2c** for additional information).

The physical burden of MCL can lead to psychological difficulties including anxiety, depression, insomnia (regular sleep disturbance), intimacy issues and mood swings.^{16, 21} A large review of quality of life data from patients with blood cancers (7,349 participants) found that overall well-being tended to be lower, with declines across most areas measured, including mental health. Specifically, patients reported that symptoms including fatigue, anaemia, insomnia and difficulties with memory and concentration had a significant detrimental impact on their quality of life.²²

Lastly, as described in **Section 2c** below, the current treatment for MCL (ASCT) may also worsen the physical and emotional challenges faced by patients, as the treatment itself has unpleasant side effects, requires long periods of time in hospital and frequent follow up and monitoring.¹⁶

Impact on caregivers and families

There is little information about the impact of MCL on families and caregivers, but it is likely that MCL has a similar impact on these people as other types of lymphoma. Patients with lymphoma may need help from family, friends or other people in their life. This may involve helping with daily tasks such as shopping, cleaning or preparing meals. Caregivers may also be involved in medical appointments and help to check on the person's health. All the responsibilities associated with being a caregiver for a loved one with MCL can place a strain on the relationship between family and their loved ones. The tasks involved with being a caregiver can be both emotionally and physically demanding.¹⁰ They can also be very time-consuming, as patients with MCL require several extended visits to the hospital, particularly with current treatment for MCL (ASCT; see **Section 2c**).¹⁶ Caregivers may need to take time off work to transport patients to access treatment, which might be very stressful and worrying. Finding out about the cancer diagnosis may also cause family and friends to feel shocked, helpless, fearful and sad.¹¹

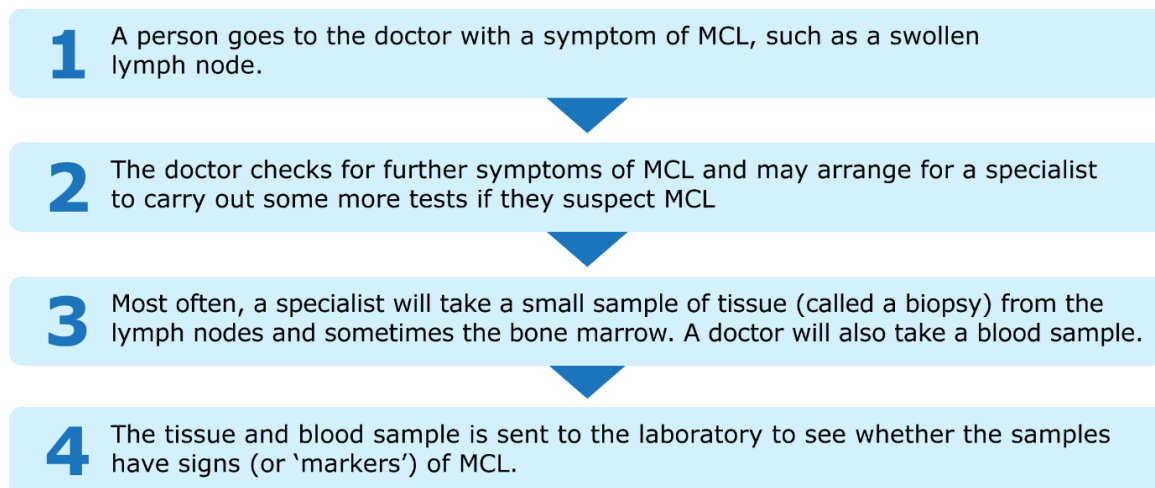
2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is MCL diagnosed?

Sometimes MCL can be found with a routine blood test before any symptoms of the disease start to show.¹

More often, MCL is diagnosed when a person has already started showing symptoms. Here is an example of how this can happen:¹



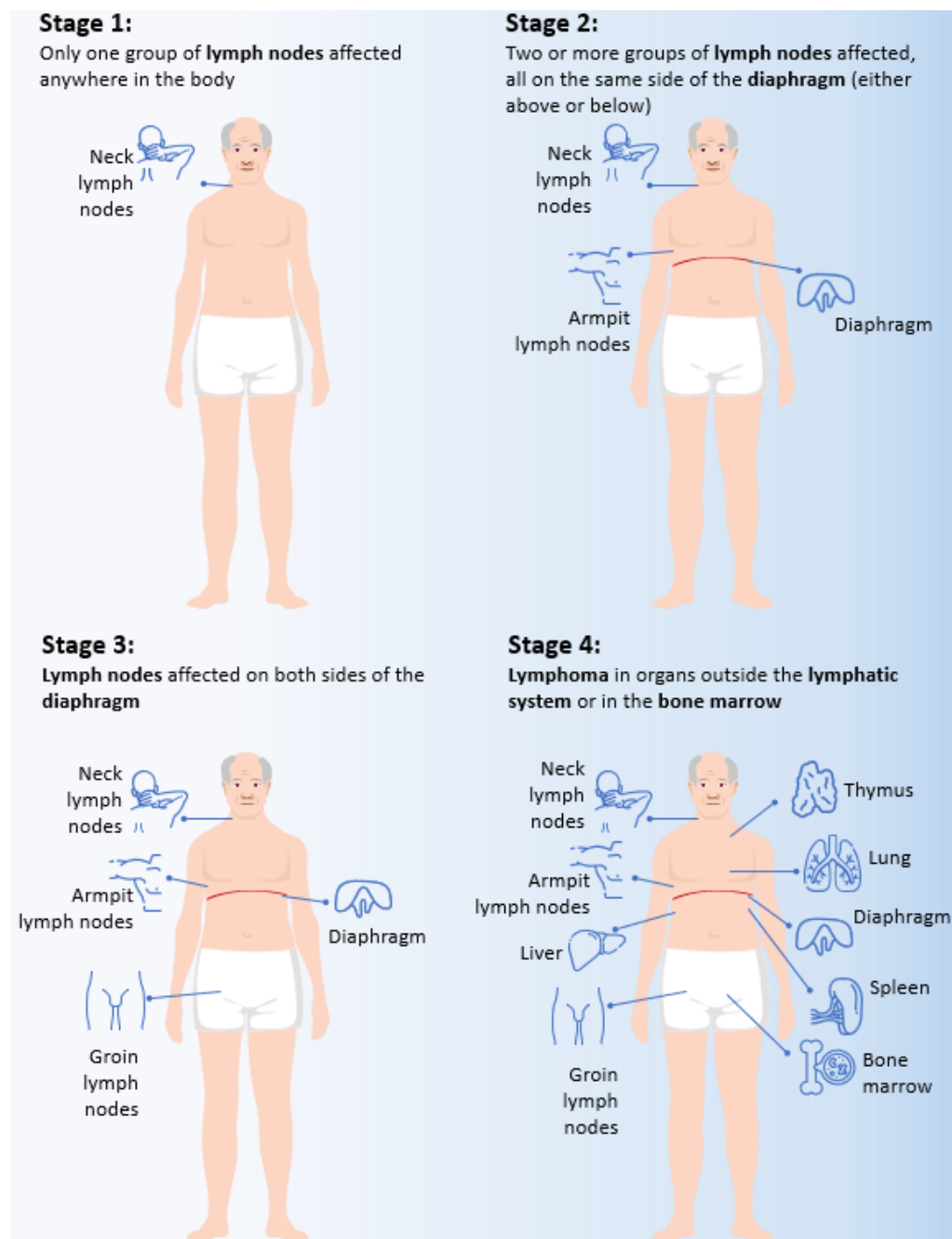
What does 'staging of MCL' mean?

If MCL is confirmed, the **specialist** doctor will try to find out how advanced the disease is. This is called a cancer **stage**. They will also try to find out how fast the cancer is growing based on the types of symptoms present. This is called the cancer grade and is indicated by a letter.^{23, 24}

The stage and grade of MCL can be determined using various tests. **Computerised tomography (CT)** or **positron emission tomography (PET)** scans detect MCL cells in the lymph nodes, organs, bone marrow, and other parts of the body.²³ Knowing the stage and grade of the MCL helps the medical team to predict how the MCL might progress over time and to determine the best treatment option.^{23, 25}

MCL has four stages, based on where swollen lymph nodes are in relation to the patient's **diaphragm**, as shown in **Figure 2**.²⁶ The location and number of swollen lymph nodes above or below the diaphragm helps the specialist doctor see the stage of MCL. The diaphragm is used as a guide because it is about halfway down the body.²⁶ Patients with Stage 4 MCL have the most severe disease and the worst outlook (**prognosis**). Because MCL grows quickly and can cause many different symptoms, most patients are diagnosed after the disease has already progressed to an advanced stage with more than 9 out of 10 patients diagnosed at Stage 3 or 4.²⁷ The treatment considered in this appraisal (ibrutinib) would be used to treat patients with Stage 2–4 MCL.

Figure 2: MCL staging²⁶



Source: Adapted from [Lymphoma Action](#).

As well as giving stage numbers, the letters A or B are used to indicate whether or not a person is showing 'B symptoms' (weight loss, fevers and night sweats).²⁴ If a person doesn't have any of these symptoms, the letter A will be added next to the stage (for example, Stage 1A). If a person has these symptoms, the letter B is added next to the stage (for example, Stage 1B).²⁴

Usually, MCL cells develop first in the lymph nodes. However, in some patients, MCL cells may develop first in other organs such as the gastrointestinal tract or liver. This is called

‘extranodal’ lymphoma. In this case, the stage will include the letter E (for example, Stage 1E).²⁴

Lymphomas such as MCL are also often grouped as either low grade (indolent) or high-grade (aggressive). Determining the grade of the lymphoma helps to guide decisions about the best treatment plan for patients. Low-grade MCL grows very slowly, and patients may need little or no treatment for months or possibly years. High-grade MCL grows more quickly and they usually need immediate treatment.²⁴

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There is a variety of clinical guidelines available in the UK for the management of MCL including the British Society of Haematology (BSH) guidelines (2023), European Society for Medical Oncology (ESMO; 2017) **clinical practice** guidelines and the NICE guidelines for the diagnosis and management of NHL (NG52).^{9, 28-31} The BSH (2023) guidelines are most commonly used to manage MCL in the UK.^{28, 32} Further information on these guidelines can be found in **Section 4a**.

How is untreated MCL managed?

Most patients who have been diagnosed with MCL require treatment immediately, in which case they will go straight to the current first-line treatments explained further below.^{3, 9} However, some patients may not need treatment immediately.³ For these patients, MCL is managed through **‘active monitoring’**.³

Active monitoring

The term ‘active monitoring’ (also known as ‘watch and wait’) describes the time between MCL diagnosis and treatment. Doctors may take an active monitoring approach for a small number of patients who do not require treatment straight away after diagnosis, such as patients with Stage 1 or 2 MCL or patients with indolent MCL (see **Section 2a** for further information on indolent MCL).³ This is because starting treatment earlier in these patients may not improve their outcomes.³³

During active monitoring, doctors will closely monitor a person’s overall health and the symptoms and stage of their disease during regular check-ups. Treatment will begin if a patient begins to show symptoms that the disease is getting worse.³⁴

First-line treatments for MCL

If a person has Stage 3 or 4 MCL and is showing symptoms when they are diagnosed, they usually require treatment straight away.⁹

MCL cannot currently be cured,⁹ but there are a range of different treatments that can be used to try to destroy MCL cells.^{1,9} Choosing the right treatment is important. Choice of first-line treatment for patients with MCL in the UK is dependent on eligibility for ASCT, which is based on fitness. Assessment of a patient's fitness is carried out by the medical team responsible for the patient's treatment and is based on factors including age, weight, mobility, comorbidities, and cognitive health.^{28, 35} The patient population for this submission is patients who are eligible for ASCT, and therefore the treatment options for these patients are described in more detail below.

What are the current treatment options for patients with MCL who are eligible for ASCT?

The main treatment for patients who have not yet received treatment for their condition and are healthy enough to receive it is called the *ASCT regimen*. This involves several steps:

- **Induction therapy:** This involves using a combination of drugs called immunochemotherapy to shrink the cancer ahead of the stem cell transplant and improve the likelihood of successful treatment.³⁶ Immunochemotherapy is a combination of immunotherapy and chemotherapy which work together to identify and attack the tumour cells. In addition, patients will often receive steroids alongside immunochemotherapies. In the UK, immunochemotherapies for MCL typically include rituximab (the immunotherapy) combined with chemotherapy. The most commonly used induction therapies are 'the Nordic approach' (alternating maxi-R-CHOP and **R-HDAC**), alternating R-CHOP and R-DHAP, or 'the LyMA approach' (four cycles of R-DHAP [± four cycles of R-CHOP]).²⁸ The treatment guidelines for MCL state that all induction therapies are associated with comparable effectiveness.²⁸
- **Consolidation therapy** with stem cell transplant: **Bone marrow stem cells** are collected before a very high-dose chemotherapy (usually **BEAM** or **BEAC**) is administered to kill any remaining cancer cells. This is followed by ASCT, in which the bone marrow stem cells are delivered back into the blood so that they can settle in the bone marrow to restore normal blood cell production.³
- **Maintenance therapy:** After ASCT, treatment with rituximab is often given for two to three years to help stop the cancer from returning by supporting the body's immune functions.

Why are new treatments for patients with MCL needed?

While the ASCT regimen can help patients live longer, it is a toxic and complex treatment option that can cause several side effects and is associated with a substantial resource use burden to the NHS. The existing burden of the ASCT regimen on patients and their caregivers, is described in detail below using quotes from patients and their caregivers of patients with MCL who have previously received the ASCT regimen.¹⁶

Physical burden of the ASCT regimen on patients

Treatment with ASCT involves receipt of high-dose chemotherapy during consolidation therapy, which can cause many side effects including mouth ulcers, anaemia, nausea, and vomiting.³ Patients often find this phase of the ASCT regimen intense and overwhelming, as highlighted by the following quotes from a patient with MCL who had received the ASCT regimen:¹⁶

"I don't think you'd probably ever realise how hard and intense that [ASCT] actually is."
– **Patient with MCL who received the ASCT regimen**

"It's as bad as I thought... I wouldn't do it again." – **Patient with MCL who received the ASCT regimen**

In the immediate recovery period following ASCT, patients experience a number of side effects which impact patients' daily lives and general quality of life. Side effects include fatigue and weakness, gastrointestinal toxicity (which sometimes leads to dehydration, inability to eat, and re-admissions to hospital), loss of appetite, taste and weight, an inflamed and sore mouth, as well as infections and fevers.¹⁶ Patients find these side effects challenging to deal with, as highlighted by the following quotes from a patient with MCL who had received the ASCT regimen and a caregiver of a patient who had received the ASCT regimen:¹⁶

"He couldn't even walk out of his room. He was that weak and tired..." – **Caregiver of a patient with MCL who received treatment with the ASCT regimen**

"The night sweats are horrible. The dry mouth, that's a lot worse than ever explained to you ... Everything tasting horrible." – **Patient with MCL who received the ASCT regimen**

Emotional burden of the ASCT regimen on patients

The side effects of the regimen can frequently lead to mood changes and depression.¹⁶ For example, fatigue is common and endurance can drop following the ASCT regimen, leading to patients experiencing challenges with exercise and personal hobbies.¹⁶ Patients' immune systems also remain weak for several weeks following the procedure, so the risk of infection is high and the majority of patients remain in isolation in hospital post ASCT-procedure.³⁷ Isolation within the hospital, and subsequently at home to reduce the risk of infection may prevent patients from socialising with friends and family, which is an additional challenge for patients and their caregivers.¹⁶ The anxiety associated with the vulnerability to infection may also negatively impact the emotional wellbeing of both patients and their caregivers, as indicated by patients who had previously received the ASCT regimen:¹⁶

"I was very conscious about getting another infection" – **Patient with MCL who received the ASCT regimen**

“Isolation, I think, is the worst thing, not being able to see people” – Patient with MCL who received the ASCT regimen

Burden of the ASCT regimen on caregivers

Patients and their caregivers often need to make adjustments to their daily lives, as after discharge, patients need intensive monitoring with weekly check-ups and blood transfusions. Caregivers frequently take on responsibilities such as medication management, monitoring symptoms, coordinating appointments and are often required to make health-related decisions and assist with daily medical tasks at home.¹⁶ This can introduce logistical and financial challenges for caregivers who may need to stop working to be able to care for the patient, as well as coordinate frequent hospital visits and unpredictable overnight stays in hospital.¹⁶ These logistical and financial challenges are highlighted in the quote below from a caregiver of a patient who received the ASCT regimen.¹⁶ Additionally, as caregivers are typically family members or close friends of the patient, the whole ASCT process can be distressing for the caregiver.

“There's a huge financial burden having to travel and stop overnight. I mean, you're talking about thousands of pounds at a time when you really don't need the extra financial burden” – Caregiver of a patient with MCL who received treatment with the ASCT regimen

Long-term burden of the ASCT regimen

As noted above, the ASCT regimen requires long hospital stays and extended follow-up after treatment.³ Patients must stay in hospital not only to receive consolidation therapy, but also for several weeks afterwards to ensure their body has recovered. This extended stay in hospital incurs a substantial cost to the NHS and reduces the number of beds available in hospitals.^{3, 38} After discharge, patients need intensive monitoring with weekly check-ups and blood transfusions, and it can take up to six months to return to normal daily life.³ This lengthy recovery results in a significant and long-lasting reduction of patients with MCL's quality of life as they must physically and psychologically recover from the treatment.

The risk of disease progression on the ASCT regimen

Finally, improvements in the efficacy of immunotherapies has led to questions about whether using ASCT as a consolidation treatment for patients with MCL is still the best treatment option.³⁹ As described above, ASCT is very demanding on patients and unfortunately does not guarantee long-term prevention of disease relapse and patients are still at risk of dying from their disease.⁴⁰ For those whose disease comes back or never fully responds, treatment options are limited and outcomes tend to worsen with each new therapy.^{14, 41}

These challenges highlight a clear need for new, better treatments that can work more effectively, cause fewer side effects, and make the recovery easier for patients. In fact,

patients with MCL who have undergone the ASCT regimen have noted that they “*wouldn’t do it again*”, nor would they “*recommend anyone else to go through [the ASCT regimen], knowing what [they] know now*”.¹⁶

What treatments do patients with MCL receive after the ASCT regimen?

Unfortunately, MCL remains an incurable disease, and therefore many patients will experience disease relapse or disease progression and will therefore have to receive additional treatments.^{28, 42} In the UK the following treatments available are:²⁸

- Ibrutinib or zanubrutinib for patients relapsing after first-line treatment (e.g. following the ASCT regimen)⁴³
- Rituximab-based immunochemotherapy (e.g. rituximab, bendamustine and cytarabine [R-BAC] and bendamustine and rituximab [BR]) for patients relapsing after second-line therapy

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

The symptoms of MCL have a significant impact on the quality of life of patients with MCL, as discussed in **Section 2a**. As described in detail in **Section 2c**, the ASCT regimen (the current treatment option for patients with untreated MCL who are fit enough to receive a transplant) is challenging for patients to undergo, and leads to long-lasting impacts on daily lives for both patients and their caregivers. However, the population of patients with MCL is relatively small and there are few studies reporting on the experience of this patient population.

The main evidence base for the burden of the ASCT regimen on patients with MCL in the UK is from a patient research study conducted by J&J IM between July and October 2025.¹⁶ In this study, patients with MCL who had undergone treatment with the ASCT regimen, and the caregivers of these patients (n=10) were interviewed about their treatment experience. The objective of this patient research study was to gain a deeper understanding of patient and caregiver experiences with the ASCT regimen. Direct quotes from this study are provided in **Section 2c**, and demonstrate that the overall impact of the ASCT regimen on both patient and caregiver lives is substantial and widespread.

Additionally, in 2024, a long-term study on patients with MCL who received treatment with the ASCT regimen aimed to understand the patient experience following treatment. There were 106 patients who responded to the survey, and the average length of time between receiving ASCT treatment and survey response was 9.3 years. Of all the patients who responded to the survey, 2 in 10 patients reported poorer physical and cognitive function, respectively, compared with the general population. These patients were also significantly less likely to be in work. Furthermore, 1 in 10 patients had more symptoms of anxiety, depression, fatigue, sleep disturbance, and pain.⁴¹ This study further demonstrates that patients experience long-term negative impacts on their physical and mental health following treatment with the ASCT regimen, which currently represents standard of care in UK clinical practice.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

About ibrutinib

Ibrutinib is a **Bruton's tyrosine kinase (BTK) inhibitor**. This is a type of **targeted therapy** that stops MCL cells from surviving and multiplying by blocking BTK, a protein that helps MCL cells survive and multiply.⁴⁴

Ibrutinib in combination with R-CHOP alternating with R-DHAP (or R-DHAox) without ibrutinib, followed by ibrutinib with or without rituximab for maintenance therapy has received marketing authorisation in the UK for patients with untreated MCL, who would be eligible for ASCT. Ibrutinib was also approved by the **European Medicines Agency (EMA)** in 2014 for the treatment of relapsed or **refractory** MCL,⁴⁵ and has since become the standard treatment for these patients in the UK.^{9, 46}

Ibrutinib is administered during both induction therapy (in combination with R-CHOP alternating with R-DHAP [or DHAox]) and maintenance therapy (as ibrutinib with or without rituximab).

Further information about ibrutinib can be found in the **Summary of Product Characteristics**, available [here](#).

About R-CHOP alternating with R-DHAP or R-DHAox (immunochemotherapy)

R-CHOP alternating with R-DHAP (or R-DHAOx) is a cancer drug combination that contains the following drugs:

• R – rituximab (immunotherapy)	• R – rituximab (immunotherapy)	• R – rituximab (immunochemotherapy)
• C – cyclophosphamide (chemotherapy)	• DH – dexamethasone (steroid)	• DH – dexamethasone (steroid)
• H – doxorubicin (chemotherapy)	• A – cytarabine (chemotherapy)	• A – cytarabine (chemotherapy)
• O – vincristine (chemotherapy)	• P – cisplatin (chemotherapy)	• Ox – oxaliplatin (chemotherapy)
• P – prednisolone (a steroid)		

Rituximab is an immunotherapy which helps the immune system to identify the cancer cells and kill them.

Cyclophosphamide, doxorubicin, vincristine, cytarabine, cisplatin and oxaliplatin are chemotherapy drugs. These drugs destroy quickly dividing cells, such as cancer cells.

Prednisolone and dexamethasone are types of steroids. They treat lymphoma by stopping the cancer cells from growing and killing them. They may also help you feel less sick during treatment, and help reduce your body's immune response, to try and prevent an allergic reaction to rituximab.

These various treatments work together as an immunochemotherapy to improve the efficacy of chemotherapy in order to accurately target and kill the cancer cells.

Ibrutinib in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib is henceforth referred to as **ibrutinib with immunochemotherapy**. This part of the regimen is only administered during induction therapy.

What is 'the ibrutinib regimen'?

'The ibrutinib regimen' refers to treatment with ibrutinib with immunochemotherapy, which is administered as an induction therapy followed by ibrutinib with or with rituximab which is administered as a maintenance therapy. Details of the administration and duration of induction and maintenance treatment with the ibrutinib regimen is provided in **Section 3c**.

Another resource that has further information on how the ibrutinib regimen works is the **Patient Information Leaflet**, available [here](#).

How is ibrutinib an innovative treatment option for patients with MCL?

The ibrutinib regimen offers several key advantages for patients with MCL, which are summarised in **Section 3h**. Firstly, it has a well-understood **safety** profile and is associated with more manageable side effects versus existing treatment with the ASCT regimen (see **Section 3g**). Secondly, the results from the clinical trial of the ibrutinib

regimen (see **Section 3d**) in patients with untreated MCL demonstrate that patients experience extended survival outcomes compared with patients receiving existing treatment with the ASCT regimen. Finally, the ibrutinib regimen reduces the need for long hospital stays and follow-up monitoring of patients (required for the ASCT regimen), which can free up time and reduce disruption to patients' and caregivers' daily lives (see **Section 3f**).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Yes, ibrutinib can be used in combination with rituximab during maintenance treatment, in line with national treatment guidelines. In the UK, rituximab is recommended by NICE for use as a two-year maintenance treatment, therefore it is anticipated that patients in the UK would receive ibrutinib in combination with rituximab during the maintenance phase of treatment.²⁹

Rituximab is a type of targeted cancer drug called a **monoclonal antibody**. It targets a protein called CD20 on the surface of the lymphoma cells. Rituximab sticks to all the CD20 proteins it finds. Then the cells of the immune system pick out the marked cells and kill them.

All **efficacy**, quality of life and safety/side effects data on the ibrutinib regimen with rituximab maintenance therapy can be found in **Sections 3e–3g**.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How much ibrutinib is given and how should it be taken?

When ibrutinib is prescribed, patients take 560 mg of it in total. The dose is taken as a single tablet containing 560 mg ibrutinib.⁴⁴ An ibrutinib tablet should be swallowed whole

with a glass of water and should not be chewed or broken before it is swallowed.⁴⁴ An ibrutinib tablet should not be taken with grapefruit juice or Seville oranges.⁴⁴

Induction phase: Ibrutinib in combination with R-CHOP, alternating with R-DHAP or R-DHAOx (immunochemotherapy)

While patients are receiving induction treatment (6 cycles), patients receive ibrutinib in combination with R-CHOP on days 1–19 of Cycles 1, 3 and 5 (each 21 days in length). On the alternating cycles (i.e., Cycles 2, 4 and 6; each 21 days in length), patients receive R-DHAP or R-DHAOx, without ibrutinib.⁴⁴ R-CHOP, R-DHAP and R-DHAOx are delivered via **intravenous (IV)** administration.

What is a cycle?

Many cancer treatments are given in cycles. Each cycle is usually split into a period where patients receive a treatment, followed by a period where the treatment is stopped to allow their body to recover. The length of each cycle and the split between treatment and rest periods can depend on the type of treatment and on the patient. For patients with MCL receiving ibrutinib, treatment cycles are 21 days.

Maintenance phase: Ibrutinib with or without rituximab

After the first 6 cycles, ibrutinib is given on its own or in combination with rituximab therapy for 24 months. Patients receive ibrutinib once a day, for the full 24 months of the maintenance phase of treatment.⁴⁴

Further information

Further information on the dosing and administration of the ibrutinib regimen can be found in the **Summary of Product Characteristics**, available [here](#).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Clinical trials investigating the ibrutinib regimen

TRIANGLE (NCT02858258) is a clinical trial studying the ibrutinib regimen for the treatment of patients with untreated MCL.⁴⁷ TRIANGLE is a **Phase 3 clinical trial** in which they looked at how well the ibrutinib regimen worked to treat MCL (its efficacy) and checked for any potential side effects or risks (its safety) compared to existing treatment. The trial therefore compared the ibrutinib regimen to current standard of care, the ASCT regimen, in patients with untreated MCL who were eligible for ASCT.

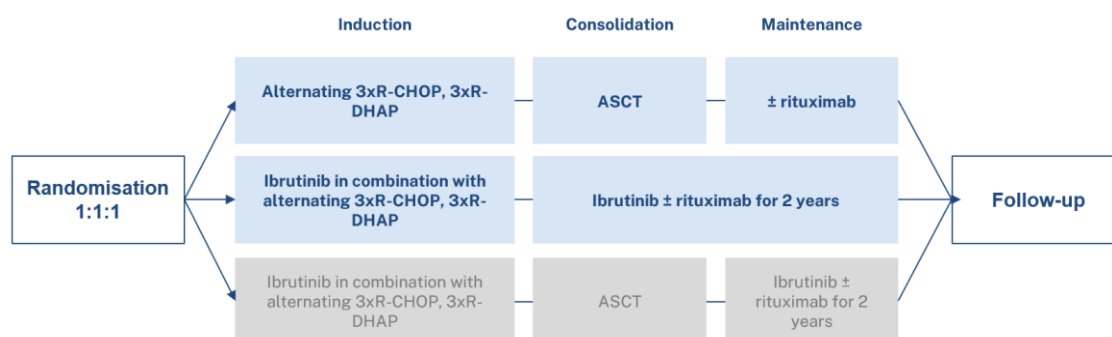
The clinical trial took place across 13 European countries (Czech Republic, Germany, Italy, Portugal, the Netherlands, Belgium, Denmark, Finland, Norway, Sweden, Poland,

Spain, and Switzerland) and Israel.⁴⁷ The results presented for this clinical trial were collected between 25th July 2016 and 9th May 2024.⁴⁷

How was TRIANGLE carried out?

There were two key groups of patients of relevance to UK clinical practice in TRIANGLE. The two groups of patients received different treatments, one group received the ibrutinib regimen (Arm I) and the other received treatment with existing standard of care, the ASCT regimen (Arm A):

- **Arm I:** R-CHOP/R-DHAP with ibrutinib followed by 2-years of ibrutinib maintenance with or without rituximab (based on national treatment guidelines)
- **Arm A:** R-CHOP/R-DHAP followed by high-dose chemotherapy and ASCT, with or without rituximab maintenance (based on national treatment guidelines)



TRIANGLE patient population

There were a total of 268 patients who received treatment with the ibrutinib regimen (Arm I) and 269 patients who received treatment with the ASCT regimen (Arm A). All patients in TRIANGLE had a confirmed diagnosis of MCL, Stage 2–4 disease, were between 18–65 years old and had not received previous treatment for MCL.

More information about TRIANGLE can be found here:

- ClinicalTrials.gov ([here](#))

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results⁴⁷

In TRIANGLE, the efficacy (how well it works) of the ibrutinib regimen was measured according to how well it improved the outcomes listed below. Data from the TRIANGLE trial below are from the Full Analysis Population of the TRIANGLE trial, which included patients that either provided consent for their data to be included within the NICE submission or were deceased at the point at which the data were collected by J&J IM. These are based on the latest available published data from the 9th May 2024 clinical cut-off, at which point patients had a median time on study of 54.9 months. These data are available in Section 2.5 of the [European public assessment report](#) available [here](#).

Failure free survival

Failure free survival (FFS) is a way to measure how long a patient's disease stays under control after starting treatment. Specifically, it is the length of time from when the treatment begins until one of the following happens:

- The disease remains stable at the end of initial treatment (meaning the disease hasn't changed since treatment started)
- The disease starts to get worse (progresses)
- The patient passes away from any cause

After around 4.5 years of following patients, those who received the ibrutinib regimen (Arm I) experienced a significant 36% reduction in the risk of their disease remaining unchanged, getting worse, or leading to death compared to patients who received the ASCT regimen (Arm A).

Since medical guidelines suggest that when the disease stays stable, it often indicates that the treatment has not fully worked and further treatment may be needed, these findings show that the ibrutinib regimen is more effective than existing treatment with the ASCT regimen in UK clinical practice in patients with untreated MCL.⁴⁸ It also shows that patients treated with the ibrutinib regimen are able to stay in remission longer and avoid further treatments, ultimately improving survival.⁴⁹

Response rates (overall or complete response rate)

Overall response rate (ORR) in TRIANGLE was measured as the proportion of patients whose disease improved during the study. This includes patients whose disease completely disappeared (called a **complete response** or CR) or got better but did not completely go away (called a **partial response** or PR). **Complete response rate** (CRR) shows the percentage of patients whose disease completely disappeared during the study.

Almost all patients (9 in 10) responded to treatment in both treatment groups. Of note, a slightly higher proportion of patients achieved CRR in the ibrutinib regimen group (closer to 7 in 10) versus the ASCT regimen group (closer to 6 in 10).

These findings suggest that patients receiving the ibrutinib regimen are able to achieve at least the same high rate and depth of response as those treated with ASCT, without the high level of toxicity associated with the ASCT regimen (see [Section 3g](#)).

Progression-free survival

Progression-free survival (PFS) measures how long a patient's disease stays under control after treatment begins, before it either worsens or the patient dies.

The PFS results from TRIANGLE were consistent with the FFS results and found that patients treated with the ibrutinib regimen (Arm I) had a 37% lower chance of their disease getting worse or dying compared to patients treated with the ASCT regimen (Arm A). When MCL progresses, symptoms often become more severe, which can make patients feel worse and require more medical care. It can also increase the risk of death.

These findings suggest that the ibrutinib regimen may help patients live longer and maintain a better quality of life compared to the ASCT regimen.

Overall survival

Overall survival (OS) shows how long patients live after beginning treatment, regardless of whether they are still alive or have passed away during the study.

At the latest data cut-off in TRIANGLE, median OS (the point at which half of the patients have died) was not reached in either treatment group, meaning many patients were still alive. However, nearly twice as many patients had died in the standard treatment group (Arm A) compared to the group receiving the ibrutinib regimen (Arm I). These results showed that patients receiving the new ibrutinib regimen had a reduced (48% lower) chance of dying compared to those receiving treatment with the ASCT regimen.

In addition, a sharp reduction in OS of patients treated with the ASCT regimen was observed at approximately month six of the clinical trial, which aligns with the point at which patients received treatment with high-dose chemotherapy followed by ASCT. This provides evidence of the high toxicity and corresponding high mortality-risk associated with treatment with the ASCT regimen.

These results indicate that the ibrutinib regimen is an important new treatment option that enables patients to stay in remission longer and avoid further treatments as well as delay disease-progression, ultimately resulting in improved survival outcomes in patients with untreated mantle cell lymphoma.

More efficacy results can be found in the **Company Submission, Section 2.6**.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of the ibrutinib regimen

As TRIANGLE is an investigator-initiated study, no quality of life data were collected in TRIANGLE. Despite this, it is anticipated that treatment with the ibrutinib regimen would result in overall improvements in patient quality of life compared to treatment with the ASCT regimen for the below reasons.

The standard of care for patients with MCL in the UK is the ASCT regimen, which is a very burdensome treatment for patients (see **Section 2c**). This toxic and complex treatment involves high-dose chemotherapy which causes side effects such as sore mouth, nausea, vomiting, diarrhoea, constipation and anaemia.³ Following ASCT, patients have a weakened immune system and therefore at high risk of severe infection and even death.³ Nearly one in two patients with MCL will experience at least one side effect following treatment with ASCT.⁵⁰ These side effects significantly impact patients' quality of life causing considerable physical, emotional and psychological burden with the risk of serious infections that may result in death further exacerbating patient anxiety surrounding treatment.³ As discussed in **Section 3g**, the ibrutinib regimen has a manageable safety profile, and therefore, compared with the toxic ASCT regimen, it is anticipated that treatment with the ibrutinib regimen would improve patient quality of life.

In addition, the ASCT regimen can involve hospitalisation for up to a month (including periods of isolation) and it can take patients up to six months to recover and return to normal day to day life (such as work).^{3, 51} This lengthy recovery results in a significant and long-lasting quality of life impairment, as patients must physically and psychologically recover from treatment.¹⁶ As the ibrutinib regimen removes the need for ASCT, and therefore the long-term recovery following ASCT, the introduction of the ibrutinib regimen is anticipated to improve patient quality of life by allowing patients to return to normal daily activities sooner, and minimise the wider impact on aspects of patients' and caregivers' lives (e.g. work, finances).¹⁶

Finally, patients with MCL who experience disease relapse and progression to later lines of treatment and/or disease progression experience an associated reduction in quality of life.⁵² Therefore, the improvements in FFS and PFS observed in TRIANGLE (see **Section 3e**) for patients treated with the ibrutinib regimen versus the ASCT regimen are anticipated to translate to improved patient quality of life. This is supported by feedback received from patients with MCL and their caregivers (n=10), who noted that "*increased life expectancy*" and "*slowing disease progression*" are the most important outcomes for new MCL treatments.¹⁶

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk

assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

What are the side effects?

Every medicine has its own **side effects** and the same medicine can produce different reactions in different people. Evidence of the safety of the ibrutinib regimen was collected for patients with untreated MCL who received at least one dose of ibrutinib in the TRIANGLE trial. These data are available in Section 2.5 of the **European public assessment report** available [here](#).

- In TRIANGLE, side effects were experienced in both treatment groups (Arm I and Arm A), with the most common side effects presented in **Table 2** below.
- In TRIANGLE, patients on the ibrutinib regimen (Arm I) stayed on their medication for a median of 28.5 months, which is more than five times longer than the 5.2 months for patients on receiving the ASCT regimen (Arm A).
- Over the whole study follow-up, the proportion of patients experiencing at least one treatment-emergent adverse event (TEAE) was comparable across treatment arms (9 in 10 patients for both treatment groups). This means that the ibrutinib regimen did not increase the risk of serious side effects or the risk of death related to side effects compared to existing treatment with the ASCT regimen, despite being given over five times longer duration.
- These results suggest that the ibrutinib regimen tends to have a better tolerability profile, meaning fewer serious side effects over time, compared to the ASCT regimen, when considering how long patients are treated.

The most common side effects experienced in both arms of the trial were blood and lymphatic system disorders with anaemia (low red blood cell count) reported in 4 in 10 patients receiving the ibrutinib regimen, and 6 in 10 patients receiving the ASCT regimen. The most common side effects, which affected at least 3 in 10 patients, are summarised in **Table 2** below:

Table 2. Summary of the most common (≥30%) side effects experienced by patients during TRIANGLE

Side effect	Proportion of patients with this side effect in TRIANGLE	
	Arm I	Arm A
Blood and lymphatic system disorders	75.1%	82.5%
Infections	70.2%	51.1%
Digestive system disorders	63.8%	70.9%

General disorders and reactions at the site of administration	54.3%	65.3%
Changes in blood test results	57.7%	57.8%
Nervous system disorders	50.9%	38.8%
Skin and under the skin disorders	34.3%	19.0%
Lung and breathing-related disorders	31.3%	23.5%
Metabolism and nutrition disorders	33.6%	35.8%
Muscle, bone or joint disorders	32.1%	21.3%

Note: further explanation of the terms in **bold** are provided in the glossary ([Section 4b](#)).

A complete list of all potential side effects associated with the ibrutinib regimen, including rare side effects, can be found in the [Patient Information Leaflet](#); available [here](#).

Managing side effects

The safety profile of the ibrutinib regimen is considered to be manageable for patients. This is shown by the fact that the side effects experienced by patients in the TRIANGLE trial were accompanied by low rate of treatment discontinuation and were generally perceived as being low in severity.

Bleeding-related side effects

Some patients treated with ibrutinib have reported bleeding-related side effects. These side effects can range from minor to major, and some major bleeds have been fatal, including gastrointestinal bleeding, bleeding inside the skull, and blood in the urine. Minor examples include easy bruising, nosebleeds, and small red spots on the skin.

To reduce the risk of bleeding-related side effects, the use of Warfarin and vitamin K antagonists should not be given at the same time as ibrutinib. Additionally, the use of **anticoagulants** or **antiplatelets** should be carefully considered. Ibrutinib should also not be administered between 3 and 7 days before or after surgery, due to the risk of bleeding.

Infections

Some patients treated with ibrutinib have reported infections, including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia (low white blood cells).

To reduce the risk of infections, patients treated with ibrutinib should be monitored for fever, liver function, low white blood cells. In the case of infection, appropriate treatment should be provided.

Heart-related side effects

Some patients treated with ibrutinib have reported fatal and serious heart rhythm problems and heart failure. There are several health factors which matter, including age, performance status, and existing heart conditions.

To reduce the risk of heart-related side effects, a thorough evaluation of heart history and function should be done before starting treatment with ibrutinib, and patients should be monitored during treatment for signs of heart problems; your doctor may order tests such as an **ECG (electrocardiogram)** or an **echocardiogram** (heart ultrasound) as needed.

Details on the management of side effects can be found in both the **Summary of Product Characteristics** of ibrutinib, available [here](#), and the **Patient Information Leaflet**; available [here](#).

Changes in ibrutinib dose received

The ibrutinib regimen was generally well tolerated in patients in the TRIANGLE trial and side effects resulting in the need for dose reduction or discontinuation were infrequent. In TRIANGLE, 2 in 10 patients discontinued treated with ibrutinib due to side effects, and 2 in 10 reduced their dose of ibrutinib due to side effects.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of the ibrutinib regimen for patients with MCL include:

High response rates and increased life expectancy: TRIANGLE demonstrates that treatment with the ibrutinib regimen results in high response rates for patients with untreated MCL, with over 9 in 10 patients responding to treatment. Importantly, these outcomes are achieved with a reduced toxicity burden compared with the more intensive treatment option of ASCT.

Beyond high response rates, treatment with the ibrutinib regimen leads to improved OS and FFS. This is particularly important for patients with MCL given that MCL has the worst prognosis among NHL subtypes.⁹ Of note, the number one treatment goal highlighted by patients with MCL as part of patient research was “*increased life expectancy*”, highlighting that extended survival is the most important factor for patients when choosing a treatment.¹⁶ As such, the ibrutinib regimen addresses the existing unmet need in UK clinical practice for a treatment option that is able to offer improved survival outcomes for these patients.

Well-characterised and manageable safety profile: As detailed in [Section 2c](#), the ASCT regimen is a highly toxic treatment option. In contrast, the ibrutinib regimen has a well-characterised safety profile with side effects that are known from its use as a treatment in second-line MCL, allowing doctors to effectively manage side effects with routine supportive care. In addition, In TRIANGLE, patients on the ibrutinib regimen stayed on their medication for a median of 28.5 months, which is more than five times longer than the 5.2 months for patients on receiving the ASCT regimen. Despite patients receiving treatment for over five times longer the total number of side effects from treatment with the ibrutinib regimen were similar to those experienced by patients receiving treatment with the ASCT regimen. The fact that patients can receive ibrutinib for a longer period of time while experiencing less severe and fewer side effects suggests that the ibrutinib regimen is a more manageable treatment for patients than the ASCT regimen. In addition, the number of deaths due to side effects was twice as high for patients receiving the ASCT regimen compared with the ibrutinib regimen, demonstrating the highly toxic nature and associated risk of death for the ASCT regimen. The greater tolerability of the ibrutinib regimen ultimately allows patients to stay on treatment with fewer or less intense side effects, improving the treatment experience for patients. Furthermore, the more tolerable safety profile of the ibrutinib regimen means that most patients are able to receive the full course of treatment without requiring dose modifications or reductions and therefore experience the full treatment benefits.

Improved treatment accessibility and reduced hospital stays: Of note, treatment with the ibrutinib regimen avoids consolidation therapy entirely; existing consolidation therapy, high-dose chemotherapy followed by ASCT, requires patients to remain in hospital for up to a month and then requires frequent hospital visits for weekly follow-ups and sometimes blood transfusions during the length recovery process.³⁷ Treatment with the ibrutinib regimen with its oral method of administration would therefore remove the requirement for lengthy hospital stays. This would minimise disruptions to both patients' and caregivers' lives freeing up their time to work and spend time with friends, whilst also helping to free up valuable NHS resources. Of note, patients with MCL who have undergone the ASCT regimen expressed their desire for alternative, more convenient treatment options as part of the patient research study conducted by J&J IM and therefore this benefit would be highly valued by patients:¹⁶

"There was so many tests and so many drugs and everything surrounded with the stem cell transplant, from preparing for actually taking the stem cells to putting them back in. It was just a really intense, long process. So, if there was an easier alternative, yeah, absolutely." – **Patient with MCL who received treatment with ASCT**

"I think if it was something that was known to be effective, I would go for something else. Yeah. Be it either tablets or infusion. I think the consultant in passing said, if it comes back, we've now got a tablet we can give you that will sort it out. Didn't go into details, but I thought, "well, that's reassuring" ... Given the opportunity to do something else that works, I would do something else [other than the transplant]." – Patient with MCL who received treatment with ASCT

Treatment choice: The ibrutinib regimen would provide an additional treatment option that allows patients to experience prolonged survival, and to avoid the toxicity associated with the ASCT regimen. Enabling patients to choose among first-line regimens and allowing clinicians to tailor treatment to individual needs are fundamental aspects of care that enhance patients' sense of control over their disease. The strong desire for alternative treatment options in this setting has been highlighted by patients with MCL who have undergone treatment with the ASCT regimen. Additionally, the effectiveness of the ibrutinib regimen in prolonging survival (**Section 3e**), is anticipated to decrease the anxiety associated with a MCL diagnosis for both patients and their caregivers.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Ibrutinib is generally well-tolerated and effective in leading to improved survival for patients, however, some things that patients may want to consider before starting treatment include:

Efficacy

Similar to all existing treatments for MCL, the ibrutinib regimen may not work for everyone, and therefore some patients may not respond to treatment or experience disease progression despite treatment. However, the results of TRIANGLE show that over 9 in 10 patients with untreated MCL responded to treatment with the ibrutinib regimen.⁴⁷ Additionally, treatment with the ibrutinib regimen resulted in substantially improved survival rates when compared with ASCT, as summarised in the TRIANGLE results section above (**Section 3e**). Patients for whom ibrutinib does not work may still experience side effects, which are detailed further below.

Side effects

Like all medicines, some patients may experience side effects while they are taking ibrutinib. The most common side effects are blood and lymphatic system disorders with anaemia (low red blood cell count) reported in 4 in 10 patients receiving the ibrutinib regimen.⁴⁷ Additionally, patients may experience gastrointestinal issues such as nausea, diarrhoea, vomiting or constipation. These side effects are monitored by a healthcare team throughout treatment. Further details of side effects can be found in **Section 3g**. These are usually manageable, and most patients do not need to stop treatment because of side effects – in the TRIANGLE trial, only 2 in 10 patients discontinued treatment due to side effects. In addition, ibrutinib is currently used in the UK for patients with MCL who

have already received one previous treatment, so doctors are familiar with how to effectively manage side effects.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. To assess this, they will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the health economic model to perform an analysis, which compares the costs and benefits of the new treatment (the ibrutinib regimen) with the existing treatment option (the ASCT regimen) over the lifetime of patients with MCL.

How the model reflects MCL

The economic model was designed to reflect the key features of MCL and clinical practice in the UK. To do this, a model structure called a **semi-Markov model** structure was chosen. This model structure predicts future survival outcomes based on clinical trial data described in **Section 3e**. The semi-Markov model was used to model the experience of having MCL over time and compares treatment with the ibrutinib regimen versus the ASCT regimen. The economic model consists of four health states, with 'failure-free' being the best health state:

- Failure-free: the patient's disease is responding to first-line treatment and improving
- Progression-free: the patient's disease is responding to second-line treatment and not actively progressing to more advanced stages

- Progressed: the patient's cancer has worsened and they are receiving third-line treatment
- Death

Modelling how much ibrutinib with immunochemotherapy improves survival

The results of TRIANGLE were used to inform the economic model, specifically movement from the failure-free health state to the progression-free health state or the death health state. The main result from TRIANGLE that was used to inform these movements in the model was FFS, as this is a good measure of what would be considered a successful outcome in patients receiving either the ibrutinib regimen or the ASCT-regimen in clinical practice (i.e., a measure of how long a patient's disease stays under control after starting first-line treatment; see [Section 3d](#)). For patients in the model who have moved out of the failure-free health state and remain alive receiving either second or third-line treatment, data from a different clinical trial (RAY-3001) were used to inform movement between health states.⁵³

The economic analysis models patients for the rest of their lifetime, a much longer period of time than the length of both TRIANGLE and RAY-3001. Therefore, the model uses extrapolations of TRIANGLE and RAY-3001 data to predict patients' long-term outcomes and therefore inform on the potential long-term benefits of the ibrutinib over the ASCT regimen. Further details are provided in the [Company Submission, Section 3.3](#).

Modelling how much the ibrutinib regimen improves quality of life

A decrease in quality of life was modelled when 1) a patient experiences treatment failure on first-line treatment and 2) a patient progresses on second-line treatment, to reflect the fact that the mental and emotional impact of MCL would likely be increased at both of these events. As TRIANGLE showed that the likelihood of experiencing treatment failure on first-line treatment with the ibrutinib regimen was lower than on first-line treatment with the ASCT regimen (see [Section 3e](#)), the anticipated improvements in patient quality of life associated with the ibrutinib regimen were captured in the economic model.

The quality of life data that informed the model were from the SHINE, RAY-3001 and SPARK studies.⁵³⁻⁵⁵ In these studies, quality of life was measured using a questionnaire called **European Quality of life-5 Dimensions-5 Levels (EQ-5D-5L)**, as this is considered a robust measure of quality of life.

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for the different MCL treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment

- The cost of subsequent treatments patients receive after disease progression
- The cost of end-of-life care

The ibrutinib regimen is expected to reduce some costs to the NHS compared to the ASCT regimen for patients with MCL. The key reasons for this include:

- Reduced cost of lengthy inpatient stays associated with the ASCT regimen
- Reduced cost of managing AEs associated with first-line treatment (i.e., lower AE management costs associated with the ibrutinib regimen versus the ASCT regimen), particularly through reducing the number of patients requiring intensive care unit stays following treatment
- Reduced costs associated with terminal care as less patients receiving the ibrutinib regimen are modelled to die versus patients receiving the ASCT regimen

Uncertainty

Although the most recent data from the trials were used in the model, there is uncertainty around how long patients would remain failure-free, progression-free and alive for each treatment, as data are only available for a certain duration of follow-up. Therefore, predictions on how long patients would remain alive were used and additional scenarios in the model were explored to minimise this uncertainty.

Variations of other inputs and assumptions in the model were also tested, and the results of these tests are explained in **Company Submission, Section 3.11**.

Overall, the results of the health economic model were consistent across all the different scenarios used, demonstrating that the uncertainty in patient outcomes has been properly accounted for.

Benefits of the ibrutinib regimen not captured in the economic analysis

Treatment with the ibrutinib regimen may have many different positive impacts for patients with MCL. The model aims to capture as many of these benefits as possible, but there are other benefits that could not be fully captured. For example:

- As noted in **Section 2c**, the ASCT regimen is a highly challenging treatment option for patients with MCL. Whilst the burden of AEs associated with the regimen is captured in the economic model, by removing the need for the ASCT regimen, the ibrutinib regimen will also reduce the substantial treatment burden beyond AEs, such as the need for long stays in hospital, the anxiety around increased risk of infection due a weakened immune system, and extensive monitoring and follow-ups throughout the lengthy recovery period
- Caregivers interviewed in the patient research study conducted by the Company reported that caring for a loved one undergoing treatment with the ASCT regimen was associated with an increased emotional, logistical and financial burden.¹⁶ By removing the need for the ASCT regimen, which requires intensive care during and

after treatment, caregivers of patients will experience a reduced emotional, logistical and financial burden, and enhanced quality of life

- By providing an additional treatment option for patients with MCL, the ibrutinib regimen allows patients to choose between treatments and clinicians to tailor treatment to patients' needs, improving the overall care they receive and enhancing patients' sense of control over their disease. Additionally, as the ibrutinib regimen extends survival among patients with MCL, the availability of a new, effective treatment option will likely reduce health-related anxiety among patients and their caregivers
- By reducing the number of and shortening the length of hospital stays, treatment with the ibrutinib regimen reduces the demand for hospital beds and helps relieve capacity constraints in healthcare facilities, which is particularly important given the resource constraints already faced by the NHS³⁸

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The ibrutinib regimen is an innovative treatment which would represent an important advancement in the treatment of patients with untreated MCL.

MCL is a condition that can have a significant effect on a patient's mental and emotional wellbeing and quality of life. Despite this, in current UK clinical practice, there is only one treatment option available to patients with untreated MCL: the ASCT regimen. The ASCT regimen is a highly toxic regimen which results in considerable burden for patients. This burden is exemplified by the high rate of side effects, and the lengthy hospital stays, experienced during and following treatment. Furthermore, the efficacy of the ASCT regimen has been put into question as disease relapse continues to occur, and disease-related deaths persist over time.⁴⁰

Ibrutinib is an innovative medicine that treats the underlying cause of disease. Of note, it would be the first treatment to be introduced for patients with untreated MCL in 20 years.⁵⁶ Patients treated with the ibrutinib regimen experience greater FFS, which results in greater disease control and a longer time before patients have to initiate any further treatments. For patients with MCL, improving disease and delaying subsequent treatment is a key treatment goal, as each additional treatment is associated with an increased symptom burden and an accompanying reduction in patients quality of life.⁹ In addition to improvements in FFS, treatment with the ibrutinib regimen demonstrated delayed time to disease progression and subsequent improvements in survival outcomes; at the latest clinical cut-off of TRIANGLE (see **Section 3g**) nearly twice as many patients receiving treatment with the ASCT regimen had died compared to those receiving the ibrutinib regimen. These results translated to patients receiving the new ibrutinib regimen having a 48% lower chance of dying compared to those receiving treatment with the ASCT

regimen. This is particularly important for patients with MCL given that MCL has the worst prognosis among NHL subtypes.⁹

Beyond the improved survival outcomes, the ibrutinib regimen is able to deliver effective disease control with fewer side effects. Treatment with the ibrutinib regimen offers a more tolerable treatment compared with the ASCT regimen, which is an intensive treatment for patients. Finally, ibrutinib is an oral treatment that patients can take at home, providing patients with a convenient option that reduces the need for lengthy overnight hospital stays.

In summary, the ibrutinib regimen would address the significant unmet need among untreated MCL patients by providing patients and their clinicians with an effective treatment option which can delay or prevent disease progression and would avoid the need for patients to undergo the toxic ASCT regimen. A positive recommendation of the ibrutinib regimen by NICE would represent a step-change in the management of MCL since the introduction of ASCT over 20 years ago.

3I) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues [here](#)

There are no equality issues that are anticipated for the use of the ibrutinib regimen in adult patients with untreated MCL who are eligible for ASCT.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information on MCL:

- Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline: <https://onlinelibrary.wiley.com/doi/10.1111/bjh.19131>
- Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: [https://www.annalsofoncology.org/article/S0923-7534\(19\)42151-0/fulltext](https://www.annalsofoncology.org/article/S0923-7534(19)42151-0/fulltext)
- NICE guidelines for the diagnosis and management of NHL: <https://www.nice.org.uk/guidance/ng52/chapter/Recommendations>
- Cancer Research UK: Mantle cell lymphoma: <https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell>
- Macmillan Cancer Support: Stage and grade of non-Hodgkin lymphoma: <https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/non-hodgkin/staging-and-grading>
- Blood Cancer United: Mantle cell lymphoma: <https://bloodcancerunited.org/research/blood-cancer-research-development-progress/lymphoma/mantle-cell-lymphoma-mcl>

Further information on NICE and the role of patients:

- Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE: <https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **black bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Active monitoring

A treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are signs or symptoms that show the condition is getting worse.

Advanced

Stage 3 or Stage 4 MCL.

Anticoagulants

Medicines to reduce clotting in the blood vessels.

Antiplatelets

Medicines that prevent platelets from sticking together to form clots. They help reduce the risk of heart attack or stroke in people with certain heart or blood vessel conditions.

Autologous stem cell transplant (ASCT)

A procedure in which a patient's healthy stem cells are collected from the blood or bone marrow before treatment, stored, and then given back to the patient after treatment. A stem cell transplant replaces a patient's stem cells that were destroyed by treatment with high doses of chemotherapy.

Aggressive MCL

A fast-growing form of MCL, where the cancer cells are rapidly dividing. This means that the cancer cells grow and spread more quickly than **indolent** MCL.

B cells

A type of white blood cell in the immune system that help to fight infections.

BEAC

High-dose chemotherapy regimen composed of carmustine, etoposide, cytarabine, and cyclophosphamide.

BEAM

High-dose chemotherapy regimen composed of carmustine, cytarabine, and melphalan.

Blood and lymphatic system disorders

Side effects that affect the blood and/or the lymphatic system, including components such as red and white blood cells, platelets, plasma, and parts of the lymphatic system (lymph nodes, lymph vessels, spleen, thymus, bone marrow).

Blood transfusions

A medical procedure in which donated blood or specific components of blood (such as red blood cells, platelets, or plasma) are given through a vein to replace blood or blood parts that are low or not functioning properly due to illness, surgery, or treatment.

Bone marrow

A soft, spongy tissue inside most bones where blood cells (red blood cells, white blood cells and platelets) are made.

Bone marrow stem cells

Immature cells in the bone marrow that can develop into all the different types of blood cells (red cells, white cells, and platelets).

Bruton's tyrosine kinase (BTK) inhibitor

A type of targeted therapy that block a **protein** called BTK, which helps cancer cells to survive and continue to multiply.

Clinical practice

The agreed-upon and customary means of delivering health care by doctors, nurses and other healthcare professionals.

Clinical trial

A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease.

Changes in blood test results

Side effects that affect the number of blood cells in the body, including **white blood cells**.

Complete response

The disappearance of all signs of cancer in response to treatment. However, this does not always mean the cancer has been cured.

Complete response rate	The percentage of patients in a group who achieve complete response .
Computerised tomography (CT)	A procedure that uses a computer and an x-ray machine to make a series of detailed pictures of areas inside the body. The pictures are taken from different angles and are used to create 3-dimensional (3D) views of tissues and organs. A dye may be injected into a vein or swallowed to help the tissues and organs show up more clearly.
Consolidation therapy	A planned course of treatment given after the initial therapy to consolidate the response, aiming to kill any remaining cancer cells and prolong response.
Diaphragm	The sheet of muscle that separates your chest from your tummy.
Digestive system disorders	Side effects that affect the organs involved in digestion (mouth, oesophagus, stomach, intestines, liver, gallbladder and pancreas) and can impact digestion, nutrient absorption or waste elimination.
ECG (electrocardiogram)	A test that records the heart's electrical activity to assess heart rhythm and conduction.
Echocardiogram	An ultrasound imaging procedure that creates a moving picture outline of the heart's valves and chambers using high-frequency sound waves that come from a handheld wand placed on your chest or passed down your throat.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial .
European Medicines Agency (EMA)	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.

European Quality of life-5 Dimensions-5 Levels (EQ-5D-5L)

A self-reported measure of current health covering five areas (mobility, self-care, usual activities, pain/discomfort and anxiety/ depression) which includes five response categories

'Extranodal' lymphoma

A type of lymphoma that occurs outside the lymph nodes, in other organs or tissues (for example, stomach, skin, brain).

Failure free survival

The length of time during and after the treatment of a disease, such as cancer, that a patient's disease improves. In a clinical trial, measuring the FFS is one way to see how well a new treatment works.

Gastrointestinal tract

The organs that food and liquids travel through when they are swallowed and digested, before leaving the body as faeces. These organs include the mouth, pharynx (throat), oesophagus, stomach, small intestine, large intestine, rectum, and anus. The gastrointestinal tract is part of the digestive system.

General disorders

A broad group of symptoms that affect the whole body or do not fit a specific organ system, such as fatigue, fever, night sweats, weight loss, malaise, weakness and sleep problems.

Grade

A description of cancer cells based on how quickly they are likely to grow and spread. **Indolent** cancer cells look more like normal cells and tend to grow and spread more slowly than aggressive cancer cells.

Health economic model

A tool used to compare the costs and benefits of different treatments. It helps decision-makers understand whether a new treatment is worth the money.

Hodgkin lymphomas

A cancer of the immune system where there is a certain type of cell called the 'Reed-Sternberg cell'. Signs and symptoms include painless, swollen lymph nodes, an enlarged spleen, fever, weight loss, extreme tiredness and night sweats.

Ibrutinib with immunotherapy

The induction therapy of the ibrutinib regimen which is composed of ibrutinib in combination with **R-CHOP** alternating with **R-DHAP (or R-DHAox)** without ibrutinib

Immune system

A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.

Indolent

A type of cancer that tends to grow and spread slowly and has few symptoms. Also called low-grade cancer.

Induction therapy

The first treatment given for a disease. If it does not cure the disease or it causes severe side effects, other treatment may be added or used instead.

Infections

Conditions which can be passed from person to person by micro-organisms like viruses or bacteria.

Intravenous (IV)

The method by which some cancer drugs are diluted in a bag of fluid which is connected to a very thin tube and goes into one of your veins.

Lactate dehydrogenase

A group of proteins found in the blood and other body tissues. An increased amount of lactate dehydrogenase in the blood may be a sign of cancer.

Lung and breathing-related disorders

Side effects that affect the lungs or airways and can make breathing harder or different, causing symptoms like cough, shortness of breath, chest tightness or wheeze.

Lymphatic system

The tissues and organs that produce, store and carry white blood cells. This system includes the bone marrow, spleen, thymus, lymph nodes and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells).

Lymph node

Small, bean-shaped organs that are part of the lymphatic system and help fight infections. These may swell with infections or cancer.

Lymphoma	A cancer of the lymphatic system. Non-Hodgkin lymphoma is a type of lymphoma.
Lymphocytes	A type of white blood cell in the immune system that help to fight infections.
Maintenance therapy	Maintenance therapy is a long-term treatment that is usually given over several years. The aim of maintenance therapy is to keep any cancer cells that may be left in the body under control.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
MCL cells	Unhealthy B cells which do not perform their normal function in the immune system. These are the cells which are responsible for mantle cell lymphoma.
Medicines and Healthcare products Regulatory Agency (MHRA)	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
Metabolism and nutrition disorders	Side effects that affect how the body uses or stores energy and nutrients, including problems with metabolism, digestion and nutrient absorption.
Monoclonal antibody	A type of protein that is made in the laboratory and can bind to certain targets in the body. Monoclonal antibodies are used in the treatment of many diseases, including MCL.
Muscle, bone or joint disorders	Side effects that affect muscles, bones or joints, causing pain, weakness, stiffness, or reduced movement and function.
Nervous system disorders	Side effects that affect the brain, spinal cord or nerves, which can alter sensation, movement, thinking or balance.

Non-Hodgkin lymphomas (NHL)	A large group of different types of cancer which affect the lymphocytes.
Overall response rate (ORR)	The percentage of patients in a group who achieve complete response or partial response .
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works.
Partial response (PR)	A decrease in the size of the cancer, or in the extent of cancer in the body, in response to treatment.
Performance status	A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.
Phase 3 clinical trial	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects .
Platelets	A tiny, disc-shaped cell that is found in the blood and spleen. They help form blood clots to slow or stop bleeding and help wounds heal.
Positron emission tomography (PET)	A procedure in which a small amount of radioactive substance is injected into a vein, and a scanner is used to make detailed, computerised pictures of areas inside the body.
Prognosis	This gives an idea about whether the cancer can be cured and what may happen in the future.
Prognostic factors	A characteristic of a patient that can be used to estimate the chance of recovery from a disease or the chance of the disease coming back later in life.

Progression-free survival (PFS)

The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works.

Protein

Structures inside all cells of our body that are important for many activities including growth, repair and signalling. They are the basis of body structures, such as skin and hair.

Quality of life

The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.

R-CHOP

Immunochemotherapy which is a combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.

R-DHAOx

Immunochemotherapy which is a combination of rituximab, dexamethasone, cytarabine and oxaliplatin.

R-DHAP

Immunochemotherapy which is a combination of rituximab, dexamethasone, cytarabine and cisplatin.

R-HDAC

Immunochemotherapy which is a combination of rituximab and high dose cytarabine.

Red blood cells

A type of blood cell that is made in the bone marrow and found in the blood. It has a range of functions in the body, including the transport of oxygen.

Regulatory bodies

These are legal bodies that review the quality, **safety** and **efficacy** of medicines and medical technologies.

Relapse

The return of a disease or the signs and symptoms of a disease after a period of improvement

Refractory	A disease or condition that is resistant to treatment and fails to respond to standard therapies, often requiring more aggressive or alternative approaches.
Safety	The number and severity of side effects.
Semi-Markov model	A mathematical way to predict how patients move between different health states over time and how this affects costs and outcomes.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Skin and under the skin disorders	Side effects that affect the skin and the tissue beneath the skin (subcutaneous tissue), including inflammation, rashes, ulcers, lumps and other abnormalities.
Specialist	An experienced doctor who only provides care for a specific range of medical conditions.
Spleen	An organ behind the rib cage that helps filter blood and helps fight infection.
Stage	A description of how severe a disease is.
Targeted therapy	Targeted cancer drugs work by 'targeting' the differences between a cancer cell and normal cell that help cancer cells survive and grow. As these therapies target cancer cells specifically, they limit damage to healthy parts of the body.
Tolerated	The ability of a patient to put up with the side effects of treatment.
White blood cells	These are cells in the body that fight disease and infection by attacking and killing germs.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Clarification questions

February 2026

File name	Version	Contains confidential information	Date
ID6596_ibrutinib_clarification questions_25Feb26_Redacted	V1.0	Yes	25 th February 2026

Section A: Clarification on effectiveness data (Heading 1)

Literature searches (Heading 2)

A 1. Priority question. The PRISMA flowcharts in the Appendices (Figures 1, 2 and 4) do not give complete and separate details of the numbers of results found in the original searches and the two updates. The EAG were also unable to discern the numbers of results for the cost and healthcare resource identification searches from the flowchart in Figure 2. Please provide new PRISMA flowcharts, one for each search, which accurately reflect the figures given in the text.

Clinical SLR

The Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) for the original clinical SLR, the first update and the second update are presented in Appendix D 1. Figure 9- Figure 11.

Economic SLR

The PRISMA for the original economic SLR, the first update and the second update, split by economic evaluation and cost and healthcare resource use (HCRU) are presented in Appendix D 2. Figure 12 – Figure 17.

Health-related quality of life (HRQoL) SLR

The PRISMA for the original HRQoL SLR, the first update and the second update are presented in Appendix D 3. Figure 18 – Figure 20.

Decision problem

A 2. Priority question. The intervention in the decision problem (DP) is a combination of ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (IMBRUVICA + R-CHOP) alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy (+/- rituximab), and therefore excludes allogeneic stem cell transplant (ASCT). The CS states that this is in line with the marketing authorisation, and that combination with ASCT would be off-label. However, the NICE scope states: “...with or without ASCT”. Also, the European Public Assessment Report (EPAR) states: *“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”.*

- a) Is ibrutinib +R-CHOP followed by ASCT used in UK clinical practice, and if so then for which percentage of patients?
- b) Please clarify whether ibrutinib +R-CHOP followed by ASCT could be used in clinical practice, supported by reference to the marketing authorisation and clinical expert opinion as required.
- c) What might be the percentage use in UK clinical practice if ibrutinib + R-CHOP were recommended by NICE?

d) If ibrutinib +R-CHOP followed by ASCT is used or might be used in UK clinical practice then, informed by all three arms of TRIANGLE (I+A, I and A), please provide a comparison of clinical effectiveness and cost effectiveness between the three sets of treatments i.e.:

- i. **ibrutinib + R-CHOP followed by ASCT followed by maintenance with ibrutinib +/- rituximab,**
- ii. **the current intervention in the DP i.e. ibrutinib + R-CHOP followed by maintenance with ibrutinib + rituximab +/-, and**
- iii. **the comparator in the DP i.e. R-CHOP alternating with R-DHAP or R-DHAOx (or NORDIC chemotherapy regimen) followed by ASCT +/- rituximab maintenance.**

This submission covers the full UK marketing authorisation for the ibrutinib regimen in the indication under consideration: ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) alternating with rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin [R-DHAOx]) without ibrutinib, followed by ibrutinib monotherapy for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who would be eligible for autologous stem cell transplantation (ASCT).¹

As detailed in the SmPC on the MHRA website, and in Section 1.2 of the Company Submission (CS), the use of ibrutinib in combination with ASCT in this indication is not licensed for use in UK clinical practice.¹ As such, the use of ibrutinib in combination with ASCT represents off-label treatment and is not relevant for UK decision making. This is supported by the fact that the BSH guidelines recommend the usage of ibrutinib explicitly in place of ASCT if licensed and reimbursed. The use of ibrutinib in combination with ASCT is therefore not expected in UK clinical practice.²

Clinical effectiveness evidence

A 3. Priority question. The May 2024 data cut-off (DCO) was used for the TRIANGLE trial results, at which point the median survival for any time to event outcome including failure-free survival (FFS), overall survival (OS) or progression free survival (PFS) had not been reached. Could the company please provide all results at a later DCO if data are available?

As detailed in Section 2.2 of the CS, the data presented within the CS are based on the [REDACTED] clinical cut-off (CCO) of TRIANGLE (09 May 2024). TRIANGLE was an investigator-initiated trial, therefore,

Johnson & Johnson Innovative Medicine (herein referred to as Johnson & Johnson) do not have any oversight on the publication plans of any upcoming data cuts.³ It is additionally important to note that whilst the TRIANGLE study is ongoing, any further data-cuts would be in the Intent-To-Treat (ITT) analysis. No further data cut-offs in the Full Analysis Set (FAS), the analysis set informing the ongoing CS will be made available. Therefore, this is the [REDACTED] DCO available from TRIANGLE for the purpose of UK decision-making.

A 4. Priority question. Regarding the generalisability of the TRIANGLE trial:

- a) please provide a comparison between the baseline characteristics in TRIANGLE and those adults with untreated MCL when an ASCT is suitable as would be observed in UK clinical practice.

As described in CS Section 1.3.2, MCL is a rare subtype of Non-Hodgkin's Lymphoma (NHL).⁴ As such, there is a paucity of published data on patients with untreated MCL who would be eligible for ASCT in the UK.

The complete baseline characteristics of patients in the FAS in TRIANGLE (09 May 2024 CCO) are presented in Section 3.3; Table 6 of the CS. Across both treatment arms, baseline demographics such as sex, weight and body mass index (BMI) were well balanced and reflective of UK clinical practice. Patients had a median age of 57 years (range 27, 65) across both treatment arms; which is largely consistent with UK clinical practice in which ASCT is only considered suitable for patients $\leq$ 65 years.⁵ Furthermore, as MCL most commonly occurs in men, the higher proportion of males in TRIANGLE (Arm I: 79.9%, Arm A: 76.2%) is in line with UK clinical practice, where men make up the majority (65%) of MCL cases in the UK.⁶

To the best of Johnson & Johnsons' knowledge, the only UK real-world evidence (RWE) against which the TRIANGLE baseline characteristics could be compared is a 2018 study by Smith *et al.* reporting data from the UK, population-based Haematological Malignancy Research Network (HMRN).⁷ The study investigated disease management in 335 patients with MCL in both the first-line and r/r setting; of these, only 20 patients with MCL received first-line chemotherapy or immunochemotherapy followed by an ASCT transplant and therefore are relevant to the population addressed within this appraisal.⁷ The available baseline characteristics for this patient population presented alongside the baseline characteristics from Arm I and Arm A of the FAS population of TRIANGLE (09 May 2024 CCO) are presented in Table 1 below.

The baseline characteristics presented in Table 1 demonstrate that, of the available data, the baseline characteristics of patients enrolled in TRIANGLE are highly comparable with respect to age, Eastern Cooperative Oncology Group (ECOG) performance score (PS) and Ann Arbor stage and broadly comparable with respect to sex and MCL international prognostic index (MIPI) risk, to relevant patients in UK clinical practice. The data from Smith *et al.* therefore provide confidence that the patient population enrolled in TRIANGLE are highly generalisable to ASCT-eligible patients with untreated MCL in UK clinical practice.

Johnson & Johnson however acknowledge that owing to the rarity of the MCL, the sample size reported in Smith *et al.* is small. As such, in the absence of extensive RWE data, clinical expert

opinion represents the best available additional evidence to evaluate the generalisability of TRIANGLE to UK clinical practice. As such, the generalisability of the TRIANGLE trial population to UK clinical practice was further supported by validation from UK clinical experts in MCL. All clinical experts unanimously agreed that the baseline demographic and disease characteristics of the TRIANGLE FAS population were broadly generalisable to ASCT-eligible patients with untreated MCL in the UK.⁸ Finally, UK clinical experts noted that a key strength of TRIANGLE is that it was conducted across multiple European countries which have similar demographics to those observed in the UK, as supported by the high comparability of the TRIANGLE trial baseline characteristics to those reported in Smith *et al.* (Table 1).

Collectively these data provide confidence that the overall baseline demographic and disease characteristics of patients in TRIANGLE are aligned to the population of patients who would be anticipated to receive ibrutinib in UK clinical practice, with the exception of the slight discrepancy in the distribution of MIPI risk and reduced rituximab maintenance usage (addressed in Question A4b) below).

Table 1: Baseline characteristics of TRIANGLE FAS and Smith *et al.*

Baseline Characteristic	Arm I (N=268)	Arm A (N=269)	Smith <i>et al.</i> : ASCT (N=20)
Age, years			
Median (range)	57.0 (27, 65)	57.0 (31, 65)	57.3 (35, 66)
Sex, n (%)			
Male	214 (79.9%)	205 (76.2%)	13 (65.0%)
MIPI risk group			
High risk	40 (14.9%)	41 (15.2%)	5 (25.0%)
ECOG PS			
0	187 (70.0%)	191 (71.8%)	20 (100%)
1	75 (28.1%)	71 (26.7%)	
Ann Arbor stage			
III	26 (9.7%)	22 (8.2%)	18 (94.7%)
IV	226 (84.3%)	236 (88.4%)	

Abbreviations: ECOG: Eastern Cooperative Oncology Group; FAS: Full Analysis Set; MIPI: MCL international prognostic index; PS: performance status.

Source: EMA. Assessment Report: Imbruvica (2025),⁵ Smith (2018).⁷

- b) Please comment on the effect of any differences, making reference to subgroup analyses and clinical expert opinion.

As detailed in the response to Question A4a) above, the baseline characteristics of patients in TRIANGLE were well balanced between treatment arms, and representative of adult patients with untreated MCL who would be eligible for ASCT in UK clinical practice. This was supported by UK RWE reported in Smith *et al.* and feedback received from five UK clinical experts during the November 2025 advisory board. The only slight discrepancies identified were the slightly lower proportion of patients with a high-risk MIPI score in TRIANGLE vs Smith *et al.* and the reduced rituximab maintenance use in TRIANGLE noted by UK clinical experts.^{7, 8}

Regarding MIPI risk, whilst the proportion of patients with a high MIPI risk was reported to be slightly higher in the UK RWE study by Smith *et al.* versus TRIANGLE, the distribution of MIPI risk reported in TRIANGLE was well balanced between treatment arms and therefore would not impact the relative efficacy of the ASCT regimen compared to the ibrutinib regimen. The relative effect demonstrated within TRIANGLE can therefore be considered generalisable to UK clinical practice

Furthermore, UK clinical experts highlighted that the only key difference between TRIANGLE and UK clinical practice was the proportion of patients who received rituximab maintenance therapy. Clinicians noted that the proportion of patients receiving rituximab maintenance therapy in TRIANGLE (Arm I: 60%, Arm A: 63%) was lower than the proportion anticipated to receive rituximab maintenance in UK clinical practice (85%). Importantly, evidence supporting the use of rituximab in this treatment setting was not established when the protocol was developed for TRIANGLE.⁹ Therefore, rituximab maintenance was not considered a study treatment in TRIANGLE.³ However, following the publication of evidence supporting rituximab maintenance treatment,¹⁰ and upon its implementation into the national treatment guidelines for a participating country, rituximab maintenance was administered to patients across all arms per the recommendation of the site's study group.³ This ensured the decision to administer rituximab maintenance was consistent across all treatment arms to avoid treatment-related bias. Importantly, as the proportion of patients receiving rituximab maintenance was balanced between trial arms, the discrepancy in rituximab use versus UK clinical practice is not anticipated to impact the generalisability of the relative treatment effect observed between the ibrutinib regimen and the ASCT regimen in TRIANGLE.

Subgroup analyses were performed on the primary endpoint (FFS) in the FAS analysis set based on receipt of rituximab maintenance, with the results presented in Section 2.8 of the CS. Of note, however, given that rituximab maintenance was only provided following completion of induction treatment in Arm I or consolidation ASCT in Arm A, these results should be interpreted with caution given the rituximab "yes" subgroup represents an enriched population of patients that successfully completed induction with ibrutinib or consolidation with ASCT.⁵ As such, the subgroups are based on a selection of patients which can break the balance of populations that randomisation ensures, thus eliminating the guarantee that treatment groups are comparable, introducing selection bias and confounding. Furthermore, the subgroup analysis was not powered to detect differences in treatment effect, and owing to the small patient numbers associated with these subgroups, these results should be interpreted with caution. Given that these subgroup analyses are subject to bias, alternative approaches to explore the difference in rituximab maintenance use was explored in a sensitivity analyses.

In this sensitivity analyses an inverse probability of censoring weighting (IPCW)-adjusted analyses was conducted in which the proportion of patients receiving rituximab maintenance in both arms was adjusted to reflect the anticipated use in UK clinical practice (85%). The methods and results of these analyses are presented in full in Section 2.9 of the CS, and an overview of the results are reproduced in Table 2 below for clarity. Importantly, the sensitivity analyses presented adjusted for any potential bias arising due to selection and confounding, which is a key limitation of the TRIANGLE subgroup analyses described above.

The results of the IPCW-adjusted analyses, demonstrate that the FFS and OS hazard ratios (HRs) from the IPCW-adjusted analyses are highly consistent with those observed in the unadjusted analyses. These results therefore demonstrate that the relative treatment effect of the ibrutinib

regimen vs. the ASCT regimen observed in TRIANGLE is robust to variations in the proportion of maintenance rituximab used, as long as the proportion is consistent across arms. These results therefore provide confidence that the slight differences between the use of rituximab maintenance in TRIANGLE vs UK clinical practice does not impact the generalisability of the relative treatment effect of the ibrutinib regimen versus the ASCT regimen observed in TRIANGLE to UK clinical practice.

Table 2: Results from the IPCW-adjusted 85% rituximab use and unadjusted analysis (TRIANGLE; FAS)

Endpoint	IPCW-adjusted analysis (85%)	Unadjusted analysis
FFS, HR (95% CI)	████ (████) p-value: █████	████ (████) ^a p-value: █████
OS, HR (95% CI)	████ (████) p-value: █████	████ (████) p-value: █████

Footnotes: ^a98.33% CI.
Abbreviations: CI: confidence interval; HR: hazard ratio; FAS: full analysis set; FFS: failure-free survival; OS: overall survival
Source: J&J IM. Data on File. Rituximab Analysis Report.¹¹

A 5. Priority question. The CS states that for the IPCW-adjusted analysis it is assumed that 85% of patients would receive rituximab maintenance therapy, which is stated to have been based on clinical expert opinion. However, the Advisory Board Report from November 2025, which the company refers to shows that the question posed to the clinical experts was whether or not the 85% was appropriate, as opposed to what the figure ought to be. Also, it appears from the responses from one of the experts that there might have been a misunderstanding of why the percentage was not 100%: one stated that it was based on the outcome of the LyMA trial, but this trial compared rituximab maintenance with no maintenance. Another stated that early progression might be the reason for less than 100%. Also, the European Society for Medical Oncology (ESMO) and British Society of Haematology (BSH) guidelines both recommend rituximab maintenance.

a) Please clarify what the basis of the 85% was i.e. what this figure was presented to the clinical experts.

During the March 2025 Advisory Board, four UK clinical experts were asked an open ended question on the use of rituximab maintenance therapy in UK clinical practice. The clinicians subsequently reached a consensus decision that 85% of patients receiving the ASCT regimen in TRIANGLE would receive rituximab maintenance therapy.¹² This value was further validated during the November 2025 Advisory Board, where five UK clinical experts unanimously agreed that 85%

rituximab maintenance use for the ASCT regimen is an accurate reflection of UK clinical practice. Additionally, the experts confirmed that the same proportion of patients would be anticipated to receive rituximab maintenance if treated with the ibrutinib regimen.⁸

b) Please clarify what the reason for less than 100% would be.

Various reasons were provided by UK clinical experts for rituximab maintenance usage not being 100% in UK clinical practice. For example, during the March 2025 Advisory Board, a UK clinical expert noted that patients may not receive rituximab maintenance due to having infections which prevent them from receiving treatment. Furthermore, it was noted that some patients don't receive rituximab maintenance because they are unable to travel every other month to a tertiary care centre where rituximab is administered.¹² Additional discussions amongst the five UK clinical experts at the November 2025 Advisory Board noted that patients with early progression events following completion of induction and consolidation treatment would result in them not receiving maintenance therapy.⁸ Overall, as noted in response to Question A5a) above, all UK clinical experts consulted at both the March and November 2025 Advisory Boards unanimously agreed that rituximab maintenance usage would not be 100% in UK clinical practice.^{8, 12} It is additionally noted that patients with chronic lung disease or Hepatitis B exposure may not receive rituximab as a maintenance treatment.^{13, 14} Furthermore, patients who experience severe rituximab toxicities, or have other negative experiences during the induction-phase linked to rituximab treatment, may decline rituximab maintenance treatment.

c) Please consider a sensitivity analysis where 100% is assumed.

As highlighted in the responses to Question A5a) and A5b) above, in UK clinical practice it is not anticipated that 100% of patients with MCL would receive rituximab maintenance for first-line treatment. Therefore, a sensitivity analysis where 100% of patients receive rituximab maintenance therapy is not reflective of UK clinical practice nor relevant for UK decision-making.

However, for completeness and transparency, an IPCW-adjusted analyses in which 100% of patients in both Arm I and Arm A of TRIANGLE were simulated to receive rituximab maintenance was conducted. Full details on the methods of adjustment for this analysis are provided in Section 2.9, Step 1 of the CS. Results of the IPCW-adjusted analysis (100%) are presented alongside the unadjusted FAS results in Table 3. Associated KMs for the adjusted analysis are presented in Figure 1 and Figure 2.

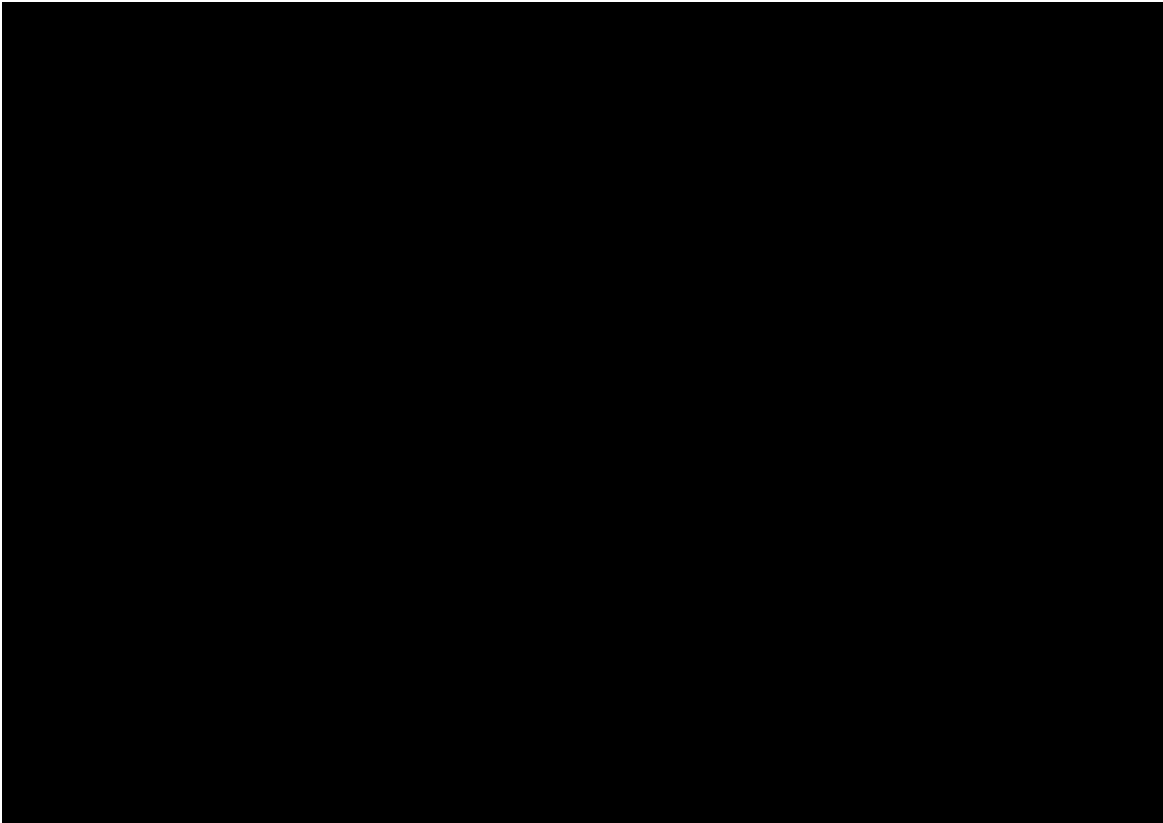
After IPCW adjustment to simulate 100% of patients in TRIANGLE receiving rituximab maintenance therapy, Arm I remained nominally significantly superior to the Arm A across all key endpoints assessed. As these significance tests were not pre-specified, results deemed significant through the two-sided tests are referred to as nominally significant throughout these clarification question responses. Importantly the FFS and OS HRs observed from the IPCW adjusted analyses were highly consistent with those observed in the unadjusted analyses. These results therefore demonstrate that the relative treatment effect of the ibrutinib regimen vs. the ASCT regimen observed in TRIANGLE is robust to variations in the proportion of maintenance rituximab used.

Table 3: Results from the IPCW-adjusted 100% rituximab use and unadjusted analysis (TRIANGLE; FAS)

Endpoint	IPCW-adjusted analysis (100%)	Unadjusted analysis
FFS, HR (95% CI)	████ (████████) p-value: █████	████ (████████) p-value: █████
OS, HR (95% CI)	████ (████████) p-value: █████	████ (████████) p-value: █████

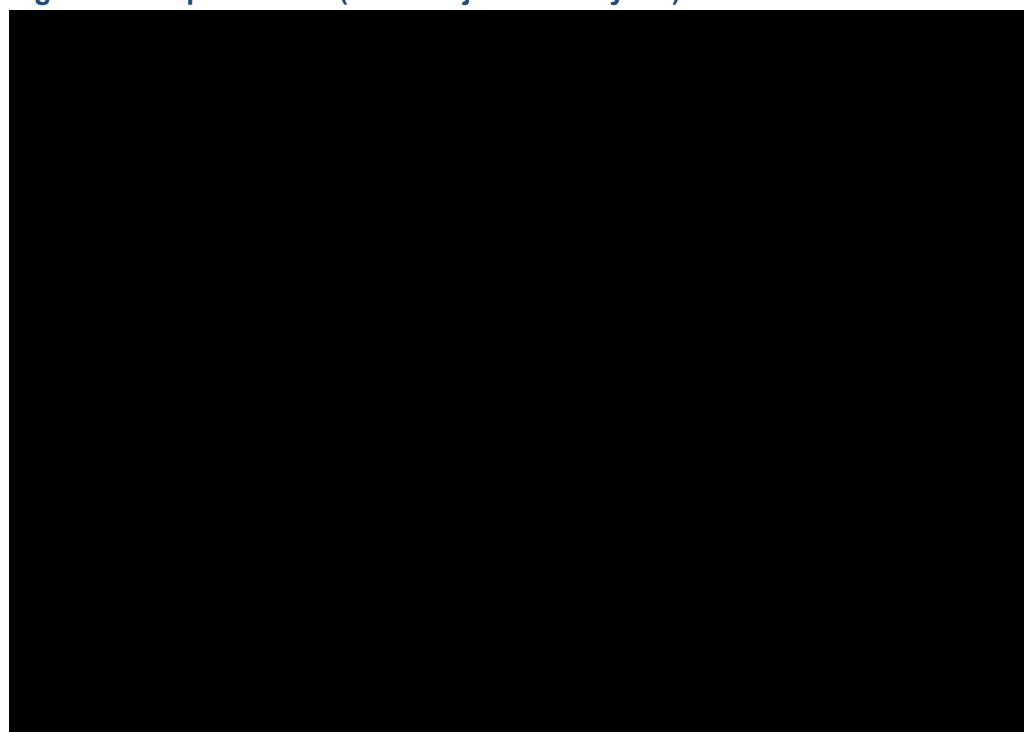
Footnotes:
Abbreviations: CI: confidence interval; HR: hazard ratio; FAS: full analysis set; FFS: failure-free survival; OS: overall survival

Figure 1: KM plot for FFS (IPCW-adjusted analyses)



Abbreviations: A: Arm A; FFS: failure-free survival; I: Arm I; KM: Kaplan-Meier; MCL: mantle cell lymphoma.

Figure 2: KM plot for OS (IPCW-adjusted analyses)



Abbreviations: A:

Arm A; I: Arm I; KM: Kaplan-Meier; MCL: mantle cell lymphoma; OS: overall survival.

A 6. Priority question. The inverse probability of censoring weighting (IPCW) method was used to adjust for insufficient rituximab maintenance in the TRIANGLE trial in comparison to clinical practice. The EAG consider that the need for such adjustment is analogous to treatment switching to a treatment that is not used in clinical practice for which IPCW is also used, although other methods are available and recommended in NICE TSD 16.

a) Please justify the use of IPCW as opposed to any other method of adjustment.

NICE DSU Technical Support Document (TSD) 16 recommends rank-preserving structural failure time model (RPSFTM), inverse probability of censoring weighting (IPCW) and two-stage estimation (TSE) as appropriate methods to address bias arising from treatment switching or deviations from the intended treatment pathway, with method selection driven by the nature of treatment switching and the plausibility of the underlying assumptions.¹⁵

RPSFTM methods are best suited to simple, direct treatment switching patterns, typically involving switching from a control arm to a single active treatment. This is not the case in TRIANGLE, where adjustment for the lower proportion of patients receiving rituximab maintenance is required in both treatment arms, rendering this approach unsuitable.

TSE methods were considered appropriate in principle, assuming a clinically meaningful secondary baseline, and were therefore explored. The results of these analyses are presented in response to Question A6b), below. In TRIANGLE, the start of ibrutinib maintenance in Arm I and the start of ASCT in arm A were used as secondary baselines. However, implementation of TSE requires several additional modelling choices, including selection of parametric survival models for each treatment arm in stage-1 estimation of the acceleration factor, decisions regarding re-censoring versus no re-censoring when deriving counterfactual survival, and identification and adjustment for time-varying confounding at the secondary baseline, which introduce additional complexity and potential sensitivity.

IPCW was therefore selected as the primary method of adjustment, as it provides a more direct adjustment approach by censoring at the potential start time of receiving rituximab maintenance treatment and re-weighting the remaining patients with similar characteristics (both baseline and time-varying), thereby preserving the randomised cohorts. Relevant baseline and time varying covariates were available in TRIANGLE and a sufficient number of patients continued rituximab maintenance in TRIANGLE to support stable and reliable weight estimation.

- b) Please consider using alternative statistical approaches (e.g. two-stage estimation [TSE] approach) to perform statistical adjustment for the analyses of the TRIANGLE trial.

Given the rationale provided in the response to Question A6a) above, Johnson & Johnson maintain that the IPCW approach was the most appropriate statistical adjustment methods to account for the reduced rituximab maintenance observed in TRIANGLE. However, for completeness, a TSE analyses assuming the same parametric distribution for both treatment arms and using the same set of prognostic factors as the IPCW analyses presented in the CS was performed.

TSE was implemented using the start of ibrutinib maintenance in Arm I and the start of ASCT in Arm A as the secondary baseline. In stage 1, parametric accelerated failure time (AFT) models were fitted from the secondary baseline, adjusting for prognostic factors, to estimate the acceleration factor associated with receiving rituximab maintenance versus not receiving rituximab maintenance. In stage 2, observed post-secondary baseline survival times for patients who did not receive rituximab maintenance were replaced with counterfactual survival times derived from the stage 1 model, and added to the observed time to secondary baseline. The adjusted treatment effect was then estimated by fitting a Cox proportional hazards model using these counterfactual outcomes with randomised treatment as a covariate.

The TSE results are broadly consistent with the IPCW analyses as well as across different parametric survival models, supporting the robustness of the IPCW results presented in the CS (see table 4).

Table 4: TSE-adjusted analyses results (TRIANGLE; FAS)

Endpoint	85% R-Maintenance Setting Adjustment Methods	HR (95% CI), p-value
FFS	IPCW	
	TSE Exponential	
	TSE Weibull	
	TSE Gamma	
	TSE Log-logistic	
	TSE Log-normal	
OS	IPCW	
	TSE Exponential	
	TSE Weibull	
	TSE Gamma	
	TSE Log-logistic	
	TSE Log-normal	

Abbreviations: CI: confidence interval; FFS: failure-free survival; HR: hazard ratio; IPCW: inverse probability of censoring weighting; OS: overall survival.

Section B: Clarification on cost-effectiveness data

Johnson & Johnson would like to highlight to the EAG that as part of the responses to the clarification questions detailed throughout Section B below, two updates have been made to the original Company base case analysis. These updates further strengthen the robustness and validity of the modelled base case to UK clinical practice. The specific changes are detailed below and in the corresponding responses in Section B. The base case analysis that incorporates these two updates forms the new base case results accompanying this clarification question response and is henceforth referred to as the “updated” base case analysis throughout the following sections.

Accordingly, all base case results presented in scenario analyses throughout Section B are reflective of this updated base case, rather than the base case in the original CS.

The modular as well as collective impact of the two updates to the original company base case is presented in Table 5 below and demonstrate that the changes have a minimal impact on the original base case results presented in the ingoing submission. Of note, the ibrutinib regimen remains dominant versus the ASCT regimen. For completeness, full results for the updated base case analysis provided alongside this clarification question response is provided in Appendix D 4.

Base case update 1: Removal of certain adverse events (AEs) related to blood abnormality values to avoid double-counting

In line with the response to Question B11, Johnson & Johnson highlight that all modelled AEs in the original base case analysis were severe or medically significant (i.e., Grade ≥ 3) AEs that occurred at an incidence of $\geq 5\%$ in at least one of the relevant treatment arms in TRIANGLE. However, Johnson & Johnson acknowledge the EAG’s note that some of the AEs relating to abnormal blood values reported in TRIANGLE may be less likely to impart an autonomous impact on HRQoL and costs. As such, in order to minimise the risk of double counting of AEs, AEs which are defined as ‘blood value

abnormalities' have been conservatively removed from the updated cost-effectiveness model. Specifically, the AEs that have been removed from the updated base case analysis are leukopenia, neutrophil count decrease, white blood cell decrease and lymphocyte count decrease. Platelet count decrease has not been removed from the updated base case given that feedback received from a UK clinical expert noted that patients with severely low platelet count require more involved care, such as prophylactic platelet transfusions, and thus low platelet count would have a significant autonomous impact on patient HRQoL and impart a financial burden on the NHS.¹⁶

The updated cost-effectiveness results based solely on this change to the modelling of AEs relating to blood abnormalities are presented alongside the original base case results in Table 5 below. The results show that the direct impact of this modelling update on incremental costs and QALYs (compared to the original base case results) is negligible. Nevertheless as noted above, these AE updates were included in the updated base case analysis informing these clarification question responses (alongside the resource use updates noted below) to ensure the economic model is as reflective as possible of the HCRU costs and HRQoL decrements incurred in UK clinical practice.

Base case update 2: Updates to resource use frequencies to more closely align with clinical expert opinion

In line with the response to Question B22, Johnson & Johnson thank the EAG for highlighting that some discrepancies were present between the resource use included in the economic model versus those provided by UK clinical experts at the March 2025 advisory board.¹² To correct these discrepancies, the following updates have been made to the resource use assumptions included in the economic model:

- 50% of patients each receive a PET scan and CT scan once per year in 1L active maintenance treatment (per cycle frequency of 0.03)
- Four haematologist visits per year are applied in 1L active maintenance treatment (per cycle frequency of 0.23)
- 50% (as opposed to 100%) of patients each receive a PET scan and CT scan once per year off 1L active maintenance treatment (per cycle frequency of 0.03; original submission assumed per cycle frequency of 0.06)
- 50% (as opposed to 100%) of patients each receive a PET scan and CT scan once per year in 2L PF and PD health states (per cycle frequency of 0.03; original submission assumed per cycle frequency of 0.06)

The updated cost-effectiveness results based on these resource use changes are presented alongside the original base case results included in the ingoing CS in Table 5. The results show that the direct impact of this modelling update on incremental costs and QALYs (compared to the original base case results) is negligible and therefore demonstrate that the economic results are robust to resource use assumptions. Nevertheless, as noted above, these resource use updates were included in the update base case analysis informing these clarification question responses (alongside the AE updates noted above) to ensure the economic model is as reflective as possible of UK clinical practice.

Table 5: Summary of modular and collective change in deterministic results from original company submission base case (ibrutinib PAS price)

Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Company base case (original submission)</i>	████	██	Dominant	██	█
Update 1: Removal of the following blood abnormality AEs: leukopenia, neutrophil count decrease, white blood cell decrease and lymphocyte count decrease	████	██	Dominant	██	████
Update 2: Update proportion of patients receiving CT and PET scans (50% per year) for 1L FF, 2L PF and PD health states and inclusion of haematological visits, CT and PET scan HCRU for patients receiving active maintenance at 1L	████	██	Dominant	██	████
Updated company base case (Update 1+2)	████	██	Dominant	██	████

Abbreviations: AE: adverse event; CT: computerised tomography; FF: failure free; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; PD: progressed disease; PET: positron emission tomography; QALY: quality-adjusted life year.

Intervention and comparator

B 1. The 1L dosing regimens were presented in CS Table 55. In the CS it is stated:

“given the predominant use of the NORDIC induction regimen in UK clinical practice, as highlighted by feedback received from UK clinical experts at the November 2025 advisory board, the ASCT regimen was modelled to include two potential induction regimens: alternating R-CHOP with R-DHAP or R-DHAox (20% of patients) or the NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine) (80% of patients).”

- a) Please discuss the chemotherapy induction regimens recommended in UK treatment guidelines, presented in Table 1 (Ibrutinib Advisory Board Report_November 2025).**

- i. Please provide distributions of use in UK clinical practice of each of the listed regimens, using additional supporting evidence.
- ii. In light of the preceding question, please justify the chosen CS 1L induction dosing regimens in the CS base-case.

Based on available relevant treatment guidelines, such as the BSH guidelines, the following induction regimens were presented to UK clinical experts during the November 2025 advisory board and the experts were asked if the regimens were an accurate reflection of the induction regimens used in UK clinical practice:^{2, 8, 17, 18}

- **R-CHOP alternating with R-DHAP**
- **R-CHOP alternating with R-DHAOx**
- **NORDIC Regimen: dose-intensified R-CHOP alternating with rituximab + high-dose cytarabine**
- LyMA regimen: R-DHAP (± R-CHOP)
- R-CHOP alternating with rituximab + cytarabine
- Rituximab + bendamustine followed by rituximab + high dose cytarabine

The clinical experts confirmed that the list was an accurate reflection of the induction regimens used in UK clinical practice. It was noted that the exact choice of induction regimen is driven by local preferences and clinician experience.⁸ All clinical experts agreed that the NORDIC regimen is predominantly used in UK clinical practice, and ultimately concluded that that 80% of patients treated with the ASCT regimen receive the NORDIC induction chemotherapy regimen.⁸ They considered that the remaining 20% of patients receive a mixture of other immunochemotherapy regimens, including alternating R-CHOP and R-DHAP (or R-DHAOx). This was validated by feedback received from a UK clinical expert during the development of the clarification question responses who independently stated that the NORDIC regimen is the most commonly used induction regimen, used in approximately 80% of patients in UK clinical practice, with the remaining 20% potentially split evenly between the remaining regimens. Importantly, all clinical experts at the November 2025 advisory board agreed that should ibrutinib receive reimbursement in the UK, all clinicians would align the induction immunochemotherapy regimen given with that specified in the ibrutinib label to ensure access to ibrutinib in the first-line setting.⁸ Furthermore, the clinical experts unanimously agreed that all induction chemotherapy regimens are considered clinically equivalent in UK practice.

As such, in line with UK clinical practice, 80% of patients in the ASCT arm are assumed to receive the NORDIC regimen. As a simplifying assumption, given the clinical equivalency of the induction regimens and the fact that usage of R-CHOP and R-DHAP (or R-DHAOx) would increase should ibrutinib be reimbursed in UK clinical practice, the remaining 20% of patients were modelled to receive alternating R-CHOP and R-DHAP (or R-DHAOx). To align with the induction regimen specified in the marketing authorisation for ibrutinib in this indication (see Question B1d), all patients in the ibrutinib arm were modelled to receive alternating R-CHOP and R-DHAP (or R-DHAOx). Further details regarding the split between R-DHAP and R-DHAOx within the latter induction regimen are provided in the response to Question B1b).

- b) Please provide justification and supporting evidence for the 1L dosing regimens with R-CHOP given in combination with a clinical expert-informed 85%/15% split between R-DHAOx and R-DHAP.**

During the November 2025 advisory board, clinical experts stated that within the alternating R-CHOP and R-DHAP (or R-DHAOx) induction regimen, R-DHAOx would be preferentially used over R-DHAP due to its more tolerable safety profile and more user-friendly method of administration given that it can be administered in an outpatient setting.⁸ Following discussion, the clinical experts reached consensus that 85% of rituximab-eligible patients would likely receive R-CHOP alternating with R-DHAOx and 15% of rituximab-eligible patients would receive R-CHOP alternating with R-DHAP in UK clinical practice.⁸ As such, to ensure that the drug costs in the model accurately reflect UK clinical practice, an 85%/15% split between R-DHAOx and R-DHAP was implemented within the model for patients receiving alternating R-CHOP with R-DHAP (or R-DHAOx) in both the ibrutinib and ASCT arms.

- c) Please provide justification and supporting evidence for the clinical expert-informed 80%/20% split between the NORDIC chemotherapy regimen and alternating R-CHOP and R-DHAP (or R-DHAOx) as induction chemotherapy regimens**

Justification for the 80%/20% split between the NORDIC and alternating R-CHOP/ R-DHAP (or R-DHAOx) induction chemotherapy regimens used for the ASCT arm within the economic model is provided in Question B1a).

- d) Please justify why the NORDIC chemotherapy regimen was not used in combination with ibrutinib (only in combination with the ASCT strategy).**

As detailed in the SmPC, the UK marketing authorisation for ibrutinib in the indication of relevance to this submission is for ibrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) alternating with R-DHAP or R-DHAOx.¹ The induction regimen for the ibrutinib arm in the economic model was therefore modelled in line with the licensed regimen for ibrutinib in this indication.

- e) R-CHOP with R-DHAP or R-DHAOx (20% of patients) and the NORDIC chemotherapy regimen (80% of patients) were assumed to be equally effective. Please support this assumption with:**

- i. empirical evidence
- ii. clinical expert statements supporting the assumption of equal effectiveness and why

Empirical evidence from the BSH guidelines indicates that no specific induction regimen is clearly superior for patients with MCL who are eligible for ASCT, with overall response rate (ORRs) of >90% and CRs of >50% reported.² This is further supported by a retrospective, multicentre comparison of induction immunochemotherapy regimens, including but not limited to, NORDIC, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate or cytarabine (R-hyper-CVAD/MA), R-CHOP or R-CHOP/DHAC (cisplatin replaced with carboplatin), in patients with untreated MCL who are eligible for ASCT.¹⁹ This study concluded that the type of induction chemoimmunotherapy did not influence PFS ($p>0.67$), OS ($p>0.35$) or ORR (0.43).¹⁹ Furthermore, at the recent November 2025 Advisory Board, the five UK clinical experts consulted unanimously agreed that the presented induction regimens (see Question B1a) are accepted as clinically equivalent in UK clinical practice.⁸ Additionally in the March 2025 advisory board, the clinical experts confirmed that efficacy and safety of all available induction regimens could be considered equal.¹² As a result, equal efficacy between the NORDIC regimen and alternating R-CHOP with R-DHAP (or R-DHAOx) regimens was assumed in the economic model in line with relevant MCL guidelines and clinical expert opinion.²

f) Please provide scenario analyses, including an updated version of the economic model, using:

- i. Alternating R-CHOP with R-DHAP or R-DHAOx for both strategies (ibrutinib regimen and ASCT regimen).

In line with the EAG's request, scenario analyses have been conducted to explore the uncertainty associated with choice of induction chemotherapy. In this scenario, all patients in both the ASCT and ibrutinib model arms are assumed to receive alternating R-CHOP with R-DHAP (15%) or R-DHAOx (85%). Results of this scenario analysis are presented in Table 7 and demonstrate that the base case ICER is robust to the induction regimen selected for the modelled arms: the ibrutinib regimen remains a cost-effective option with no change to the cost-effectiveness conclusions of the base case analysis.

Table 6: Deterministic scenario analysis results (ibrutinib PAS price): induction chemotherapy regimens

Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case:</i> - Arm A: 80% of patients receiving the ASCT arm receive the NORDIC regimen and 20% receive alternating R-CHOP/R-DHAP [or R-DHAOx]) - Arm I: 100% of patients receive alternating R-CHOP/R-DHAP [or R-DHAOx])	■	■	<i>Dominant</i>	■	-

All patients receive alternating R-CHOP/R-DHAP [or R-DHAOx])	■	■	Dominant	■	■

Footnotes: Among patients receiving alternating R-CHOP/R-DHAP (or R-DHAOx), 85% of patients received R-DHAOx and 15% of patients received R-DHAP, in line with clinical expert opinion.

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP: rituximab, dexamethasone, high-dose cytarabine and platinum.

- ii. The NORDIC chemotherapy regimen for both strategies (ibrutinib regimen and ASCT regimen).

A scenario analysis in which all patients in both the ibrutinib and ASCT arm of the model receive the NORDIC regimen has not been conducted because, as noted in response to Question B1d) above, use of the NORDIC regimen with the ibrutinib regimen would be off-license and is therefore not relevant for UK decision making. It should however be noted that this scenario is not anticipated to significantly impact results, given that the induction regimens are associated with broadly similar costs. Incremental costs are anticipated to slightly increase for the ibrutinib regimen, but this increase would not meaningfully impact the ICER and therefore would not alter cost-effectiveness conclusions.

B 2. According to the CS, rituximab maintenance therapy might be 2 or 3 years:

“Following ASCT, the BSH recommends three years of treatment with rituximab maintenance therapy, based on the LyMA trial; however, rituximab maintenance treatment is only reimbursed by NICE for two years following ASCT. As such, most regional NHS trusts recommend and prescribe rituximab maintenance for two years. Feedback from UK clinical experts at the November 2025 advisory board indicated that there are discrepancies in prescribing practice across the UK, with some NHS trusts reimbursing up to three years of rituximab maintenance.

Additionally, clinical experts noted that some patients may self-fund the third year of rituximab maintenance treatment.”

- a) **Please provide supporting evidence for the reimbursement of a third year of rituximab maintenance for 10% of patients, and discuss its coherence with the NHS and Personal Social Services (PSS) perspective.**

As noted in the Section 1.3.4 of the CS, in UK clinical practice, the length of time that rituximab maintenance therapy is reimbursed varies regionally from two to three years. While guidelines recommend a three year course of treatment, most NHS trusts only reimburse two years of treatment, as validated by UK clinical experts.^{2, 13, 20-22} Specifically, feedback received from five UK clinical experts at a recent November 2025 advisory board noted that the majority of patients in UK

clinical practice receive two years of rituximab maintenance, however that some trusts fund a third year of treatment for all patients and some patients chose to self-fund the third year of treatment.⁸ This was independently validated by a clinician consulted during the development of CQ responses, who noted that the majority of centres provide two years of rituximab maintenance therapy in UK clinical practice, but acknowledged that regional variation is present. The UK clinical experts consulted at the November advisory board subsequently unanimously validated that a 90:10 split between two versus three years of rituximab maintenance is representative of usage in UK clinical practice.⁸

In the absence of available real-world data to inform the proportion of patients receiving two or three years of rituximab maintenance therapy in UK clinical practice, the 90:10 split provided by the UK clinical experts was used within the economic model to ensure duration of the rituximab maintenance is reflective of UK clinical practice. While it is acknowledged that patients who self-fund the third year of treatment reflect out of pocket costs that would not be incurred by the NHS and as such, are not relevant to the NHS and PSS perspective, such patients are considered to represent a only a very small proportion of the 10% provided by the clinical experts. Nevertheless, to explore uncertainty surrounding these proportions, scenario analyses assuming that either all patients receive 2 years of rituximab maintenance or all patients receive 3 years of rituximab maintenance were explored, with results presented in b) of this question.

b) To explore the impact of the abovementioned uncertainty (either 2 or 3 years of rituximab maintenance therapy). Please provide scenario analyses, including an updated version of the economic model, assuming:

- i. All patients get 2 years of rituximab maintenance therapy.
- ii. All patients get 3 years of rituximab maintenance therapy.

In line with the EAG's request, scenario analyses have been conducted to explore uncertainty associated with the assumption that 90% of patients receive two years and 10% of patients receive three years of rituximab maintenance therapy in UK clinical practice across both model arms. Results of two scenario analyses in which all patients either receive rituximab maintenance therapy for 2 years or 3 years, respectively are presented in Table 7 and demonstrate that assumptions relating to the proportion of patients receiving two or three years of rituximab maintenance therapy have a negligible impact on the base case results.

Table 7: Deterministic scenario analysis results (ibrutinib PAS price): duration of rituximab maintenance therapy

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case (90% of patients receive 2 years of rituximab maintenance therapy and 10% receive 3 years)</i>	■	■	<i>Dominant</i>	■	-

All patients get 2 years of rituximab maintenance therapy	■	■	Dominant	■	■
All patients get 3 years of rituximab maintenance therapy	■	■	Dominant	■	■

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Population

B 3. The characteristics of patients entering the model were based on the baseline characteristics of the TRIANGLE FAS population, pooled across Arm I and Arm A (CS Table 28).

a) Please justify (with supporting evidence) that the patient characteristics provided in CS Table 28, are reflective of UK clinical practice patient with previously untreated, stage II–IV mantle cell lymphoma and suitable for ASCT.

The patient characteristics used within the model (and detailed in Table 28 of the CS) are derived from the TRIANGLE FAS population, pooled across Arm I and Arm A. Commentary on the generalisability of the TRIANGLE FAS population to the population under consideration in the decision problem is provided in the response to Question A4a).

For completeness, when consulted at the November 2025 advisory board, clinical experts considered that this population was generalisable to patients that currently receive the ASCT regimen in UK clinical practice.⁸ The relatively low median age is reflective of the fact that in UK clinical practice patients need to be ≤ 65 years to be considered suitably fit for ASCT. The high proportion of males reflects that men make up the majority (65%) of MCL cases in the UK.⁶ As such, the patient characteristics included within the model can be considered reflective of UK clinical practice. Johnson & Johnson acknowledge that the paucity of real-world data investigating MCL patients in the UK is a challenging but inherent limitation of evaluating rare diseases and consider that in the absence of real-world data, clinical expert opinion represents the best available evidence to evaluate the generalisability of the TRIANGLE trial to UK clinical practice.

b) Please justify why the median, rather than the mean age was used to inform the baseline patient characteristics.

Compared to the median, the mean can be disproportionately influenced by extreme values within the data set. As such, the median was used within the model to minimise any potential influence of outliers on the model inputs.

The mean and median ages from the TRIANGLE FAS population, pooled across Arm I and Arm A, are presented in Table 8. As the mean and median values are similar, the likelihood of bias

associated with either value is low. For completeness, the uncertainty associated with the use of the median value within the model is explored in Question B3c).

Table 8: Mean and median age from the TRIANGLE FAS population

Characteristic	MCL population
Median age, years	57
Mean age, years (SD)	██████████
Range, years	27, 65

Abbreviations: BSA: body surface area; FAS: Full Analysis Set; MCL: mantle cell lymphoma.
Source: EMA. Assessment Report: Imbruvica (2025),⁵ J&J IM. Data on File. TRIANGLE CSR (FAS; May 2024 DCO).³

c) Please provide the mean age of the TRIANGLE FAS population, pooled across Arm I and Arm A as well as a scenario analysis, including an updated version of the economic model, using this mean age.

In line with the EAG’s request, a scenario analysis has been conducted to explore the uncertainty associated with the use of the median age from the TRIANGLE FAS population instead of the mean age. The mean and median values, pooled across Arm I and Arm A, are presented in Table 7. Results of this scenario analysis are presented in Table 8 and demonstrate that the use of the median or mean age from TRIANGLE has a minimal impact on the base case results.

Table 9: Deterministic scenario analysis results (ibrutinib PAS price): mean age

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (median age: 57 years)	██████████	██████████	Dominant	██████████	-
Mean age: ██████████ years	██████████	██████████	Dominant	██████████	██████████

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

B 4. The final scope stipulates “If evidence allows, subgroups based on baseline clinical disease characteristics, cytology of mantle cell lymphoma, p53 expression and receipt of rituximab maintenance may be considered”. Moreover, subgroup analyses are provided considering clinical effectiveness (CS Figure 9). However, no subgroup analyses were provided in CS Section 3.12. In CS Table 1, it is stated “subgroups are not considered in the cost-effectiveness analysis (see Section 3) given that they are not anticipated to be important for decision-making in UK clinical practice”. According to the EAG, the importance of subgroups for decision-making should be decided upon by the committee.

a) Please provide scenario analysis, including an updated version of the economic model, for the subgroup analyses specified in CS Figure 9.

Based on clinical guidelines and UK clinical expert opinion, Johnson & Johnson do not consider that treatment with ibrutinib would, or should, be limited to any subgroups in UK clinical practice.

Current treatment guidelines for patients with untreated MCL eligible for ASCT do not recommend any subgroups based on baseline disease characteristics to guide treatment selection. The most up to date treatment guidelines for MCL, BSH 2024 and ESMO 2025, do not present any baseline clinical disease characteristics which are necessary or recommended for decision-making in clinical practice for the treatment of first-line patients with MCL who are eligible for ASCT.^{2, 17} Importantly, both of these guidelines recommend the ibrutinib regimen as a treatment option for all symptomatic patients with MCL who are fit enough to receive ASCT.^{2, 17} The latest guidelines available, ESMO 2025, even highlight that first-line treatment with the ibrutinib regimen is preferred over treatment with ASCT in this patient population.¹⁷ This clearly demonstrates that consensus amongst the clinical community is that there are no subgroups that would guide treatment with the ibrutinib regimen for patients with untreated MCL eligible for ASCT.

Beyond treatment guidelines, four UK clinical experts consulted during the March 2025 Advisory Board also highlighted that first-line treatment choice decisions for patients with MCL are not based on baseline disease characteristics. The clinicians highlighted that baseline disease characteristics such as MIPI risk group, KI-67 index, and p53 expression are not relevant for decision-making in UK clinical practice. In further discussions, physicians also noted that markers such as p53 expression are not tested in routine care, therefore no treatment choices are based on p53 expression. These discussions confirm that subgroups based on baseline disease characteristics are not relevant to UK clinical practice. Furthermore, sample sizes for all subgroups based on baseline clinical disease characteristics, cytology of MCL and p53 expression are extremely limited. As such, cost-effectiveness analyses within these subgroups in the economic model would yield results that are insufficiently robust and uncertain, as well as being not relevant to UK clinical practice, and therefore have not been provided.

Regarding rituximab maintenance usage, the difference in the proportion of patients who received rituximab maintenance therapy in TRIANGLE compared with UK clinical practice was highlighted by five UK clinical experts in the November 2025 Advisory Board.⁸ As detailed in the response to Question A4b), evidence supporting the use of rituximab maintenance therapy was not established at the point of TRIANGLE protocol development, and therefore rituximab was not initially considered a study treatment.^{3, 9} However, upon implementation into national guidelines, rituximab maintenance was administered to TRIANGLE patients across all arms per the recommendation of the site's study group.³ The effect of rituximab maintenance use was therefore investigated with an IPCW-adjusted analysis in which the proportion of patients receiving rituximab maintenance in both arms of TRIANGLE was adjusted to reflect the anticipated use in UK clinical practice (85%). The methods and full results of these analyses are presented in Section 2.9 of the CS. Additionally, an IPCW-adjusted analyses in which all patients receive rituximab maintenance is presented in the response to Question A4b). The results of these two analyses clearly demonstrate that the FFS and OS hazard ratios (HRs) observed from the IPCW-adjusted analyses are highly consistent with those observed in the primary analysis of TRIANGLE FAS.

As the proportion of patients receiving rituximab maintenance in TRIANGLE is balanced between trial arms, it is not anticipated to impact the relative treatment effect observed between the ibrutinib regimen and the ASCT regimen in TRIANGLE. These results therefore provide confidence that the observed relative treatment effect between the ibrutinib and ASCT regimens in the TRIANGLE FAS stands, regardless of rituximab maintenance use. In conclusion, these analyses support Johnson & Johnson's position that the TRIANGLE FAS, which presented direct comparative evidence of the ibrutinib regimen vs the ASCT regimen in patient with untreated MCL remains the most suitable data source of decision making. Therefore, subgroups based on receipt of rituximab maintenance therapy are not included in the CS cost-effectiveness analyses.

b) Please provide scenario analysis, including an updated version of the economic model, for the subgroup analyses specified in the final scope.

All subgroups requested in the final scope overlap with the subgroups presented in CS Figure 9. Therefore, in line with the justification provided in response to Question B4a) above, no scenario analyses have been provided.

Model structure

B 5. Priority question. Transitions from the FF 1L health state to the PF 2L health state were modelled using time to treatment failure (TTF) data from TRIANGLE. TTF was defined as time from randomisation to stable disease at the end of induction immunochemotherapy, or progressive disease, whichever came first.

a) Please justify the suitability of TTF as a proxy for initiation of second-line treatment.

More specifically, provide justification for the assumption that patients in the FF 1L health state with stable disease at the end of induction immunochemotherapy would move on to second-line therapy (i.e. transition to the PF 2L health state).

As detailed in the CS and unanimously validated by UK clinical experts at a November 2025 Advisory Board, FFS (the primary endpoint in TRIANGLE) represents a key measure of treatment efficacy in MCL.⁸ FFS measures treatment efficacy based on PR and CR only, considering stable disease at the end of induction immunochemotherapy as well as progression or death as a sign of treatment failure.^{5, 18} TTF (used to model the transition from FF 1L health state to the PF 2L health state) was derived from FFS data from TRIANGLE. Specifically, patients who experienced a pre-failure mortality event were censored from FFS, and thus TTF reflects the time from randomisation to stable disease at the end of induction immunochemotherapy, or progressive disease, whichever came first.

Critically, BSH treatment guidelines for MCL state that stable disease following induction immunochemotherapy is an indication of treatment failure given that only patients achieving at least

a PR can proceed to the next phase of first-line treatment.² As such, patients who have stable disease after induction chemotherapy in the FF 1L health state are considered to have failed first-line treatment, and thus, as per treatment guidelines, would progress to second-line treatment.² This was validated by feedback received from a UK clinical expert during the development of the clarification question responses who confirmed that if a patient had stable disease following induction chemotherapy, they would be considered for second-line treatment. The aforementioned transition in the economic model is therefore directly in line with relevant treatment guidelines and clinical expert opinion and is therefore an accurate representation of the management of MCL in UK clinical practice. This is further supported by the fact that the model structure and its associated transitions were validated by five UK-based Consultant Haematologists at the November 2025 advisory board, with all clinical experts agreeing that the model structure accurately captured the disease course and management of MCL in UK clinical practice.⁸

- b) Please discuss whether immediate initiation of second-line therapy after stable disease at the end of induction immunochemotherapy is reflective of UK clinical practice. Are there potential alternatives (e.g. watch-and-wait, BSC, consolidation treatment without immediate second-line therapy) for patients with stable disease after induction treatment in UK clinical practice, and how are these reflected in the economic model?

As per the response to Question B5a) above, the assumption that patients in the FF 1L health state with stable disease at the end of induction immunochemotherapy move on to second-line therapy is in line with relevant MCL treatment guidelines in UK clinical practice.²

The potential second-line treatments and their associated distribution included in the PF 2L health state of the economic model were derived based on the independent clinical expert opinion of five UK-based Consultant Haematologists.⁸ Of note, the five clinical experts were not constrained by pre-specified subsequent treatments, and were therefore able to indicate what they considered to be the most appropriate treatments or strategies in the second-line setting, alongside their proposed distributions.⁸ Despite this, upon aggregating the clinical experts' treatments and proposed distributions, a maximum of 1.1% of patients were assumed to receive BSC in the second-line setting across the ibrutinib and ASCT model arms and no watch and wait strategies were listed. This is in line with expectations given that key treatment guidelines in this setting do not list "watch and wait" as a recommended treatment strategy.^{2, 17, 18} The ESMO guidelines only reference a "watch-and-wait strategy" for asymptomatic patients with disseminated MCL, whilst BSH guidelines only reference "active observation" in the context of untreated, asymptomatic MCL.^{2, 17} As such, the inclusion of "watch and wait" in this setting would directly contradict treatment guidelines for MCL management. This was validated by feedback received from a UK clinical expert during the development of the clarification question responses who confirmed that a "watch and wait" approach would never be suitable for patients in this setting.

Of note, the aggregated second-line treatment distributions provided from the five UK clinical experts were unanimously validated as appropriate at the November 2025 advisory board before being used in the economic model.⁸ The second-line treatments included in the economic model are therefore considered highly reflective of UK clinical practice. Furthermore, the high proportion of patients

receiving active second-line treatment is in line with expectations given that ASCT-eligible patients are required to be of a certain level of fitness and therefore patients failing first-line treatment are likely to be fit enough and willing to receive active second-line treatment in order to have the best chance at preventing subsequent disease progression.^{2, 21, 23} This was validated by feedback received from a UK clinical expert during the development of the clarification question responses.

Finally, Johnson & Johnson would like to highlight that whilst the majority of patients are modelled to receive “active” second-line treatment following failure on first-line treatment, the model captures the small minority of patients (1.1%) receiving BSC as second-line treatment, in line with clinical expert feedback. As such, the model accounts for all potential treatment strategies employed in UK clinical practice in this setting (active treatment and BSC).⁸

- c) Please comment on the plausibility of the assumption that all non-death failures in first-line treatment receive second-line treatment, i.e. the assumption that patients cannot transition from FF 1L to PD, and support this with empirical (trial) evidence.

It should be noted that the three alive health states in the economic model (FF 1L, PF 2L and PD) are representative of lines of therapy received in MCL, i.e., first-line treatment for patients who are failure-free, second-line treatment for patients who have failed on first-line treatment, and third-line treatment for patients with progressed disease (following progression on second-line therapy). As patients cannot receive a third-line treatment until they have received a second-line treatment, it is not clinically plausible for patients to transition directly from the FF 1L health state in the model (where first-line treatment is received) to the PD health state (where the third-line treatment is received).

Johnson & Johnson acknowledge that in UK clinical practice, there may be a small number of particularly sick patients with aggressive disease who may fail on first-line treatment, be too frail to receive an “active” second line treatment and therefore experience progressed disease not long after failure on first-line treatment. It should however be noted that these patients would still transition through the PF 2L health state in the economic model, albeit briefly. Furthermore, given that the target population for this submission is previously untreated ASCT-eligible patients, and therefore all patients must have been fit enough to receive ASCT at first line, it is anticipated that the proportion of patients following this disease trajectory would be minimal. Nonetheless, as detailed in response to Question B5b), the second-line therapies in the model were not constrained to “active” treatments, with a small minority (1.1%) modelled to receive BSC post-failure on first-line therapies. Furthermore, as the proportion of patients receiving BSC was informed by feedback received from five UK clinical experts (see response to Question B5b) above), the negligible proportion of patients modelled to receive BSC in itself provides evidence to support that modelling all non-death failures on first-line would receive second-line treatment, is reflective of UK clinical practice.⁸

This was further validated by feedback received from a UK clinical expert during the development of the clarification question responses, who confirmed that very few patients, if any, would not receive second-line treatment, given that patients eligible for ASCT therapy represent young, fit patients who would receive active second-line treatment upon progression. Furthermore, the clinician emphasised that, as explained in the response to Question B5b), a “watch and wait” approach where a patient progresses on first-line treatment but does not receive any further care, would not be a clinically

appropriate option for these relatively young and fit patients with MCL and is therefore not used in UK clinical practice.

Finally, Johnson & Johnson would like to reiterate that the model structure and its associated transitions were unanimously validated by five UK-based Consultant Haematologists at the November 2025 advisory board as accurately capturing the natural disease course and management of MCL in UK clinical practice.⁸ As such, the allowed transitions in the economic model are considered reflective of UK clinical practice and suitable for UK decision-making.

- d) Please provide an updated economic model and scenario analyses assuming that only a proportion (not all) of first-line treatment failures initiate second-line treatment (i.e. transition to the PF 2L state), with other directly transitioning to the PD or death health states.

In line with the responses to parts a) to c) of Question B5 above, Johnson & Johnson maintain that the current model structure and associated transitions accurately captures the natural disease course and management of MCL in UK clinical practice, as unanimously validated by UK clinical experts.⁸ As such, Johnson & Johnson have not provided the requested scenario analysis as it is not relevant for UK decision-making.

- e) **The CS states that “The model follows patients in the PF 2L and PD health states to facilitate the consideration of time-varying transition probabilities, which were applied relative to the timepoint at which a patient first enters these health states”. Please provide details of how this time dependency was implemented in the economic model. In case tunnel states are used, please specify all tunnel states used.**

Details of how time dependency was accounted for in the model transition probabilities are provided in Sections 3.3.4 and 3.3.5 of the CS. Implementation of time-varying transition probabilities was achieved in the model using VBA, not through use of tunnel states. A description of the VBA approach is provided below.

Time dependency for the PF 2L and PD health states was implemented using the ‘CohortSurvival’ VBA function (which can be found in the ‘SurvivalFunctions’ Module).

Detailed comments and notes explaining how the function works are provided within the macro code itself; in summary, the macro functions by creating a cohort that joins the relevant health state in each new cycle of the model, so that the time from entry can be tracked for each cohort as well as the overall time/cycle in the model. For every cohort and every subsequent model cycle the function then calculates and applies:

- Risk of progression in that cycle (relevant for PF 2L health state only), using the relevant PFS data (RAY-3001 in the base case) and accounting for time since entry into the 2L PF health state

- Risk of death in that cycle, by taking into account time since entry into health state and applying the relevant OS data and the model time/cycle to ensure the relevant general population mortality rates are applied
 - The function applies capping to ensure mortality risk from modelled OS data/AMR cannot be lower than the general population mortality risk in any given cycle of the model

The function aggregates the cohort-level results into cycle-level totals for the proportion of patients who remain in the current health state ('stable'), experience disease progression ('incremental progression') or experience death ('incremental death') for the whole population (columns BG:BI and BM:BO in the 'model engine' tab).

- f) Please provide an updated economic model and scenario analyses using PFS (i.e. not including stable disease at the end of induction immunochemotherapy as an event) from TRIANGLE to inform the transition from FF 1L to PF 2L.

PFS is defined as the time to progression or death from any cause, and therefore, in contrast to FFS, does not consider stable disease as an event. As detailed in the response to Question B5a), key treatment guidelines for MCL class stable disease following induction immunochemotherapy as a sign of treatment failure and therefore progression to second-line therapy.² Specifically, as per treatment guidelines, patients who do not achieve at least a PR following the end of induction immunochemotherapy cannot proceed to consolidation treatment with ASCT, which together represents the current first-line SoC in the indication of relevance to this submission in UK clinical practice. Consequently, patients with stable disease would progress to second-line treatment. As such, the inclusion of stable disease events following induction as failure events on first-line treatment in the economic model is crucial to ensure the model represents an accurate reflection of management of MCL in the UK.²

The superiority of FFS as an endpoint over PFS in this setting was unanimously validated by five UK clinical experts at the November 2025 advisory board who all confirmed that FFS is a more appropriate measure of disease control and treatment efficacy than PFS in this setting.⁸ Therefore, in line with clinical expert feedback, as well as treatment guidelines in MCL, Johnson & Johnson maintain that data derived from FFS (i.e., TTF) are the most appropriate data to model the transition from FF 1L to PF 2L. Using data derived from PFS data (i.e., treat to progression [TTP]) as opposed to TTF would not be reflective of UK clinical practice, given the nuance of stable disease as a treatment failure event would not be captured.

Johnson & Johnson would however like to highlight that, as presented in Section 2.6.1 of the CS, only 0.4% and 1.9% of all FFS events in Arm I and Arm A, respectively, were due to stable disease at end of induction.⁵ As such, whilst Johnson & Johnson maintain that the use of TTF is the most clinically appropriate approach to modelling FF 1L to PF 2L (for the reasons outlined above), the use of TTP (derived from TRIANGLE PFS) as opposed to TTF (derived from TRIANGLE FFS) to inform the transition from FF 1L to PF 2L would have limited impact on the cost-effectiveness results. To demonstrate this, for completeness and transparency, a scenario analysis was conducted in which TTP (derived from TRIANGLE PFS) was used to inform the transition from FF 1L to PF 2L, as opposed to TTF (derived from TRIANGLE FFS). Results of this scenario analysis are presented in

Table 13 and demonstrate that any uncertainty associated with the use of FFS as opposed to PFS in the economic model is minimal.

Table 10: Deterministic scenario analysis results (ibrutinib PAS price): Use of PFS

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (FFS used to inform 1L efficacy)	████	██	Dominant	██	-
PFS used to inform 1L efficacy	████	██	Dominant	██	████

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

B 6. Priority question. The company modelled ASCT as part of the comparator treatment. However, in the TRIANGLE trial only patients in arms A and A+I received ASCT, whereas transitions beyond first line in the economic model were informed by RAY-3001, in which ASCT use was limited. As a result, any effects of ASCT on remission duration and survival appear to be implicitly captured only through first-line (FF 1L) transitions, with no explicit distinction between ASCT-related and non-ASCT-related outcomes in later health states. Additionally, ASCT-related toxicity and (long-term) HRQoL benefits appear not to be explicitly modelled. This raises concerns that the impact of ASCT may not be consistently or transparently reflected across health states and lines of therapy, with potential implications for incremental costs and QALYs.

- a) It is unclear for the ASCT regimen what proportion of patients will eventually get ASCT in the company's economic model and how this is determined. Please provide details on the proportion of patients receiving ASCT in the CS base-case and how this is calculated. Please elaborate whether this is expected to be consistent with UK clinical practice

In the economic model, the proportion of patients modelled to undergo ASCT in the ASCT model arm is █████%. This proportion is informed by data from TRIANGLE (May 2024 CCO), whereby among the 248 participants in Arm A who completed induction immunochemotherapy treatment, █████ participants (████%) in Arm A started and completed HDT followed by ASCT.^{3, 5} For the EAG's awareness, this is located on the 'Frontline Tx Cost' tab of the model, Column N.

The proportion of patients who did not receive ASCT in TRIANGLE (████%) is consistent with the rate in UK clinical practice, as validated by feedback received from a UK clinical expert during the

development of the clarification question responses. The UK clinical expert noted that there are various reasons, including but not limited to failure to obtain stem cells, toxicity to induction therapies, progression or complications of the disease, which result in patients not receiving ASCT following completion of induction immunochemotherapy. This is supported by evidence from the ITT population in the LyMa trial in which 14.0% of patients failed to progress from induction treatment to ASCT.²⁴ The reasons for failure to undergo ASCT in the LyMa trial aligned to those provided by the UK clinical expert and included lack of patient eligibility, failure to obtain stem cells, patient withdrawal, toxic effects, disease progression and other malignancies.²⁴

TRIANGLE is the pivotal trial informing the clinical evidence base for this submission, and therefore TRIANGLE represents the best available evidence to inform the proportion of patients who receive ASCT as part of the ASCT regimen in the economic model. Furthermore, this approach is consistent with that used to inform the proportion of patients receiving ibrutinib in the ibrutinib model arm and ensures the modelled costs are reflective of the modelled efficacy data.

- b) Please provide justification for modelling the impact of ASCT implicitly, discuss the implications of this choice and justify why ASCT was not modelled as a separate health/tunnel state.

ASCT was modelled implicitly because its clinically beneficial material effects are concentrated in first-line and, as such, are already captured in the existing 1L TTF/FFS curves. Responses following treatment with the ASCT regimen are not curative for a large proportion of patients and many are likely to receive subsequent treatment.²⁵⁻²⁷ After failure on first-line treatments, outcomes are driven mainly by subsequent therapies and disease biology. UK and European guidance for refractory or relapsed MCL emphasise relapsed/refractory standards of care rather than historical ASCT receipt as key determinants of outcomes.^{2, 17} As such, imposing state dependent post first-line modifiers for patients who receive prior treatment with the ASCT regimen risks structural misspecification.

Furthermore, it is important to note that, whilst the impact of first-line treatment is not explicitly modelled in the second-line setting, given the distribution of second-line treatments patients received was modelled to be dependent on the first-line regimens patients received, continued differential efficacy between the ibrutinib and ASCT regimen was captured in the model beyond the first-line setting. Finally, as detailed in the response to Question B6c) below, Johnson & Johnson would like to highlight that the approach to modelling subsequent treatment efficacy likely represents a conservative approach to capturing the differential long-term efficacy of the ibrutinib regimen over the ASCT regimen.

- c) Please elaborate whether and how the short-term risks (i.e. increased risk of mortality and toxicity) and the long-term benefits (i.e. improved remission, survival and HRQoL) of ASCT were modelled.

Short-term

In the economic model, TRIANGLE data were used to inform first-line treatment efficacy (i.e., FF 1L to PF 2L) and mortality (i.e., FF 1L to Death), given TRIANGLE represents the pivotal evidence base for the ibrutinib regimen versus the ASCT regimen in this setting.³ As such, both short-term toxicities

and short-term mortality risks associated with the ASCT regimen were mostly captured in the economic model via the direct use of TRIANGLE data.

Toxicities

To account for the HRQoL impact resulting from the toxicity of the ASCT regimen (as well as the ibrutinib regimen), a one-off disutility was applied to patients in each arm in the first model cycle. As detailed in Section 3.4.4 of the CS, the applied utility decrements for each regimen were derived from the AEs observed in TRIANGLE, and for each AE, a disutility was applied to the proportion of patients who experienced AEs in TRIANGLE (based on the duration of AEs). To note, the median time on study for TRIANGLE (54.9 months) is far longer than the induction and consolidation phase of the ASCT regimen (induction: 6 x 21-day cycles, followed by ASCT within two weeks) and therefore all acute toxicities associated with the ASCT consolidation phase of the ASCT regimen are captured within TRIANGLE. The application of a one-off disutility for both regimens ensures that the considerable short-term toxicities of the ASCT regimen relative to the ibrutinib regimen are partially captured within the economic model.

However, as noted in Section 3.13 of the Company Submission, the ASCT regimen is a highly toxic regimen that imposes a substantial burden on patients. Patients typically spend up to a month in hospital during treatment, with engraftment lasting 2–3 weeks and immunosuppression increasing infection risk.²⁸ The recovery extends over several months with intensive monitoring, weekly follow-ups, and transfusions, and during this period symptoms, such as fatigue and treatment-related pain, increase.²⁸ Recovery to normal daily life, such as work, can take up to six months, leading to a long-lasting HRQoL impairment as patients must physically and psychologically heal. A lymphoma patient described the experience as the “lowest point of [their] life,” noting that it took them “two to five months to feel [they] were recovering”.²⁹ Collectively, these demonstrate the significant additional burden existing first-line treatment in the UK has on patients’ lives and HRQoL, over and above the AE toxicities associated with ASCT. Despite this pronounced impact, given that the HSUV in the FF 1L health state was applied in a treatment independent manner, the significant disutility resulting from ASCT is not formally captured within the economic model beyond the disutility associated with specific AEs. Given the lack of HRQoL data from TRIANGLE, this detrimental impact is also not captured intrinsically within the FF 1L HSUV. The base case approach to modelling the short-term toxicities associated with the ASCT regimen are therefore highly conservative.

Mortality

The short-term increased mortality-risk associated with the ASCT regimen is also inherently captured in the modelling approach to the first-line transitions. Specifically, a pre-failure AMR was calculated by dividing the number of pre-failure mortality events observed in Arm I and Arm A in TRIANGLE by the number of person-years of follow-up in TRIANGLE for each arm.³ The annual rate derived was then converted to a per-cycle probability (i.e., a 21-day rate), by assuming that the risk of death was spread equally across cycles. The resulting per cycle probability of pre-failure mortality for ASCT regimen was over double that for the ibrutinib regimen, which is reflective of the acute

toxicity-related mortality risk associated with existing SoC in UK clinical practice (see Section 1.3.5 of the CS). Notably, at the November 2025 advisory board, UK clinical experts considered that the relative ~2:1 difference in pre-failure mortality risk between the ASCT regimen and the ibrutinib regimen was generally appropriate, although highlighted that if anything, the pre-failure mortality risk for the ASCT regimen was underestimated.⁸

Long-term

Given the aim of TRIANGLE was to evaluate treatments in the 1L treatment setting, TRIANGLE did not routinely collect the treatment efficacy data required to inform transitions from the PF 2L and PD health states in the model. Additionally, as the majority of patients remained alive and failure-free as of the latest data cut of TRIANGLE (CCO: 09 May 2024), use of post-failure data in TRIANGLE would be limited in its ability to robustly inform transitions beyond the first-line setting, as unanimously validated by feedback received from UK clinical experts.⁸

As discussed previously, there is a paucity of published literature in MCL and therefore no trials were identified in which patients received second-line treatments reflective of UK clinical practice following a relevant (ASCT regimen or ibrutinib regimen) first-line treatment. Given the need for a data source to inform transitions from PF 2L and PD, it was critical that the selected evidence source accurately captured relevant second- and third-line treatments, as confirmed by a health economic expert.⁸

RAY-3001 was subsequently identified as a suitable source of data to provide more mature PFS and post-progression data to inform PF 2L and PD transitions than TRIANGLE.³⁰ RAY-3001 was a randomised, open-label, multicentre, Phase III trial evaluating the efficacy of ibrutinib among patients with r/r MCL who had received at least one rituximab-containing chemotherapy regimen.³⁰ As the majority of MCL patients are expected to receive a BTKi as a second-line treatment following failure on first-line therapy in UK clinical practice, RAY-3001 was considered by UK clinical experts to be a suitable data source to model transitions beyond the first-line setting given the paucity of published literature in this setting.

Johnson & Johnson acknowledge that by using data from RAY-3001 to inform second-line and third-line transitions in the economic model, the long-term efficacy of the ASCT regimen is not explicitly captured in the model beyond first line; although it should be acknowledged that a non-insignificant proportion (■%) of patients in RAY-3001 received first-line treatment with ASCT.³¹ This limitation reflects an inherent limitation of the evidence base, as is common when assessing rare conditions. In order to mitigate this limitation, Johnson & Johnson sought feedback from UK clinical experts on long-term OS estimates in patients receiving the ASCT regimen at key landmark timepoints. As detailed extensively in Section 3.3 of the CS, these estimates were used to help select the base case curve choices informing transitions for second-line treatments. As such, the long-term impact of prior ASCT was implicitly captured within the economic model. This is demonstrated via the fact that the predicted median OS estimate for treatment with the ASCT regimen derived from the economic model (12.5 years) is highly aligned with the landmark survival estimate of the MCL2 trial assessing the Nordic regimen (alternating cycles of maxi-CHOP and cytarabine), followed by ASCT in 159 patients with previously untreated MCL (median OS of the Nordic regimen: 12.7 years).³² Furthermore, any difference between clinical expert estimates and model-predicted estimates for OS

remained less than <2.3% across all landmarks.⁸ Together, these results provide confidence that long-term impact of the ASCT regimen is adequately captured in the economic model.

It should additionally be noted that the limitation regarding the lack of explicit capturing of the long-term efficacy of the ASCT regimen beyond the first line setting is consistent across model arms, given that no patients in RAY-3001 had received prior treatment with ibrutinib. As such, Johnson & Johnson would like to highlight that use of data from the ibrutinib arm of RAY-3001 as the reference curve for later line transitions for both the ibrutinib and ASCT model arms likely represents a conservative approach to capturing the differential long-term efficacy of the ibrutinib regimen over the ASCT regimen. This is supported by direct data from TRIANGLE; after a substantial median time on study of ~4.5 years, a nominally significant 36.7% reduction in the risk of disease progression or death in Arm I versus Arm A was observed.³ As disease progression is associated with worsening symptoms and therefore an increased clinical burden, as well as an increased risk of death, extending the time to progression is expected to translate to improvements in patient HRQoL and overall improvements in survival.³³ This is further supported by OS data from TRIANGLE whereby a nominally significant 48% reduction in the risk of death observed in patients receiving the ibrutinib regimens vs. the ASCT regimen was reported.³

These results, combined with further efficacy results presented in Section 2.6 of the CS, clearly demonstrate that treatment with the ibrutinib regimen at first line is associated with extended survival and improved treatment efficacy in patients with untreated MCL, compared to the ASCT regimen at first line. These results would translate to long-term HRQoL and survival benefits in patients receiving first-line ibrutinib over the ASCT regimen. However, by using a common reference arm to model later-line treatment efficacy for both the ASCT and the ibrutinib regimen, any continued survival benefits associated with the ibrutinib regimen are not captured in the model. As such, the approach utilised in the economic model is likely conservative.

Additionally, as detailed extensively in Section 1.3.5 of the CS, the ASCT regimen burden of the ASCT regimen on patients (and their caregivers) is persistent and long lasting, with one study demonstrating that the ASCT regimen continues to detrimentally impact patients wellbeing, even ~9 years post-completion of the ASCT regimen.³⁴ Whilst Johnson & Johnson conducted a scenario analysis to start to explore the impact of a long-term utility decrement applied to patients receiving the ASCT regimen, the long-term burden of the ASCT regimen is not directly captured in Johnson & Johnson's modelling approach, further indicating that the base case analysis is likely to be highly conservative.

Conclusion

As detailed above, the current modelling approach captures the short-term mortality risk associated with the ASCT regimen through direct use of TRIANGLE trial data in the first-line setting. TRIANGLE represents the gold-standard of clinical evidence, providing head-to-head evidence for the ibrutinib regimen versus the ASCT regimen in the population of relevant to this appraisal.³ However, as noted above, whilst short-term mortality of the ASCT regimen is captured, the short-term toxicity is likely not fully captured; the short-term burden of the ASCT regimen captured within the model therefore likely represents a conservative estimate of the true short-term burden of ASCT.

Regarding long-term efficacy, it is important to acknowledge that, as the focus of TRIANGLE was on the first-line treatment setting, an alternative evidence source was required to inform transitions for later treatment lines, which represents an inherent limitation of the evidence base. However, UK clinical experts agreed that the ibrutinib arm of RAY-3001 (one prior line subgroup) was a suitable source of data to provide more mature PFS and post-progression data to inform PF 2L and PD transitions than TRIANGLE, and thus was used to inform later transitions.⁸ Whilst the use of RAY-3001 data means that the long-term efficacy of the ASCT regimen is not explicitly captured in the model beyond the first line setting, this limitation applies to both arms. Importantly, for the reasons detailed above, this limitation leads to the base case analysis being a conservative representation of the relative long-term survival and HRQoL benefits of the ibrutinib regimen as compared with the ASCT regimen. As such, both the approach to modelling the short-term and long-term impacts of ASCT are likely conservatively captured within the economic model.

- d) Please justify why the short-term risks (i.e. increased risk of mortality and toxicity) and the long-term benefits (i.e. improved remission, survival and HRQoL) of ASCT were not explicitly modelled and discuss the implications of this choice.

Justification for modelling the impact of ASCT implicitly as opposed to explicitly via separate tunnel states and the implications of this choice, in particular the conservative nature of the current modelling approach, is provided in response to Question B 6. c) above.

- e) Please provide an updated economic model and scenario analysis including ASCT-specific (tunnel) state(s) to reflect potential ASCT-related long-term HRQoL and survival benefits as well as potential long-term cost savings.

In line with the response to Question B6b), ASCT was modelled implicitly as the clinical benefits of the ASCT regimen are concentrated in first-line and thus captured in the existing 1L TTF and FFS curves. Furthermore, the long-term impact of the ASCT regimen was captured by insights from UK clinical experts, who provided long-term survival estimates for patients receiving ASCT in UK clinical practice.⁸ These estimates informed the selection of curves used to model the transition probabilities for later lines of treatment, therefore ensuring the long-term impacts of the ASCT regimen were implicitly captured in the base case approach. Importantly, there was a high rate of alignment between UK clinical expert long-term survival estimates for the ASCT regimen and the predicted long-term survival estimates for the ASCT regimen from the economic model, as highlighted in Section 3.14 in the CS and detailed in response to B 6. c) above. This therefore provides confidence that the long-term impact of the ASCT regimen was adequately captured within the economic model.

As such, an updated economic model including ASCT-specific tunnel states has not been provided. It should however be noted that, as detailed in the response to Question B6c), Johnson & Johnson consider that, if anything, the base case modelling approach is conservative in capturing the relative long-term survival and HRQoL benefits of the ibrutinib regimen versus the ASCT regimen. Specifically, after a median time on study of ~4.5 years, TRIANGLE demonstrated a clear survival benefit of the ibrutinib regimen compared to the ASCT regimen in patients with untreated MCL.^{3, 5} The use of a common reference arm (the ibrutinib arm of RAY-3001) to model subsequent transitions from later-line health states therefore does not capture the expected continued differential

long-term efficacy of the ibrutinib regimen over the ASCT regimen. As such, this approach is likely conservative. Additionally, the extensive long-term HRQoL burden of the ASCT regimen which is widely reported in the literature, is not captured by the base case modelling approach.³⁴ As such, any scenario in which ASCT tunnel states are included within the economic model would likely result in more favourable cost-effectiveness results for the ibrutinib regimen versus the ASCT regimen.

B 7. Priority question. In the economic model, data from TRIANGLE were used to inform transition from FF 1L, whereas data from RAY-3001 informed transitions from PF 2L and PD.

- a) Please provide justification for the mismatch between the first line population from TRIANGLE and the second line population from RAY-3001 in terms of patient and disease characteristics, ASCT use and previous line(s) of treatment (e.g. ASCT treatment was not required before entering RAY-3001 and patients did not have prior ibrutinib exposure).

As noted in response to Question B 6. b), given the aim of TRIANGLE was to evaluate treatments in the 1L treatment setting, TRIANGLE did not routinely collect the treatment efficacy data required to inform transitions from the PF 2L and PD health states in the model.⁸ Furthermore, as the majority of patients remained alive and failure-free as of the latest data cut of TRIANGLE (CCO: 09 May 2024), use of post-failure data in TRIANGLE would be limited in its ability to robustly inform transitions beyond the first-line setting, as unanimously validated by feedback received from UK clinical experts.⁸ A key benefit of the semi-Markov model structure therefore is that it enabled additional external data sources to be incorporated, to reduce uncertainty in long-term OS estimates.

As highlighted in response to Question B 6. b), there is a paucity of published literature in MCL and therefore no trials were identified in which patients received second-line treatments reflective of UK clinical practice following a relevant first-line treatment (ASCT or ibrutinib regimen). Given the need for a data source to inform transitions from PF 2L and PD, it was critical that the selected evidence source accurately captured relevant second-line treatments, as confirmed by a health economic expert.⁸ Data from the ibrutinib arm of RAY-3001 trial were therefore identified as the most relevant trial to inform second-line transitions in the economic model given that most patients are expected to receive BTKis at 2L in UK clinical practice. Furthermore, while prior ASCT treatment was not a requirement of RAY-3001, a non-insignificant proportion (■%) of patients received ASCT.³ Furthermore, given the recency of ibrutinib's license in the first-line setting, to the best of Johnson & Johnson's knowledge no trials in this setting include patients who have received prior treatment with ibrutinib. As such, whilst Johnson & Johnson acknowledge that the fact that not all patients received prior ASCT and no patients received prior ibrutinib is a limitation, it should be noted that this represents an inherent limitation of the evidence base, given the recency of ibrutinib license in this setting and the rare nature of MCL, and therefore is not a specific limitation of RAY-3001. It should additionally be highlighted that UK clinical experts consulted at the recent November 2025 advisory board, unanimously agreed that the RAY-3001 trial was an appropriate data source to inform these transitions, given the paucity of available evidence in this setting.⁸

It is additionally important to note that, as highlighted above, TRIANGLE data informing FF 1L to PF 2L or death transitions were included in the model to inform first-line patients, whereas RAY-3001 data, informing the PF 2L and PD transition, were included in the model to inform second-line patients. As such, the patient population in RAY-3001 are older (median age: ■■■) and frailer (ECOG 1: ■■■; ECOG 2: ■■■%) compared to TRIANGLE (median age: 57.0; ECOG 1: 28.1%; ECOG 2: 1.9%), which is in line with clinical expectations for a later-line population.^{5, 31} In particular, the difference in mean age between trials, is reflective of median time to treatment failure, (and therefore the time until patients would progress onto second-line treatment) in patients receiving existing SoC.³² The older, frailer nature of patients in RAY-3001 is further supported by the fact that patients in the ibrutinib arm of RAY-3001 had a higher proportion of patients with a high risk MIPI score versus those in TRIANGLE (Arm I: ■■■% high risk s-MIPI versus 14.2% high risk MIPI),^a although it should be caveated that two studies used slightly different MIPI scores to assess prognostic risk.³⁶ Johnson & Johnson would therefore like to clarify that the baseline characteristics between patients in TRIANGLE and RAY-3001 are not intended to be aligned but are intended to reflect the relevant populations for which they inform efficacy data for in the economic model.

As data from RAY-3001 were incorporated to inform transitions from PF 2L to PD, the generalisability between the trial's baseline characteristics and patients at 2L in UK clinical practice was considered. To maximise generalisability of the population to those seen in UK clinical practice, the model used data from the one prior line of therapy subgroup of the ibrutinib arm of RAY-3001. The number of prior lines of therapy received by patients in RAY-3001 was therefore fully aligned with those in the PF 2L and PD health states (where post-progression survival data are used).

In conclusion, whilst it is acknowledged that use of data from the one prior line subgroup RAY-3001 to inform PF 2L to PD transitions is associated with limitations, given the paucity of data in this setting, RAY-3001 represents the most suitable source of data to inform transition probabilities in this setting, as was unanimously confirmed by clinical experts consulted at the November 2025 advisory board.⁸

b) Please comment on the plausibility of using the ibrutinib arm of RAY-3001 to inform PF 2L and PD transitions for the ibrutinib regimen, given that these patients did not have prior ibrutinib exposure (i.e. assuming that patients relapsing after first-line ibrutinib derive the same benefit from second-line BTKi therapies as ibrutinib-naïve patients).

As noted in the response to Question B7a), Johnson & Johnson acknowledge that the lack of inclusion of prior BTKi-exposure in RAY-3001 represents a limitation. However, this represents an inherent limitation of the available evidence base, as opposed to a specific limitation of RAY-3001, given the paucity of evidence in this setting. Given the lack of evidence in patients treated at both first- and second-line with a BTKi therapy, there are no available data to indicate what, if any, impact

^a Prognosis in MCL is often measured by the MIPI system, which allows risk to be calculated as low, medium or high based on a computed formula (MIPI) or a simplified score-based index (s-MIPI)³⁵. Jain P, Wang ML. Mantle cell lymphoma in 2022-A comprehensive update on molecular pathogenesis, risk stratification, clinical approach, and current and novel treatments. Am J Hematol 2022;97:638-656.

prior BTKi exposure would have on second-line use of ibrutinib. Therefore, in the absence of data to support any potential differential efficacy based on prior BTKi exposure, this was not included in the model, as any assumptions would be purely arbitrary. Furthermore, it should be noted that it is assumed that any patients who experience early disease relapse on treatment with the ibrutinib regimen at first-line would be considered BTKi-resistant in clinical practice and therefore would not receive a BTKi at second-line. These patients are captured in the economic model via the proportion of patients in the second-line treatment distributions post-ibrutinib not receiving treatment with a BTKi at second-line. Thus, it is assumed that all patients modelled to be re-treated with a BTKi at second-line following first-line ibrutinib would not be resistant and therefore would derive the same benefit as a patient who had not received prior BTKi exposure.

Johnson & Johnson would additionally like to highlight that, as described in Section 3.3.4 of the CS, to account for the uncertainty in differential efficacy at second-line based on treatment received at first-line, weighted average HRs were derived for the ibrutinib and ASCT model arms. These HRs were based on the proportion of patients receiving subsequent treatment with ibrutinib or zanubrutinib, who were assigned a HR of 1, and the proportion of patients receiving R-BAC, BR or BSC, who were assigned a HR of 1.26. When the resulting weighted average HRs for the ibrutinib arm and ASCT arm of the model were applied to the reference curve based on RAY-3001 data, the resultant curves indicate that fewer second-line progression events are experienced in the model for the ASCT arm compared with the ibrutinib arm. Whilst this approach does not specifically consider whether patients who had prior ibrutinib exposure derive the same benefit as those without prior ibrutinib exposure, it does capture a potential difference in efficacy at second-line as a result of the treatment received at first-line based on the available data. Furthermore, uncertainty surrounding this differential efficacy was addressed via the DSA whereby the upper and lower estimates for the weighted second-line HR were informed by its upper and lower 95% confidence intervals. The results of the DSA demonstrate that varying the second-line HR resulted in minimal changes to the base results, with a maximum change to the INHB of $\pm$ [REDACTED] % for the ibrutinib regimen and $\pm$ [REDACTED] % for the ASCT regimen. These results therefore demonstrate that the base case results are robust to uncertainty relating to differential efficacy between the ibrutinib and ASCT regimen at second-line. [Placeholder: Potentially to remove text, given large impact for ibrutinib]

In conclusion, the use of RAY-3001 data to inform PF 2L to PD transitions for the ibrutinib arm is considered plausible, despite these patients having not received prior ibrutinib exposure, given there is no evidence to indicate prior exposure would impact outcomes. It should additionally be noted that UK clinical experts unanimously validated that data from the one prior lines subgroups of the ibrutinib arm of RAY-3001 represents the most appropriate efficacy source to inform PF2 2L to PD transitions, including that for the ibrutinib arm, despite the lack of prior BTKi exposure in RAY-3001.⁸

- c) Please comment on the plausibility of using the ibrutinib arm of RAY-3001 to inform PF 2L and PD transitions for the ASCT regimen, given that a minority of patients received prior ASCT treatment (i.e. assuming that patients relapsing post-ASCT have the same progression dynamics as a mixed relapsed/refractory population).

As discussed in the response to Question B7a), while prior ASCT treatment was not a requirement of RAY-3001, a non-insignificant proportion of patients ([REDACTED]%) received ASCT.³ Whilst Johnson & Johnson acknowledge that it is a limitation that not all patients received prior ASCT, to the best of

Johnson & Johnson's knowledge there is no evidence nor clinical rationale to indicate that patients with a prior history of ASCT would experience differential efficacy on a BTKi to those who were ASCT-naïve at first-line. As such, given the paucity of available evidence in this setting, use of the ibrutinib arm of RAY-3001 to inform PF 2L to PD transitions for the ASCT regimen is considered clinically suitable. Furthermore, as highlighted in the above responses, the one prior lines subgroups of the ibrutinib arm of RAY-3001 was unanimously validated as the most appropriate evidence source to inform PF 2L to PD transitions for the ASCT arm by UK clinical experts, even with knowledge of patients prior ASCT use.⁸

d) Please discuss the implications of the mismatch described in the preceding sub-questions for the economic modelling and the CS base-case results.

As discussed in the responses to the sub-questions above, given the lack of available evidence suggesting that prior BTKi-exposure in MCL patients would impact the efficacy of ibrutinib at second-line, the impact of the lack of inclusion of prior exposure to ibrutinib on the base case results is unknown. Similarly, given the lack of relevant published data, the impact of all patients having not received prior ASCT in RAY-3001 is unknown. Despite this, as outlined in response to Question B6c), given that the burden the ASCT regimen has on patients (and their caregivers) is persistent and long lasting, if anything, the fact that not all patients had received prior treatment with the ASCT-regimen in RAY-3001 likely means the base case results are conservative. Especially given the long-term disutility associated with ASCT is not captured in the 'reference' source informing the ASCT arm beyond the first-line setting.³⁴

Despite the above limitations, Johnson & Johnson maintain that RAY-3001 represents the most appropriate source of evidence to inform 'reference' transitions from PF 2L and PD given the paucity of available evidence in this setting, as was unanimously validated by clinical experts consulted at the November 2025 advisory board.⁸

e) Please provide an updated economic model and scenario analysis using alternative real-world and/or registry data that reflects the 2L modelled population to inform transitions from PF 2L and PD.

Johnson & Johnson are not aware of any real-world or registry data that reflects the modelled 2L population and addresses the limitations of RAY-3001. As such, it was not possible to provide the requested scenario.

f) Please provide an updated economic model and scenario analysis using extrapolated data from TRIANGLE to also inform PF 2L and PD transitions.

As noted in the response to Question B7a), given that the aim of TRIANGLE was to evaluate treatments in the first-line setting, following failure on first-line treatment, patients entered the 'long-term follow-up' period of the study where they were only followed up every six months with minimal information collected (survival, treatment, lymphoma status and secondary primary malignancies).⁹ As such, TRIANGLE did not routinely collect the efficacy data required to inform transitions from the PF 2L and PD health states in the model. Johnson & Johnson are therefore unable to provide the requested scenario.

B 8. Priority question. The company modelled different transition probabilities for FF 1L to death for the ibrutinib and ASCT regimens, implying differences in pre-failure mortality and time to 1L treatment failure. For both FF 1L to death and PF 2L to death, an annual mortality rate (AMR) was preferred over fitting parametric survival models.

- a) Please justify why pre-failure mortality (FF 1L to death) would be different between the ibrutinib and ASCT regimens.**
- i. Please comment on whether this could be coincidental, considering the low number of mortality events in TRIANGLE?**
 - ii. Please comment on whether there is an expected impact of ASCT on pre-failure mortality, and if so, please provide an updated economic model and scenario analysis including ASCT-related mortality separately.**
 - iii. Please elaborate to what degree the CS base-case results are driven by assumptions related to pre-failure mortality (differences) and provide scenario analyses, including a breakdown of disaggregated results, to demonstrate this.**

As noted within the submission, the high toxicity and resultant mortality-risk associated with the ASCT regimen translates to an increased risk of pre-failure mortality. This is reflected in the TRIANGLE OS KM data presented in Section 2.6.2 of the CS in which an increase in early fatal events is observed shortly after the end of induction treatment for patients treated with the ASCT regimen versus the ibrutinib regimen, correlating to when HDT-ASCT would be received.⁵ These data provide evidence of the high toxicity-related burden associated with HDT-ASCT, which is associated with an increased mortality-risk versus the ibrutinib regimen.

This increase in pre-failure mortality associated with the ASCT regimen is intrinsically captured in the AMR used within the economic model, which is directly calculated from TRIANGLE data. As the TRIANGLE data provides direct head-to-head evidence between the ASCT regimen and the ibrutinib regimen, use of this AMR reflects the most accurate available data to inform pre-failure mortality between the two regimens. Additionally, as highlighted by the EAG given that the patient numbers informing pre-failure events are low, including ASCT-related mortality separately would further decrease the sample size informing this transition, introducing additional uncertainty with minimal improvement in granularity. As such, this scenario has not been implemented within the economic model.

Whilst it is acknowledged that the number of pre-failure mortality events in TRIANGLE is low, the increased events in the ASCT arm compared to the ibrutinib arm is not considered to be coincidental. When consulted at the November 2025 advisory board clinical experts unanimously agreed that the relative ~2:1 increase in pre-failure mortality events associated with the ASCT regimen compared to the ibrutinib regimen was appropriate, due to the increased treatment-related mortality associated with ASCT.⁸ Furthermore, the clinical experts considered that the patient mortality events in the ASCT arm of TRIANGLE may even be slightly lower than expected in UK clinical practice and therefore if anything, may be conservative.⁸

Based on the above, use of the AMR from TRIANGLE to inform pre-failure mortality in the 1L FF health state in the economic model is considered the most robust evidence to inform this transition. Given that any scenario analyses conducted would be purely arbitrary in nature and therefore associated with increased uncertainty compared to the current base case approach, no scenario analyses have been explored. This approach is in line with NICE's methods for health technology evaluations (PMG36) where it is stated that there is a strong preference for high-quality RCTs to form the primary source of evidence.³⁷ Johnson & Johnson would however like to highlight that when varied in the deterministic sensitivity analysis (DSA), the AMR for the ASCT regimen and ibrutinib regimen resulted in minimal variation in the base case ICER (maximum ± 10%), as presented in Appendix D 5. The DSA therefore demonstrates that the base case results are robust to uncertainty in the AMRs utilised for both the ibrutinib and ASCT regimen in the economic model.

b) Please justify why the use of an AMR-based approach for the transitions of FF 1L to death and PF 2L to death was preferred over parametric survival modelling.

As noted in Section 3.3.1 of the CS, the number of pre-failure mortality events as of the latest data cut of TRIANGLE were limited across both arms (11/268 [4.1%] patients for the ibrutinib regimen and 22/269 [8.2%] patients for the ASCT regimen, respectively).⁵ As such, standard parametric extrapolation was not used to extrapolate time to pre-failure mortality from TRIANGLE in the model. This is because when there are limited events, parametric extrapolations are highly sensitive to the chosen distribution, and are therefore associated with considerable uncertainty when extrapolated over the model time horizon. As such, to minimise uncertainty, AMRs for the ibrutinib and ASCT regimens were utilised given that they could be directly derived from TRIANGLE data and therefore relied on fewer modelling assumptions. This approach was validated as preferential over the use of parametric extrapolation by an independent health economic expert consulted during the November 2025 advisory board.⁸ Furthermore, clinical experts consulted at the November 2025 advisory board validated that the relative difference in AMR between the ASCT arm and the ibrutinib arm was in line with clinical expectations.⁸

c) Considering the low number of death events, please provide an updated economic model and scenario analysis assuming equal pre-failure survival on first line treatment (FF 1L to death) between the two regimens and estimate a single parametric survival model, potentially including a temporary (once-off) mortality increase due to ASCT.

As noted in the response to Question B8a), the increased pre-failure mortality risk associated with the ASCT regimen compared to the ibrutinib regimen (modelled via the AMR) is derived from TRIANGLE data. TRIANGLE is a randomised controlled trial providing direct data on the ibrutinib regimen versus the ASCT regimen in a relevant population to this appraisal (ASCT-eligible patients with MCL).³ As such, the increased mortality risk is a direct reflection of the observed data derived from the gold standard of evidence; a RCT versus a relevant comparator in the population of interest.

The increased number of pre-failure mortality events observed in TRIANGLE in the ASCT arm is in line with clinical expectations, given the significant toxicity associated with the ASCT regimen which patients receiving the ibrutinib regimen are not subject to. This is supported by the fact that the ~2:1 relative number of pre-failure mortality events in the ASCT arm versus the ibrutinib arm recorded in TRIANGLE was unanimously validated as being in line with clinical expectations by five UK clinical experts during the November 2025 advisory board.⁸ Modelling equal pre-failure mortality was therefore not considered appropriate as it would go against direct RCT data and lack clinical plausibility, as such the requested scenario has not been provided. Johnson & Johnson would additionally like to highlight that uncertainty surrounding the AMRs utilised in the economic model were tested both within the probabilistic and deterministic sensitivity analyses presented within the original submission. The probabilistic base case results were highly aligned to the deterministic base case results (see Section 3.10 of the CS) and as noted in response to Question B8a) above, the DSA results demonstrate that the AMR does not significantly impact the INHB. These results therefore provide confidence that the base case results are robust to any perceived uncertainties surrounding first-line AMRs.

- d) Considering the low number of death events, please provide an updated economic model and scenario analysis assuming equal survival on second line treatment between the two regimens and estimate a single parametric survival model.

Following confirmation from the EAG that this question refers to equal survival on first line treatment between the two regimens, the response to this question is captured in the response to B8c).

B 9. Priority question. To inform the transition from PF 2L to PD, the company accounted for differential efficacy of second-line treatment options received by patients following first-line treatment with the ibrutinib or ASCT regimen by applying weighted average HRs to the ‘reference’ TTP curve to form TTP curves for the ASCT regimen and the ibrutinib regimen, respectively.

- a) **Please justify the assumption of different second-line treatment options for the ibrutinib and ASCT regimens.**

The second-line treatments and their associated distributions included in the economic model for the ibrutinib and ASCT arm respectively, were informed by feedback received from five UK clinical experts. The experts were independently asked to provide the second-line treatments and their associated distributions for two sets of patients: (1) Patients who received first-line treatment with the

ibrutinib regimen and (2) Patients who received first-line treatment with the ASCT regimen. As noted in the response to Question B5, the experts were not constrained by the treatments they could provide at second-line and yet all experts provided differing second-line treatment distributions between patients receiving the ibrutinib regimen or the ASCT regimen at first-line (see response to Question B20B 20.). This therefore provides confidence that the second-line treatment options received by patients in UK clinical practice would differ between the two regimens. Furthermore, the individual estimates provided by the clinical experts were subsequently aggregated and presented back to the experts during the November 2025 advisory board. The aggregated estimates included differing distributions of second-line treatments between patients receiving the ibrutinib regimen or the ASCT regimen at second-line and were unanimously validated as appropriate by all UK clinical experts.⁸ In addition, during the advisory board, clinical experts clearly highlighted that treatment decisions at second-line were influenced by treatment received at first-line.⁸ As such, the modelled differences in second-line treatment distributions between the ibrutinib and ASCT regimen are in line with clinical expectations.

b) Please provide a comparison of second-line treatments currently modelled for the ibrutinib and ASCT regimens with second-line treatments received in TRIANGLE and comment on the observed differences.

The subsequent treatments received by patients in TRIANGLE are presented in Section 2.7 of the CS. As TRIANGLE was a global, investigator-initiated trial, the subsequent treatments received by patients included options which are not currently available in UK clinical practice. As such, the subsequent treatments in TRIANGLE differed to those modelled for the ibrutinib and ASCT regimen, which were informed by feedback received from UK clinical experts and therefore only include treatments reimbursed in UK clinical practice (see response to Question B 20.). For example, some patients in TRIANGLE received treatments pirtobrutinib, venetoclax or obinutuzumab none of which are reimbursed in UK clinical practice for the treatment of r/r MCL.³⁸ Furthermore, the subsequent treatment data collected in TRIANGLE are not differentiated by line of treatment so it is unclear which treatments patients received at second-line, third-line or beyond. A detailed comparison of the subsequent treatment data in TRIANGLE versus the modelled subsequent treatments was therefore not feasible.

It is important to note that TRIANGLE data were only used to inform time to failure on first-line treatment (FF 1L to PF 2L) as well as mortality pre-failure on first-line treatment (FF 1L to Death) in the economic model. As such, subsequent treatment data from TRIANGLE did not inform efficacy in the economic model.

c) Please justify the mismatch between second-line treatment inputs to inform effectiveness (based on BTKis) and inputs to inform costs (based on different treatments, including non-BTKis).

The second-line treatments, and their distributions, used to inform costs and efficacy data for second-line treatments in the economic model were both derived from clinical expert feedback for the November 2025 advisory board. The derivation of these estimates are detailed in full in response to Question B9a).³⁹ In terms of costs, the subsequent treatment distributions elicited from clinical

experts were multiplied by the cost per cycle to calculate the total costs associated with subsequent treatment costs. This is detailed further in Section 3.5.2 of the CS.

In terms of second-line treatment efficacy, transitions from PF 2L to PD (progression on second-line treatment) for patients receiving second-line treatment with ibrutinib (regardless of first-line treatment) were modelled using time-to-progression (TTP) data from the ibrutinib arm of RAY-3001 (one prior line of therapy subgroup). As detailed in the response to Question B6c), given the paucity of data in this setting, five UK-based clinical experts validated that RAY-3001 represents an appropriate source of data to inform transition probabilities from this health state.⁸ However, to overcome the “mismatch” between modelling second-line treatment efficacy based on patients receiving second-line treatment with ibrutinib (a BTKi) and modelling the costs of several subsequent treatments (including non-BTKis), the extrapolated TTP data from the ibrutinib arm of RAY-3001 (one prior line subgroup) was considered to be the ‘reference’ curve, to which weighted averaged HRs derived for the ibrutinib regimen and the ASCT regimen were applied. As detailed in Section 3.3.4 of the CS, these weighted HRs were based on the subsequent treatment distributions elicited from UK clinical experts (identical to those used to inform cost estimates), and data/assumptions around the relative efficacy between subsequent treatments. As such, the resulting TTP curves for the ibrutinib and ASCT regimens account for the varied subsequent treatments used at second line (both BTKi and non-BTKi) and thus are aligned with the treatments used to inform second-line subsequent treatment costs. Of note, both the approach to modelling differential efficacy between BTKi and non-BTKi treatments at second-line as well as the specific HRs used were validated as appropriate by clinical experts at the November 2025 advisory board.⁸

d) Please elaborate on the appropriateness of the MANTLE-FIRST study to inform the weighted average HRs in terms of population, intervention(s), comparator(s) and outcomes.

The MANTLE-FIRST study provides direct evidence on the relative efficacy of ibrutinib vs. R-BAC in patients (n=126) with r/r MCL following first-line treatment with intensive regimens including R-HDAC.³⁹ As detailed in the CS, at the November 2025 advisory board, UK clinical experts were presented with a choice of the following options to inform the HR between BTKis and R-BAC:

- Option 1a (TA502): Bucher indirect treatment comparison of ibrutinib (RAY-3001) vs rituximab-based immunochemotherapies (OPTIMAL; adjusted to account for the addition of rituximab to chemotherapy)⁴⁰
- Option 1b (TA502): Bayesian network meta-analysis of ibrutinib (RAY-3001) vs rituximab-based immunochemotherapies (OPTIMAL; adjusted to account for the addition of rituximab to chemotherapy)⁴⁰
- Option 2: MANTLE-FIRST study (cohort study of R-BAC versus ibrutinib)

A UK clinical expert noted that the HRs derived from TA502 were not appropriate given that none of the patients in the OPTIMAL study received R-BAC and instead received a basket of investigator choice therapy.⁴⁰ The UK clinical expert highlighted that R-BAC is the most toxic chemotherapy and therefore that the adjustment made to incorporate the addition of rituximab to chemotherapy was associated with significant uncertainty. Furthermore, the clinical expert highlighted that the OPTIMAL study data, which were published in 2009, were outdated. In contrast, the health economic expert

noted that the MANTLE-FIRST study was the obvious choice to inform differential subsequent treatment efficacy, given it is a head-to-head trial in the correct patient population with the correct treatments. Ultimately, all clinical experts unanimously agreed that the HRs derived from TA502 were associated with validity issues and therefore that the MANTLE-FIRST study represents the best available evidence to inform the differential efficacy between BTKis and rituximab-based chemotherapy in this setting.⁸ Furthermore, of significance, UK clinical experts also independently identified the MANTLE-FIRST study as the most appropriate source of evidence to inform the HR between BTKis and R-BAC, prior to the list of potential sources being presented to the experts during the November 2025 advisory board.⁸.

Finally, the specific PFS HR obtained from the MANTLE-FIRST study (HR: 1.26; 95% CI: 0.76, 2.09; p-value=0.373) was validated as in line with clinical expectations for the relative efficacy of R-BAC versus a BTKi during the November 2025 advisory board.^{8, 39} As such, the MANTLE-FIRST study is considered the most appropriate source to inform the relative efficacy of ibrutinib versus R-BAC in the second-line setting in the economic model.

e) Please elaborate on the appropriateness of assuming BSC efficacy to be equal to rituximab-based chemotherapy.

To the best of Johnson & Johnson's knowledge, no studies comparing BSC to ibrutinib in the relevant setting exist. As such, whilst it is acknowledged that BSC is likely to be less effective in clinical practice than rituximab based chemotherapy, given the lack of data to support this, any input used to model the relative efficacy of BSC versus rituximab-based chemotherapy would have been purely arbitrary and therefore would not help resolve uncertainty. As such, in the absence of empirical evidence on the relative efficacy of BSC versus ibrutinib, as a simplifying assumption, the efficacy of BSC was assumed equal to that of the second least efficacious second-line treatment provided by the UK clinical experts (rituximab-based chemotherapy). This simplifying assumption was deemed appropriate given only a very small proportion of patients were modelled to receive BSC at second-line (1.1% or 0.8% following the ibrutinib or ASCT regimen, respectively) and therefore this assumption would have minimal impact on results.

f) Please provide an updated economic model and scenario analysis assuming

- i. second-line treatment distributions to be independent of first-line treatment received (i.e. equal for both regimen).**
- ii. second-line treatment distributions informed based on the second-line treatments received in TRIANGLE.**
- iii. all patients receiving BTKis in second line.**
- iv. reduced efficacy for BSC (relative to rituximab-based chemotherapy).**

As discussed in the responses to the prior parts of the question, the approach to modelling second-line treatment options is appropriate and in line with clinical expectations. The second-line treatment options within the model and their distributions were informed by, and unanimously validated as appropriate, by clinical experts at the November 2025 advisory board; the derivation of these estimates are detailed in full in response to Question B20B 20. .³⁹ Additionally, as noted in Question B9c), differential efficacy between BTKi and non-BTKi treatments at second-line was applied via the use of HRs which were validated as appropriate by clinical experts at the November 2025 advisory board.⁸

However, for completeness and in line with the EAG's requests, several scenario analyses have been conducted. Firstly, a scenario has been conducted where the distribution of treatments at second-line were set equal. Specifically, the distribution for the ASCT regimen was set equal to that of the ibrutinib regimen using the distributions that clinical experts thought appropriate for patients who had received the ibrutinib regimen at first-line (Question B 9. f)i). Secondly, a scenario analysis has been conducted in which all patients were assumed to receive BTKis at 2L (Question B 9. f)iii). For this scenario it was assumed that 100% of ibrutinib patients would receive zanubrutinib at 2L, given feedback received from UK clinical experts that patients would not be retreated with ibrutinib at 2L. For ASCT patients, non-BTKi distributions were redistributed equally between ibrutinib and zanubrutinib. The results of both scenario analyses are presented in Table 11 and demonstrate that the model is sensitive to the distribution of subsequent treatments within the model. However, it is important to note that the distributions used within the base case are the most accurate to UK clinical practice, as validated by consensus achieved at an advisory board of UK clinical experts.³⁹ Of significance, none of the experts thought it reasonable that all patients would receive BTKis at 2L, as outlined in response to Question B20a) where each of the expert's individual second-line distributions are provided. Furthermore, during the advisory board, the clinical experts were clear that the decisions around subsequent treatments would be dependent on the treatments received at first-line; as such, assuming equal distributions between the two treatments is not an appropriate or clinically justifiable assumption. The subsequent treatment distributions used within the model, as informed and unanimously validated by clinical expert opinion, are therefore the most relevant to inform UK decision-making.

Regarding the scenario requested in part ii), as noted in the response to Question B9b), as TRIANGLE was a global, investigator-initiated trial, the subsequent treatments received by patients included options which are not currently available in UK clinical practice and therefore are not relevant for UK decision-making. Furthermore, in line with the FFS data presented in Section 2.6 of the CS, a relatively small proportion of patients in both Arm I and Arm A experienced stable disease at the end of induction or disease progression at the time of the latest CCO. Thus, only 18.7% of patients in Arm I and 24.2% of patients in Arm A would have been eligible for 2L treatment in TRIANGLE.⁵ As such, the subsequent treatment data in TRIANGLE is limited to a small sample size and therefore may not be representative of the cohort as a whole. Additionally, owing to the investigator initiated nature of TRIANGLE the subsequent treatment data were not differentiated by line of treatment. Finally, of particular importance, data from TRIANGLE were only used to inform transitions from the first-line health states within the model (FF 1L to PF 2L and FF 1L to Death) as such, subsequent treatment data from TRIANGLE do not inform any efficacy data within the economic model. As such, it is not appropriate to use the treatment distributions from TRIANGLE to inform the second-line treatment distributions within the model as they are neither relevant to the

existing efficacy data nor aligned to UK clinical practice. A scenario analysis based on TRIANGLE subsequent treatment data has therefore not been conducted.

Finally, regarding the scenario requested in part iv), as noted in the response to Question B9e), in the absence of empirical evidence on the relative efficacy of BSC versus ibrutinib, as a simplifying assumption, the efficacy of BSC was assumed equal to that of the second least efficacious second-line treatment (rituximab-based chemotherapy) in the economic model. Given the lack of available evidence to inform differential efficacy assumptions between these two treatments, and therefore that any scenario would be purely arbitrary and therefore would not help resolve uncertainty, no scenario analysis has been conducted. Johnson & Johnson would however like to highlight that given the proportion of patients receiving BSC at second-line across both model arms was very low (~1%) such a scenario would have a minimal impact on the results of the cost-effectiveness analysis and therefore would not impact cost-effectiveness conclusions.

Table 11: Deterministic scenario analysis results (ibrutinib PAS price): subsequent treatment assumptions

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case	████	██	<i>Dominant</i>	██	-
B9 f)i. ASCT second-line treatment distributions set equal to ibrutinib	████	██	████	██	██
B9 f)iii. All patients receive BTKis at 2L (100% of ibrutinib patients receive zanubrutinib at 2L. For ASCT patients, non-BTKi distributions were redistributed equally between ibrutinib and zanubrutinib)	████	██	████	██	██

Abbreviations: 2: second-line; AE: adverse event; ASCT: autologous stem cell transplant; BTKi: Bruton's tyrosine kinase inhibitor; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

B 10. According to the CS, for the estimation of TTF, patients alive without failure at the latest contact were censored at the latest tumour assessment date, whilst patients without any lymphoma restaging during or at the end of induction were censored at the date of randomisation. Pre-failure deaths were separately captured in the FF 1L to death transition.

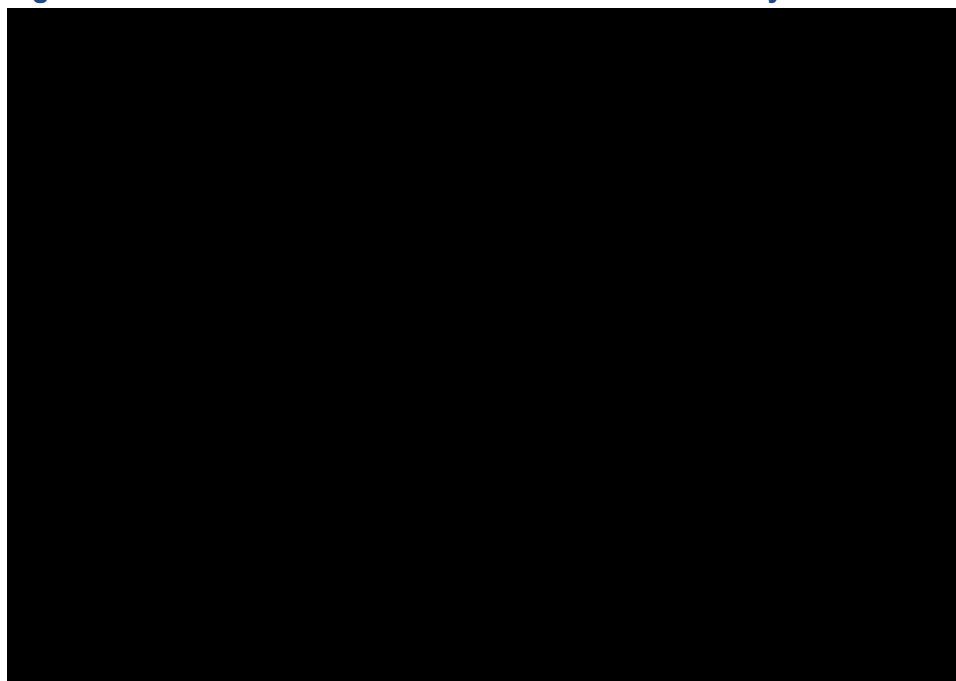
- a) In the CS it is stated that “Censoring for pre-failure deaths in the transition from FF 1L to PF 2L, and subsequently capturing pre-failure deaths separately as part of FF 1L to Death transition (as described in Section 3.3.1 above) addresses previous criticism of a prior four-state semi-Markov model for ibrutinib in chronic lymphocytic leukaemia (CLL [TA891])”. Please elaborate in detail what the committee’s and EAG perspectives were on the TA891 model (including any criticism) and how the company in the current appraisal tried to address this.

In Section 4.2.6 of the EAG report for TA891, the EAG noted that “The company’s approach to estimating the transition probability from PF 1L to PF 2L, by subtracting the estimated pre-progression risk of mortality (capped by general population mortality) from the extrapolated risk of progression or death (based on fitted PFS curves also capped by general population mortality), has some pronounced implications in the older FCR unsuitable cohort. With higher background mortality in this older group, the extrapolated PFS curves and pre-progression mortality both converge to age sex/matched general population mortality at an earlier stage in the model when a substantial proportion of the cohort remain alive and progression free. The calculated risk of progression (to PF 2L) becomes zero from this point onwards, inferring that a proportion of patients are essentially cured. Table 17 below shows the time in years and the proportion alive and progression free for each comparator when extrapolated risks of progression or death and pre-progression mortality converge. This appears to be more an artefact of the approach rather than a well justified assumption.”⁴¹

The committee concluded that the model structure and its outcomes remained appropriate for decision making despite the limitations of the data used to inform its parameters.⁴¹

In the semi-Markov model presented by Johnson & Johnson in this submission, these limitations were addressed by capturing mortality during FF 1L on the basis of separate estimates of TTF, and time to pre-failure death whereby the risk of pre-failure death was capped by general population mortality, derived directly from the patient level data available from TRIANGLE. As part of TA891, the EAG raised concerns of an implied cure fraction as a consequence of the modelling assumptions.⁴¹ Johnson & Johnson would like to reassure the EAG that no cure fraction has been assumed. Whilst a general population mortality cap is applied to the annual mortality rates (AMRs) across health states to ensure survival does not exceed that of the general population, the mortality hazard ratio in both arms in the model exceeds that of the general population throughout the entire model time horizon. Furthermore, at no point in the model is it assumed that the first-line time-to-failure hazard is equal to zero, which was a concern raised in TA891.⁴¹ As a result, no patients with MCL are assumed to be cured, as reflected in Figure 3 below.

Figure 3: OS risk in the cost effectiveness model over 30 years



Abbreviations: ASCT: autologous stem-cell transplant; OS: overall survival.

- b) Please provide an overview of the number of patients without any lymphoma restaging during or at the end of induction for the ibrutinib regimen and ASCT regimen separately.**

In TRIANGLE, FFS is 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 As part of this assessment, patients alive without failure at the latest contact will be censored at the latest tumour assessment date. Patients without any lymphoma restaging during or at the end of induction will be censored at the date of randomisation.³

In TRIANGLE, by the CCO, 87 and 61 patients experienced an FFS event in Arm A and Arm I, respectively.⁵ A total of 182 patients in Arm A and 207 patients in Arm I were censored.⁵ Of these, only █ patients in Arm A and █ patients in Arm I were censored at the date of randomisation, consistent with the definition above for patients without lymphoma restaging during or at the end of induction.³ The dataset available to Johnson & Johnson does not specify the exact reason for censoring beyond indicating the randomisation date; this interpretation was therefore inferred based on the FFS definition. Given the small number of such cases and the similar distribution across arms, this is not expected to have a meaningful impact on the model.

- c) Please elaborate what the implications of imbalances between the two regimens would be for the economic modelling.**

See response to Question B10b) above.

- d) Please provide an updated economic model and scenario analysis exploring alternative censoring rules, e.g. also censoring patients without any lymphoma restaging during or at the end of induction or at the latest contact.**

As detailed in the response to Question B10b) above, the number of patients assumed to be without any lymphoma restaging during or at the end of induction for the ibrutinib regimen and ASCT regimen (based on the timepoint at which they were censored) was small and well balanced across treatment arms. As such, these patients are not anticipated to have a meaningful impact on the economic model and therefore alternative censoring rules were not explored via scenario analyses.

- e) Censoring pre-failure deaths in the TTF analysis used to inform transitions from FF 1L to PF 2L with deaths instead modelled separately via the FF 1L to death transition relies on strong assumptions regarding the independence of treatment failure and death. Please comment on the appropriateness of these assumptions and discuss the potential implications for the estimated transition probabilities.**

The current model calculates the per cycle hazards from the time to failure and time to death in 1L survival models, then uses the pre-cycle hazard (not the survival estimates themselves) of time to failure and time to death in 1L curves to calculate the proportion of patients who are failure free as well as incident failure from 1L and incident death from 1L. This is consistent with the competing risk application and therefore does not rely on the assumption of independence of probabilities of treatment failure and death.

- f) To explore the potential impact of assuming that failure and death are independent: please provide an updated economic model and scenario analysis including alternative handling of pre-failure deaths using:**

- i. a competing-risks framework
- ii. a composite endpoint where death is treated as a failure event rather than censored.

As discussed in the response to Question B10e) above, the current model implementation of time to failure and pre-failure death relies on the pre-cycle hazard and not the survival estimates themselves. This approach is viewed to be consistent with the competing risks framework and therefore an updated economic model or scenario analysis that includes alternative handling of pre-failure deaths has not been provided.

Adverse events

B 11. The model includes several adverse events related to abnormal blood values, including leukopenia, decreased platelet count, decreased neutrophil count, decreased white blood cell count, and decreased lymphocyte count. Assumptions were required to inform the impact of these events on health-related quality of life (CS Table 50) and costs (CS Table 72). The EAG notes that these events are typically reported as laboratory abnormalities in clinical trials and might often be asymptomatic. It is therefore unclear whether they have an autonomous impact on health-related quality of life or costs, or whether their impact overlaps with that of other modelled toxicities, potentially resulting in double counting.

- a) Please justify, with empirical evidence and clinical expert statements,, that these blood value abnormalities have an autonomous (i.e. non-overlapping with other toxicities) impact on patients' health-related quality of life.

The model considers Grade ≥ 3 AEs, that occurred at an incidence of $\geq 5\%$ in at least one of the relevant treatment arms in TRIANGLE (i.e., the ibrutinib arm [Arm I] or the ASCT arm [Arm A]).^{3, 5} By definition, Grade 3 AEs are classified as severe or medically significant but not immediately life-threatening, indicated for hospitalisation or prolongation of hospitalisation, disabling and/or limiting self-care activities of daily living such as bathing, dressing, feeding and toilet use.⁴² Grade 4 AEs are defined as life-threatening or where urgent intervention is required, and Grade 5 AEs are events related to death.⁴² Therefore, by definition it is anticipated that Grade ≥ 3 AEs would impact patients HRQoL, as supported by the disutilities associated with these AEs, which were sourced from prior NICE TA891 as per NICE TA487.^{41, 43} The approach to include autonomous impacts of blood value abnormalities on HRQoL is therefore intended to capture the direct burden that each AE imparts on patients. This is in line with the approach adopted in a previous and relevant appraisal in MCL (TA1081), which was accepted as suitable for decision making by the EAG and committee.³³

Johnson & Johnson however acknowledge that some of the blood value abnormalities included in the economic model may be less likely to impart an autonomous impact on HRQoL in UK clinical practice. As such, whilst both the modelling of Grade ≥ 3 AEs and including the autonomous impact of blood value abnormalities is commonplace in NICE appraisals, in order to minimise the risk of double counting, Johnson & Johnson have conservatively updated the Company base case to remove both the disutilities and costs associated with AEs that may be frequently reported as laboratory abnormalities and may be asymptomatic. Specifically, leukopenia, neutrophil count decrease, white blood cell decrease and lymphocyte count decrease have been removed from the economic model. Platelet count decrease has not been removed from the updated base case given feedback from a clinical expert that patients with severely low platelet count may require more involved care, such as prophylactic platelet transfusions, and thus low platelet count would have a significant autonomous impact on patient HRQoL and impart a financial burden on the NHS.¹⁶

The updated cost-effectiveness results based solely on this change to the modelling of AEs relating to blood abnormalities (including both the removal of costs and disutilities) are presented alongside the original base case results in Table 5 in the introduction to Section B above. The results show that the direct impact of this modelling update on incremental costs and QALYs (compared to the original base case results presented in the CS) is negligible and therefore demonstrate that the base case results are robust to AE assumptions related to blood value abnormalities.

b) Please justify, with empirical evidence and clinical expert statements, that these blood value abnormalities generate autonomous costs (for example, additional monitoring, treatment, or hospitalisation) that are not already captured through other modelled events or disease management costs.

As detailed in the response to Question B11a) above, only severe (Grade ≥ 3) AEs related to blood value abnormalities were captured in the original economic model.^{3, 5} The inclusion of the autonomous impacts of blood value abnormalities on costs was intended to capture the direct burden that each specific AE imparts on the NHS. This was in line with the approach adopted in a previous and relevant appraisal in MCL (TA1081), which was accepted as suitable for decision making by the EAG and Committee.³³ Therefore, based on the available data, and the use of autonomous costs to model AEs in prior NICE appraisals, costs to inform severe AEs related to blood value abnormalities were sourced from NHS Reference Costs 2024/25 and included in the original economic model.⁴⁴

However as noted in response to Question B11a) above, Johnson & Johnson acknowledge that some of the blood value abnormalities included in the economic model may be less likely to impart an autonomous impact on costs in UK clinical practice. As such, whilst both the modelling of Grade ≥ 3 AEs and including the autonomous impact of blood value abnormalities is commonplace in NICE appraisals, in order to minimise the risk of double-counting, Johnson & Johnson have conservatively updated the Company base case to remove both the disutilities and costs associated with leukopenia, neutrophil count decrease, white blood cell decrease and lymphocyte count decrease from the economic model.

The updated cost-effectiveness results based solely on this change to the modelling of AEs relating to blood abnormalities (including both the removal of costs and disutilities) are presented alongside the original base case results in Table 5 in the introduction to Section B above. The results show that the direct impact of this modelling update on incremental costs and QALYs (compared to the original base case results presented in the CS) is negligible and therefore demonstrate that the base case results are robust to AE assumptions related to blood value abnormalities.

c) Please provide scenario analyses, including an updated version of the economic model, in which

- i. disutilities associated with these blood value abnormalities are excluded
- ii. costs associated with these blood value abnormalities are excluded

As explained in response to Question B11a) and b) above, Johnson & Johnson have conservatively updated the base case analysis to remove specific AEs related to blood abnormality values that are anticipated to be associated with a risk of double-counting (neutropenia, anaemia, thrombocytopenia, febrile neutropenia, hypokalaemia, and blood platelet count decrease). The updated cost-effectiveness results based on the removal of these AEs are presented alongside the original base case results in Table 5 in the introduction to Section B above to show the direct impact of this modelling update. This update, combined with the resource use frequencies updates outlined in response to Question B22c)) make up the updated base case results submitted alongside this clarification question response and presented in Table 12 below.

For completeness, scenario analyses have also been conducted to explore the uncertainty associated with the inclusion of disutilities and costs associated with *remaining* blood value abnormalities in the economic model (that is, the disutilities and costs associated with neutropenia, anaemia, thrombocytopenia, febrile neutropenia, hypokalaemia, and blood platelet count decrease). The first scenario analysis removed the disutility applied for all *remaining* blood value abnormalities, whilst the second scenario analysis removed the costs applied for all *remaining* blood value abnormalities.

Results of the two scenario analyses are presented in Table 12. Both scenarios had a negligible impact on the base case incremental costs and QALYs, with the ibrutinib regimen remaining dominant over the ASCT regimen. These scenarios therefore demonstrate that the base case analysis is robust to uncertainties relating to resource use and disutility assumptions relating to the *remaining* blood value abnormalities included in the economic model.

Table 12: Disutilities and costs associated with blood value abnormalities scenario analysis results (ibrutinib PAS price)

Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base Case (disutilities and costs applied for all remaining AEs^a included in the model)</i>	████	██	<i>Dominant</i>	██	-
No disutility applied for remaining blood value abnormalities	████	██	Dominant	██	████
No costs applied for remaining blood value abnormalities	████	██	Dominant	██	████

Footnote: ^a Neutropenia, anaemia, thrombocytopenia, febrile neutropenia, hypokalaemia, and blood platelet count decrease.

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

B 12. The CS model includes first-, second-, and third-line treatments; however, only adverse events associated with first-line treatment are explicitly modelled. Given that the model might predict differential incidences in second- and third-line

treatments between strategies, it is unclear whether excluding adverse events in later lines may bias results.

- a) Justify why adverse events associated with second- and third-line treatments are excluded, particularly in light of differential exposure between strategies.

As detailed in the final scope, the focus of this appraisal is for first-line treatment of adults with untreated MCL when an ASCT is suitable. As established by several prior NICE technology appraisals (TAs) in first-line NHL indications, the approach to only model adverse events (AEs) associated with the treatment line under consideration is a commonly utilised and accepted approach to avoid the introduction of unnecessary complexity and uncertainty in the model.^{45, 46} Similarly, a prior appraisal in MCL for second-line treatment also only modelled AEs associated with the treatment line of relevance to the indication.³³

Accordingly, the inclusion of AEs associated with second and third-line treatments is seen as overly complicated and superfluous for assessing the cost-effectiveness of the ibrutinib regimen versus the ASCT regimen in this indication.

- b) Please provide scenario analyses, including an updated version of the economic model, in which adverse events associated with second- and third-line treatments are incorporated, or alternatively demonstrate that their exclusion does not materially affect cost-effectiveness results.

In line with the rationale presented in the response to Question B12a), and due to the time limited nature of the Clarification Question responses, the requested scenario analyses would add significant complexity to the model and as such have not been presented.

However, a scenario analysis has been explored in which the impact treatment-related AEs are removed from the model for both first-line treatment options. The results of this scenario analysis, presented in Table 13, demonstrate that the exclusion of AEs has a limited impact on the incremental costs, incremental QALYs and the ICER. As such, these results demonstrate that any impact of AEs at later lines would be minimal, and not impact decision-making.

Table 13: Deterministic AE scenario analysis results (ibrutinib PAS price)

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case (AEs for first-line treatments only)</i>	■	■	<i>Dominant</i>	■	-
No AEs	■	■	Dominant	■	■

Abbreviations: AE: adverse event; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

B 13. First-line health-state utilities were informed by the SHINE trial, while disutility values for first-line adverse events were derived from published literature. Please justify the use of external literature rather than SHINE trial data to inform adverse event disutilities. In addition, please provide scenario analyses, where feasible, exploring the impact of alternative disutility assumptions for first-line adverse events consistent with the utility data observed in SHINE.

Disutility values for first-line AEs were derived from relevant published literature as this was the most appropriate data source available to inform the cost-effectiveness analysis. Disutility values for first-line AEs were not informed by SHINE trial data, as the SHINE trial did not collect disutility values for first-line AEs. Therefore, an alternative source of data was required to inform disutility values for first-line AEs. In line with the standard approach taken across prior NICE TAs in MCL and other NHL indications, the CS sourced disutility values for AEs from the published literature.^{33, 45, 46}

As SHINE trial did not collect disutility values for first-line AEs, it is not feasible to explore the impact of alternative disutility assumptions for first-line AEs consistent with the utility data observed in SHINE. Thus, scenario analyses exploring alternative disutility assumptions have not been presented. However, as presented in the response to Question B12b), a scenario analysis has been explored in which the impact treatment-related AEs are removed from the model for both first-line treatment options. The results, presented in Table 13 above, demonstrate that the disutility values for first-line AEs applied to first-line treatments have a limited impact on the incremental QALYs, and ultimately a limited impact on the ICER.

Health-related quality of life

B 14. Priority question. The EAG considers internal consistency of health-state utilities across lines of therapy to be a potential key driver of incremental QALYs and therefore decision uncertainty. Health-related quality of life (HRQoL) in the economic model was informed by EQ-5D data from the SHINE trial for the failure-free on first-line treatment (FF 1L) health state, and pooled EQ-5D data from the RAY-3001 and SPARK trials for the progression-free on second-line treatment (PF 2L) and progressed disease (PD) health states.

a) According to the CS, “HRQoL were not routinely collected in TRIANGLE”. Please clarify:

- i. whether any EQ-5D (or other preference-based HRQoL) data were collected in TRIANGLE,**

ii. at which time points, and

iii. for which patient subsets.

Johnson & Johnson confirm that, due to the investigator-initiated nature of TRIANGLE, no HRQoL data were collected within TRIANGLE.⁵ Johnson & Johnson would however like to note that, whilst the investigator nature of TRIANGLE means there are some unavoidable limitations in terms of data availability, the investigator-nature of the trial underscores the substantial unmet need and therefore desire in the clinical community for an alternative treatment to the ASCT-regimen. Furthermore, the outcomes presented in Section 2 of the CS are expected to translate to improvements in patients HRQoL and psychological status. The avoidance of the acute toxicity and associated mortality risk associated with the HDT-ASCT regimen will likely result in a reduced toxicity burden as well as reduced anxiety, due to a reduced fear of death in patients. Additionally, given that disease progression is associated with worsening symptoms and prognosis, the extended time to progression in patients receiving the ibrutinib regimen over the ASCT is expected to translate to improvements in patient HRQoL, as patients are able to remain in a state with a reduced clinical burden for longer.⁵ Despite this, owing to the lack of HRQoL data from TRIANGLE, treatment independent HSUVs were conservatively utilised in FF 1L health state in the economic model.

b) Please justify the decision not to use TRIANGLE HRQoL data to inform health state utilities, with reference to data completeness, timing, and representativeness.

N/A – As stated in response to Question B14a) above, HRQoL data were not collected within TRIANGLE and therefore it was not possible to use TRIANGLE HRQoL data to inform health state utilities.⁵

c) Please discuss the implications of informing FF 1L utilities from SHINE and PF 2L/PD utilities from RAY-3001 and SPARK for internal consistency across health states and lines of therapy, with specific reference to:

- i. comparability of patient populations (e.g. disease severity, treatment exposure, response status) across the contributing trials**
- ii. observed differences in mean utility values between FF 1L, PF 2L and PD, and whether these differences plausibly reflect disease progression rather than between-trial or modelling artefacts (i.e. difference between the regression approaches used for FF 1L vs PF 2L and PD).**

iii. the implied utility decrements when comparing health states (FF 1L to PF 2L, PF 2L to PD) and whether these are clinically credible

iv. how any remaining structural inconsistency is explored in scenario or sensitivity analyses.

As noted above, given no HRQoL data were collected in TRIANGLE, external sources of utility were required. To the best of Johnson & Johnson's knowledge, given the paucity of evidence in this setting, no data sources exist that could inform utility values for all three health states. Given the absence of utility data from a single trial that is appropriate to inform values for all three health states, the utility values used within the model reflect the best available data.

The utility inputs informing the FF 1L health state (from SHINE) and the PF 2L and PD inputs (from RAY-3001 and SPARK) were selected to best reflect the patient populations and disease trajectories of patients at different lines of therapy and progression status.

As discussed in Section 3.4 of the CS, as the humanistic SLR did not identify any studies reporting EQ-5D data in previously untreated, transplant-eligible patients with MCL, data in transplant-ineligible patients was considered the most relevant by clinical experts.¹² Of the two studies identified in transplant-ineligible patients, SHINE was considered most appropriate given patients received ibrutinib in combination with immunochemotherapy, in line with the TRIANGLE regimen. SHINE provides EQ-5D data in patients aged ≥ 65 with untreated MCL who are ineligible for ASCT and receive ibrutinib in combination with BR (plus rituximab maintenance). The trial population is inherently frailer and older than typical ASCT-eligible patients who would receive first-line treatment in clinical practice as was noted by clinical experts consulted at the November 2025 advisory board. In order to minimise the impact of this on the utility values, age-adjustment was applied to adjust the SHINE-derived utilities towards the FF 1L patient population (aligned with the patient population from TRIANGLE). The availability of IPD enabled alignment adjustments to better reflect the TRIANGLE Arm I population, and adjustment was conducted considering the following covariates: sex, presence of AEs during the EQ-5D measurement, latest available ECOG performance status; baseline disease stage, presence of B-symptoms, creatinine clearance below 30 ml/min and bone marrow involvement. This approach ensured that the utility value reflected the characteristics of the TRIANGLE population, where available covariates allowed.

As discussed in Section 1.3.4 of the CS and validated by feedback received from UK clinical experts, following 1L treatment, patients with MCL commonly receive BTKis in UK clinical practice.⁸ It was therefore considered most appropriate to use utility values elicited from patients with MCL receiving BTKis at 2L to inform these health states. In line with the accepted values informing the equivalent health states in the ibrutinib (TA502) and zanubrutinib (TA1081) NICE appraisals, the health state utility values for PF 2L and PD were informed by pooled data from the RAY-3001 and SPARK trials.^{33, 40}

The decline in utility values seen between the different health states are considered to be reflective of clinical practice, with patients anticipated to experience a decrease in quality of life following failure on first-line treatment due to increased symptom burden.²⁵ Furthermore, when consulted at the November 2025 advisory board, clinical experts unanimously agreed that as patients' disease

progresses, there symptom burden would increase and therefore they would have a worse quality of life.⁸ As such, the clinical experts validated that the utility decrement between the PF 2L and PD HSUVs used in the base case economic analysis was appropriate.⁸ As such, the utility decrements between health states are considered to be clinically plausible and not just a modelling artefact.⁸

Based on the above, the utility values used within the model are considered to represent the best available data. Furthermore, as noted in Section 3.11.3 of the CS, a scenario analysis was conducted to explore the impact of any uncertainty surrounding the base case HSUVs. In this scenario (#6 of the CS), the HSUVs for PF 2L and PD were informed by RAY-3001 alone as opposed to pooled RAY-3001/SPARK data, to align with the efficacy data informing the transitions for these health states. As a result, HSUVs for the PF 2L and PD health states were assumed to be equal. The results of this scenario analysis are represented in Table 14 below for completeness and demonstrate that removal of the decrement between the PF 2L and PD health states included in the economic model has a minimal impact on cost-effectiveness results. These results therefore provide confidence that any uncertainty surrounding the decrement between HUSVs included in the base case analysis would not alter cost-effectiveness conclusions.

Table 14: Deterministic scenario analysis results (ibrutinib PAS price): HSUV

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (HSUVs: RAY-3001/SPARK for PF 2L and PD)	■	■	Dominant	■	-
HSUVs: RAY-3001 for PF 2L and PD	■	■	Dominant	■	■

Abbreviations: 2L: second line; HSUV: health-state utility value; ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; PD: progressed disease; OF: progression-free; QALY: quality-adjusted life year.

B 15. The company used EQ-5D-5L data from the SHINE trial (progression-free patients in the ibrutinib arm), mapped to EQ-5D-3L and analysed using a mixed-model repeated measures (MMRM) approach to inform FF 1L health state utilities.

a) Please justify the choice of an MMRM framework with reference to:

- i. the longitudinal structure of the SHINE EQ-5D data
- ii. the extent and pattern of within-patient repeated measurements

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

b) Please provide a concise summary of the EQ-5D data used, including:

i. number of patients and observations

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

ii. assessment time points

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

iii. proportion of missing data over time

iv. assumptions made regarding missingness (e.g. MAR)

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

c) Please present the estimated mean EQ-5D utility profile over time from SHINE, and comment on whether utilities appear stable, improving, or declining within the FF 1L period.

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

d) Please clarify the final model specification (fixed effects included, random intercept and/or slope) and justify why this structure was selected.

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

e) Please provide the following scenario analyses to assess robustness:

- i. FF 1L utility estimated using a pooled mean EQ-5D value (ignoring time)
- ii. FF 1L utility estimated using an MMRM including both treatment arms and a treatment indicator (including SHINE trial data from both arms)
- iii. FF 1L utility estimated using a progression-adjusted model including progressed disease as a covariate (including SHINE trial data from both progression-free and progressed patients/observations).

In line with the agreed extension to the CQ responses, the response to Question B15 will be provided by the 4th March 2026.

B 16. EQ-5D-5L data from the ibrutinib arms of the RAY-3001 and SPARK trials were pooled and analysed using a mixed model to estimate PF 2L and PD health state utilities.

a) Please describe how EQ-5D data from RAY-3001 and SPARK were combined, including:

- i. alignment of assessment schedules
- ii. consistency of EQ-5D instruments and value sets
- iii. any differences in baseline patient characteristics relevant to HRQoL
- iv. statistical methods used

In line with the agreed extension to the CQ responses, the response to Question B16 will be provided by the 4th March 2026.

b) Please justify the pooling of these trials for utility estimation and explain how potential between-trial heterogeneity was addressed (e.g. trial indicator, random effects, or adjustment for baseline covariates).

In line with the agreed extension to the CQ responses, the response to Question B16 will be provided by the 4th March 2026.

c) Please summarise the EQ-5D data used, including:

- i. number of patients and observations per trial
- ii. distribution of observations across PF 2L and PD
- iii. extent and handling of missing data

In line with the agreed extension to the CQ responses, the response to Question B16 will be provided by the 4th March 2026.

d) Please describe the final mixed-model specification used and justify why this approach was considered appropriate given the structure of the data.

In line with the agreed extension to the CQ responses, the response to Question B16 will be provided by the 4th March 2026.

e) Please provide the following scenario analyses:

- i. separate utility estimates for PF 2L and PD derived independently from each trial
- ii. utility estimates based on pooled mean EQ-5D values without longitudinal modelling
- iii. a model including an explicit trial effect to test sensitivity to cross-trial differences

In line with the agreed extension to the CQ responses, the response to Question B16 will be provided by the 4th March 2026.

B 17. Autologous stem cell transplantation (ASCT) is associated with short-term toxicity but may confer long-term improvements in remission duration and health-related quality of life.

a) Please clarify whether, and how, potential long-term HRQoL benefits of ASCT are reflected in the CS base-case analysis.

The response to this question is provided within the response to Question B6 above.

b) If not explicitly modelled, please discuss the implications of this omission and provide scenario analyses exploring plausible long-term HRQoL benefits post-ASCT.

The implications of the omission of the long-term effects of the ASCT regimen from the economic model, and in particular the conservative nature of this omission, as well as the rationale for the lack of exploration of the requested scenario, are provided in response to Question B6c)–e) above.

Cost and healthcare resource use

B 18. Priority question. In the economic model, a relative dosing intensity (RDI) of 100% was used for all treatments but ibrutinib.

a) Please provide the definition of RDI in the current submission.

Relative dosing intensity (RDI) in the CS is defined as the ratio of the actual delivered dose intensity to the planned dose intensity for a given treatment. It reflects how closely the administered therapy matches the intended schedule and dose plan.

- b) Please clarify whether information on RDI was missing and thus assumed to be 100%, or where it was actually 100%. For this, please also provide an overview of medications and their RDI's, specifying references/assumptions made.**

In TRIANGLE, RDI data were only collected for ibrutinib during both the induction and maintenance treatment periods and are presented in Table 20 of the CS. As such, no RDI data were available for the ASCT regimen from TRIANGLE and no RDI data in a relevant setting for subsequent treatments were identified in the published literature. As such, as a simplifying assumption an RDI of 100% was assumed for the ASCT regimen and subsequent treatments included in the economic model. Specifically regarding the ASCT regimen, an assumption that 100% of planned conditioning treatments are delivered is supported by the fact that standard protocols and guidelines specify fixed mg/m² doses without recommending routine pre-emptive reductions.⁴⁷ Furthermore there is currently no high-quality evidence that Johnson & Johnson is aware of which quantifies the frequency or magnitude of real-world dose reductions for MCL conditioning treatments. As such, it is reasonable to assume an RDI of 100% for all treatments in the economic model apart from ibrutinib, for which RDI data from TRIANGLE is available.

- c) Please justify and provide supporting evidence for the chosen RDIs.**

The justification and supporting evidence for the RDIs included in the economic model are provided in the response to Question B18d).

- d) Please provide a scenario analysis exploring consistent RDI's for all treatments, i.e. either all 100% or less than 100% unless clinically implausible.**

As requested, to explore the impact of alternative RDI assumptions on the base case results, a scenario analysis in which all treatments RDI, including that of ibrutinib, was set to 100% has been provided. The results of this scenario analysis, presented in Table 15, demonstrate that increasing the RDI of ibrutinib to 100%, in line with other treatments does not alter cost-effectiveness conclusions, with the ibrutinib regimen remaining cost-effective over the ASCT regimen.

Table 15: Deterministic scenario analysis results (ibrutinib PAS price): RDI

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case (RDI per TRIANGLE, where data permits)</i>	■	■	<i>Dominant</i>	■	-
RDI 100%	■	■	■	■	■

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; RDI: relative dosing intensity; QALY: quality-adjusted life year.

- B 19. Priority question. For the comparator (ASCT regimen), the CS differentiated between costs associated with stem-cell apheresis and ASCT. Procedures**

captured within ASCT costed with £42,040.84 were not further specified, yet for instance assumed that stem-cell apheresis was excluded.

- a) Please provide justification and supporting evidence for the ASCT unit cost, together with an overview of therein captured items and their contribution to the overall ASCT unit cost.

As noted in NICE NG52 (Appendix A), the cost of the autologous transplantation procedure was estimated to be £34,000 based upon the current tariff from NHS England Specialised Services Clinical Reference Group for Blood and Marrow Transplantation (tariff identified by transplanting haematologist on the NICE guideline committee). This cost, originally published in 2016, was inflated to 2024 costs (using a 1.23 inflator from years 2013 to 2024 PSSRU), which results in an ASCT cost of £42,040.84. Importantly, the cost of ASCT at £34,000 inflated to current value has been accepted by NICE as suitable for decision-making in two prior appraisals of treatments for NHL.^{29, 48} In addition, these prior appraisals also referenced a separate cost for stem-cell apheresis (see the response to Question B19b). Therefore, based on precedence, Johnson & Johnson presented the cost of ASCT as recommended in the NG52 guidelines inflated to current day.

NICE NG52 does not explicitly state the components of treatment included in the £34,000 cost of autologous transplantation procedure.²⁰ However, per the title of the tariff, it has been interpreted that the cost refers only to the transplant procedure itself. Further justification for the inclusion of both stem-cell apheresis cost and transplant cost is presented in the response to Question B19b), below.

- b) Please provide justification for the current differentiation between stem-cell apheresis and ASCT, as the referenced NICE NG52 did not include stem-cell apheresis separately.

As summarised in the response to Question B19a), NICE NG52 does not explicitly state the components included in the £34,000 cost of autologous transplantation procedure.²⁰ However, based on the name of the tariff and precedence established in prior NICE appraisals, it is assumed that this cost only includes the transplant procedure. Stem-cell apheresis is a procedure that occurs separately to transplant and therefore incurs additional, distinct resource use and time in hospital. As such, the cost-effectiveness model applies stem-cell apheresis costs separately to the transplant cost itself. This approach is aligned with that taken in both TA895 and TA1048, and was considered suitable for decision by the NICE Committee in both prior appraisals.^{29, 48} Additionally, when consulted during the November 2025 advisory board, clinical experts considered that ASCT was associated with considerable cost and resource use.⁸ Clinical experts specifically caveated that ASCT cost calculations frequently do not include 'pre-ASCT' costs including stem cell collection and storage, which incur high cost and are resource intensive.⁸ Therefore, based on established precedence in prior NICE appraisals and clinical expert opinion, it was considered reflective of UK clinical practice to include both the cost of autologous transplantation and stem-cell apheresis as part of the cost of the ASCT regimen.

c) Please provide a scenario analysis excluding stem-cell apheresis.

In line with the EAG's request, a scenario analysis has been conducted to explore uncertainty associated with the inclusion of the cost for stem-cell apheresis. The scenario analysis excludes the cost associated with stem-cell apheresis. Results of the scenario analysis are presented in Table 16 and demonstrate that even when the cost of stem-cell apheresis is excluded, the ibrutinib regimen remains a cost-effective use of NHS resources. However, as detailed in the responses to Questions B19a) and B19b) above, Johnson & Johnson reiterate that this is an underestimation of the costs of the ASCT regimen. It is clear from both prior NICE appraisals in NHL and UK clinical expert opinion that stem-cell apheresis and autologous transplantation are cost and resource use intensive procedures which should be accurately reflected by including both costs, as preferred by prior NICE Committees and UK clinical experts.^{8, 29, 48}

Table 16: Deterministic scenario analysis results (ibrutinib PAS price): exclusion of stem-cell apheresis cost

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (cost of stem-cell apheresis included)	████	██	Dominant	██	-
Cost of stem-cell apheresis excluded	██	██	████	██	████

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

d) Please provide a scenario analysis using the most recent, applicable NHS reference unit cost for ASCT, in NICE NG52 assessed as £16,359.

While a cost for autologous peripheral stem cell transplant is available from the NHS Reference costs, this is considered to be a considerable underestimate of the true unit cost for ASCT and as such, was not considered appropriate for use in the economic analysis.²⁰ However, in line with the EAG's request, a scenario analysis has been conducted in which the latest NHS reference cost of £21,247 (SA26A, average of elective and non-elective inpatient stays and night/day admissions) was used to inform the ASCT unit cost, the results of which are presented in Table 16. However, based on NICE NG52, as well as prior NICE TAs in NHLs which utilised the £34,000 cost of autologous transplantation procedure inflated to current value, Johnson & Johnson strongly reiterate that the NHS Reference costs for ASCT is a significant underestimate of the unit cost of ASCT in UK clinical practice, making it unsuitable for decision-making. As such, the base case value of £42,040.84 for the ASCT unit cost should be used for decision-making.

Table 17: Deterministic scenario analysis results (ibrutinib PAS price): ASCT unit cost from NICE NG52

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (ASCT unit cost of £42,040.84; excluding stem-cell transplant)	████	██	Dominant	██	-

ASCT unit cost from NHS reference unit cost 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions); £21,247. This excludes the cost of stem-cell transplant.	■	■	■	■	■

The scenarios presented above only change the unit cost of ASCT, defined as the cost of undergoing the autologous peripheral stem cell transplant procedure. This cost does not capture the cost of stem-cell apheresis, which is applied as a separate unit cost as detailed in the response to Question B19c) above which is unchanged from the base case.

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

The R-DHAOx regimen used during induction contains IV administration, and literature seems to indicate that it can be both given in an inpatient or outpatient setting. Currently, no inpatient administration costs are assigned in the CS.

e) Please provide supporting evidence of R-DHAOx administration patterns in UK clinical practice.

As noted in response to Question B1b), during the November 2025 advisory board, five UK clinical experts ultimately concluded that R-DHAOx would be used preferentially over R-DHAP as part of the ibrutinib induction regimen owing to its more tolerable safety profile and more convenient method of administration. In particular, the clinical experts highlighted that a key reason R-DHAOx would be used preferentially over R-DHAP is because it can be administered in an outpatient setting unlike R-DHAP.⁸ As such, R-DHAOx was modelled to be administered in an outpatient setting, in line with feedback received from UK clinical experts.

f) Please provide scenario analyses, including an updated version of the economic model, incorporating inpatient administration costs for R-DHAOx aligned with UK administration patterns.

In line with the response to Question B19e), given that a key reason R-DHAOx would be preferentially used over R-DHAP is owing to its more convenient method of administration in an outpatient setting, it is assumed that all patients receiving R-DHAOx would receive it in an outpatient setting in UK clinical practice. Furthermore, in the absence of available UK data any updates to the existing costing approach for R-DHAOx would be purely arbitrary and therefore would be unlikely to reduce uncertainty. As such, the requested scenario has not been provided. Despite this, given that the difference in inpatient versus outpatient costs for R-DHAOx is relatively low, and patients in both model arms receive R-DHAOx, a scenario in which a proportion of patients are modelled to receive R-DHAOx inpatient would not be anticipated to meaningfully increase the incremental costs for the ibrutinib regimen, and therefore would not alter the overall cost-effectiveness conclusions.

B 20. Subsequent treatment distributions. The document ‘Ibrutinib Advisory Board Report_November 2025’ provides more granularity on 2L and 3L treatment pathways and distributions.

a) The CS and document ‘Ibrutinib Advisory Board Report_November 2025’ states that individual clinical expert estimates of 2L and 3L treatment distributions following initial treatment with either the ASCT or ibrutinib regimen in UK clinical practice were averaged and discussed to derive model input parameters (Tables 2 and 3).

i. Please provide these individual estimates.

Ahead of the November 2025 advisory board, the five participating UK clinical experts (all Consultant Haematologists) were asked to independently estimate the proportion of patients who would receive each subsequent treatment at second line following first-line treatment with (1) the ibrutinib regimen or (2) the ASCT regimen. The clinical experts were then asked to estimate the proportion of patients who would receive each subsequent treatment at third line, following each second-line treatment they provided. As detailed in response to Question B5, to ensure that responses were reflective of current UK clinical practice, the clinical experts were not constrained by pre-specified subsequent treatments, and were therefore able to indicate what they considered to be the most appropriate treatments or strategies in the second-line setting, alongside their proposed distributions.⁸

For full transparency, the clinical experts’ individual estimates, and the step-by-step methodology to calculate the final treatment distributions incorporated into the economic model are provided below.

Second-line treatment distribution (based on first-line regimen)

Clinical experts’ individual estimates

Table 18–Table 22 below present each of the five UK clinical experts’ individual estimates for the proportion of patients who would receive each subsequent treatment at second line following first-line treatment with the ibrutinib regimen or the ASCT regimen.

Table 18: Expert 1 –individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BR
Ibrutinib	-	20%	40%	40%
ASCT	20%	60%	10%	10%

Abbreviations: ASCT: autologous stem cell transplant; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 19: Expert 2 –individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	Clinical trials	BSC

Ibrutinib	-	60%	30%	5%	5%
ASCT	0%	90%	2%	4%	4%

Abbreviations: ASCT: autologous stem cell transplant; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 20: Expert 3 – individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	Other (pirtobrutinib/clinical trial)
Ibrutinib	-	80%	0%	20%
ASCT	0%	100%	0%	0%

Abbreviations: ASCT: autologous stem cell transplant; R-BAC: rituximab, bendamustine and cytarabine.

Table 21: Expert 4 –individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BR
Ibrutinib	-	20%	70%	10%
ASCT	30%	70%	0%	0%

Abbreviations: ASCT: autologous stem cell transplant; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 22: Expert 5 – individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC
Ibrutinib	-	85%	15%
ASCT	0%	100%	0%

Abbreviations: ASCT: autologous stem cell transplant; R-BAC: rituximab, bendamustine and cytarabine.

Step 1: Removal of treatments that are not currently reimbursed by NICE; subsequent reweighting of estimates

To ensure that the clinical experts' estimates were entirely reflective of subsequent treatments available in the NHS in clinical practice, where necessary, treatments and treatment strategies that are not currently reimbursed by NICE were removed from the clinical experts' estimates. The remaining subsequent treatment distributions were reweighted accordingly to ensure that each row summed to 100% (i.e., all patients requiring second-line treatment following the ibrutinib regimen and the ASCT regimen were accounted for). The reweighted second-line treatment distributions removing non-reimbursed subsequent treatments are provided in Table 23–Table 27.

Table 23: Expert 1 – reweighted individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BR
Ibrutinib	-	20%	40%	40%
ASCT	20%	60%	10%	10%

Abbreviations: ASCT: autologous stem cell transplant; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 24: Expert 2 – reweighted individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BSC
Ibrutinib	-	63%	32%	5%
ASCT	0%	94%	2%	4%

Abbreviations: ASCT: autologous stem cell transplant; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 25: Expert 3 – reweighted individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC
Ibrutinib	-	100%	0%
ASCT	0%	100%	0%

Abbreviations: ASCT: autologous stem cell transplant; R-BAC: rituximab, bendamustine and cytarabine.

Table 26: Expert 4 – reweighted individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BR
Ibrutinib	-	20%	70%	10%
ASCT	30%	70%	0%	0%

Abbreviations: ASCT: autologous stem cell transplant; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 27: Expert 5 – reweighted individual estimates for second-line treatment distributions

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC
Ibrutinib	-	85%	15%
ASCT	0%	100%	0%

Abbreviations: ASCT: autologous stem cell transplant; R-BAC: rituximab, bendamustine and cytarabine.

Step 2: Aggregate clinical experts' estimates

To calculate the final distribution of second-line subsequent treatments based on first-line regimen, the five clinical experts' estimates in Table 23–Table 27 were aggregated, and the mean value calculated for each subsequent treatment. The final aggregated distribution for each regimen is presented in Table 28 below.

Table 28: Aggregated estimates: distribution of subsequent treatment use in second line (based on first-line treatment regimen)

First-line treatment	Ibrutinib	Zanubrutinib	R-BAC	BR	BSC
Ibrutinib	-	57.6%	31.3%	10.0%	1.1%
ASCT	10.0%	84.8%	2.4%	2.0%	0.8%

Abbreviations: ASCT: autologous stem cell transplant; BR: bendamustine and rituximab; BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Step 3: Clinical validation

At the November 2025 advisory board, the aggregated distribution (Table 28) was presented to five UK clinical experts. The clinical experts unanimously agreed that the presented subsequent treatment distributions for the second-line treatment setting were in line with clinical expectations.⁸ As such, the distribution in Table 28 (equivalent to Table 62 of the CS) informed the modelled second-line treatment distribution for each regimen (see the 'Subsequent Tx Cost' tab).

Third-line treatment distribution (based on second-line regimen)

Clinical experts' individual estimates

Table 29–Table 33 below present each of the five UK clinical experts' individual estimates for the proportion of patients who would receive each subsequent treatment at third line following the second-line treatments they provided.

Table 29: Expert 1 –individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	R-chemotherapy
Ibrutinib	60%	40%
Zanubrutinib	60%	40%
R-BAC	-	100%
BR	20%	80%

Abbreviations: BR: bendamustine and rituximab; R: rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 30: Expert 2 –individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Clinical trials	BSC
Ibrutinib	80%	10%	10%
Zanubrutinib	80%	10%	10%
R-BAC	-	50%	50%

Abbreviations: BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 31: Expert 3 –individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Future possibilities (e.g., sonrotoclax, pirtobrutinib, zanubrutinib)
Ibrutinib ^a	80%	50%
Zanubrutinib ^a	80%	50%
R-BAC	-	100%

Footnotes: ^a Clinical expert 3s third-line treatment distribution for given second-line treatment summed to >100%, however, following removal of treatments that are not currently reimbursed by NICE, and subsequent reweighting, 100% of patients were considered to receive R-BAC at third line following second-line treatment (see Table 36).

Abbreviations: R-BAC: rituximab, bendamustine and cytarabine.

Table 32: Expert 4 –individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Palliative chemotherapy
Ibrutinib	20%	80%
Zanubrutinib	80%	20%

R-BAC	-	0%
BR	0%	100%

Abbreviations: BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 33: Expert 5 –individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Future possibilities/clinical trials	Less intensive chemotherapy (R-CHOP/BR)	Died before third line
Ibrutinib	0%	0%	0%	0%
Zanubrutinib	20%	10%	25%	45%
R-BAC	-	20%	20%	60%

Abbreviations: BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Step 1: Removal of treatments that are not currently reimbursed by NICE; subsequent reweighting of estimates

In line with the approach used to derive the second-line distributions, to ensure that the clinical experts' estimates were reflective of subsequent treatments used in UK clinical practice, where necessary, treatments and treatment strategies that are not currently reimbursed by NICE were removed from the clinical experts' estimates. The remaining subsequent treatment distributions were reweighted accordingly to ensure that each row summed to 100% (i.e., all patients requiring third-line treatment following each second-line treatment were accounted for). The reweighted third-line treatment distributions removing non-reimbursed subsequent treatments are provided in Table 34–Table 38.

Table 34: Expert 1 – reweighted individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	R-chemotherapy
Ibrutinib	60%	40%
Zanubrutinib	60%	40%
R-BAC	-	100%
BR	20%	80%

Abbreviations: BR: bendamustine and rituximab; R: rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 35: Expert 2 – reweighted individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	BSC
Ibrutinib	89%	11%
Zanubrutinib	89%	11%
R-BAC	-	100%

Abbreviations: BSC: best supportive care; R-BAC: rituximab, bendamustine and cytarabine.

Table 36: Expert 3 – reweighted individual estimates for third-line treatment distributions

Second-line treatment	R-BAC
Ibrutinib	100%
Zanubrutinib	100%
R-BAC^a	-

Footnotes: ^a Clinical expert indicated that all patients receiving R-BAC at second line would receive “future possibilities” (see Table 30). Thus, with the removal of treatments that are not currently reimbursed by NICE, patients receiving R-BAC at second line were assumed not to receive any further treatment.

Abbreviations: R-BAC: rituximab, bendamustine and cytarabine.

Table 37: Expert 4 – reweighted individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Palliative chemotherapy
Ibrutinib	20%	80%
Zanubrutinib	80%	20%
R-BAC	-	0%
BR	0%	100%

Abbreviations: BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Table 38: Expert 5 - reweighted individual estimates for third-line treatment distributions

Second-line treatment	R-BAC	Less intensive chemotherapy (R-CHOP/BR)
Ibrutinib	0	0
Zanubrutinib	44	56
R-BAC	-	100

Abbreviations: BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Step 2: Aggregate clinical experts' estimates

To calculate the distribution of third-line subsequent treatments based on second-line regimen, the five clinical experts' estimates in Table 34–Table 38 were aggregated, and the mean value calculated for each subsequent treatment. During aggregation, treatments anticipated to be associated with very similar efficacy and costs were grouped together, for example, “palliative chemotherapy” and “BSC” were grouped under ‘BSC’; likewise, “R-chemotherapy” and “less intensive chemotherapy (R-CHOP/BR)” were grouped under ‘BR’. The aggregated distribution of third-line subsequent treatments (based on second-line treatment regimen) is presented in Table 39 below.

Table 39: Aggregated estimates: distribution of subsequent treatment use in third line (based on second-line treatment regimen)

Second-line treatment	R-BAC	BR	BSC
Ibrutinib	67.2%	10.0%	22.8%
Zanubrutinib	74.7%	19.1%	6.2%
R-BAC	-	66.7%	33.3%
BR	10.0%	40.0%	50.0%

Abbreviations: BSC: best supportive care; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

Step 3: Clinical validation

At the November 2025 advisory board, the aggregated third-line treatment distribution (Table 39) was presented to five UK clinical experts. Clinical experts unanimously agreed that the presented

subsequent treatment distribution for the third-line treatment setting was broadly in line with clinical expectations.⁸ However, clinical experts highlighted that the third-line subsequent treatment distributions following treatment with ibrutinib or zanubrutinib at second line would be identical in UK clinical practice, and therefore the two rows (ibrutinib at second line and zanubrutinib at second line) should be merged.⁸ As a result of this feedback, the third-line subsequent treatment distributions (following second-line treatment) were updated to ensure that subsequent treatments following ibrutinib or zanubrutinib at second line were identical (i.e., by setting both rows to equal the mean proportion). The updated aggregate estimates are presented in Table 40.

Table 40: Updated aggregated estimates: distribution of subsequent treatment use in third line (based on second-line treatment regimen)

Second-line treatment	R-BAC	BR	BSC
Ibrutinib	70.9%	14.6%	14.5%
Zanubrutinib	70.9%	14.6%	14.5%
R-BAC	-	66.7%	33.3%
BR	10.0%	40.0%	50.0%

Abbreviations: BSC: best supportive care; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

ii. Please provide additional supporting evidence for the final inputs.

The step-by-step process to derive the second-line and third-line subsequent treatment distributions included in the economic model, including all steps taken to ensure the distributions are as reflective as possible of UK clinical practice, is described in full in the response to Question B20ai). As stated above, the final distributions were comprehensively validated at the November 2025 advisory board, where all UK-based experts agreed that the distributions were in line with clinical expectations.⁸ Additionally, the subsequent treatments included in the model are in line with subsequent treatments recommended by the BSH guidelines (as noted in Section 1.3.4 of the CS); BSH guidelines represent the most relevant guidelines for the management of untreated MCL in the UK, as confirmed by UK clinical experts.^{2, 8}

b) Please justify why 3L treatment was conditioned on 1L treatment (CS Table 63) instead of 2L (which presumably drives 3L choices) and discuss its disadvantages and implications for incremental costs.

As detailed in response to Question B20a)B 20. above, the clinical experts were asked to provide third-line treatment distribution estimates based on the treatments received at second line. As such, the third-line treatments included in the economic model were conditional on second-line treatments (which in turn, were themselves conditional on the first-line treatment). For the purposes of the model, however, it was necessary to present the distribution of available third-line treatments based on the first-line regimens received by patients (i.e., the ibrutinib regimen or the ASCT regimen). As such, a final step was undertaken whereby the third-line distributions (conditional on second-line treatments received; Table 40) were multiplied by relevant second-line distributions (conditional on first-line treatment received; Table 28) to derive third-line distributions per the first-line ibrutinib regimen or the ASCT regimen (Table 41) to be used in the model. For simplicity, and to align with the inputs included

in the economic model, these third-line per first-line treatment distributions were presented in the CS. Johnson & Johnson apologise for any confusion caused by the presentation of this table but would like to clarify that the third-line treatments were indeed conditioned based on second-line treatments.

Table 41: Distribution of subsequent treatment use in third line (based on first-line treatment regimen)

First-line treatment	R-BAC	BR	BSC
Ibrutinib	41.9%	33.3%	24.8%
ASCT	67.4%	16.2%	16.4%

Abbreviations: BSC: best supportive care; BR: bendamustine and rituximab; R-BAC: rituximab, bendamustine and cytarabine.

c) Please provide supporting evidence for the 2L to 3L estimates derived in ‘Ibrutinib Advisory Board Report_November 2025’, Table 3.

The response to Question B 20. details step-by-step methodology used to derive the third-line subsequent treatment distributions presented in Table 3 of the ‘Ibrutinib Advisory Board Report_November 2025’.⁸ As stated, the distribution provided in Table 3 of the report was comprehensively validated at November 2025 advisory board, where all UK-based experts agreed that the distributions were broadly in line with clinical expectations, with the exception of the differing third-line distributions for the two BTKis.⁸ Specifically, the experts noted that there is no clinical reason why the subsequent treatment distribution for the two BTKis should differ. As such, to ensure the third-line distributions included in the economic model were as reflective of UK clinical practice as possible, the third-line distributions for ibrutinib and zanubrutinib were set equal (Table 40).⁸ Thus, the final third-line subsequent treatment distributions (following second-line treatment) are directly reflective of UK clinical practice.

d) Please update the health economic model, using the information on 2L to 3L treatment distribution transitions from ‘Ibrutinib Advisory Board Report_November 2025’, Table 3 while keeping the therein provided differentiation between treatments.

As clarified in response to Question B 20. , the third-line distributions included in the economic model are informed by the third-line distributions, based on second-line treatments, provided by the UK clinical experts at the November 2025 advisory board. As such, the third-line treatment distributions included in the economic model are conditional on second-line treatments (which are in turn are conditional on the first-line treatments received). As such, no changes have been made to the economic model.

B 21. To map resource use, the CS used the ESMO 2017 guidelines and expert validation. In the CS and the file ‘Ibrutinib Advisory Board Report_November 2025’, experts stated that the ESMO guidelines are currently not relevant to UK clinical practice.

a) Please justify the choice of the ESMO guideline to map resource use, presenting and discussing differences in advised resource use between the BSH and ESMO guidelines.

Even though BSH guidelines provide a description of the diagnostic work-up, recommendations about frequency and type of examinations carried out during follow-ups are not specified.² The information on disease management provided in the BSH guidelines was therefore insufficient to inform inputs for the cost-effectiveness model. On the contrary, the ESMO guidelines provide detailed recommendations about the examinations as well as frequencies of these follow-ups.¹⁷ After a review by the Johnson & Johnson Medical team, the ESMO recommendations were seen as reasonable and validated as such by clinical experts consulted during the March 2025 advisory board meeting.¹² The discussion during the advisory board meeting focused on possible differences in resource use before and after progression as well as on and off treatment. Additionally, measures taken at therapy initiation, such as ASCT or ibrutinib or rituximab maintenance, were discussed, as these were expected to differ between the TRIANGLE study arms. The expert feedback was simplified to avoid double-counting of examinations and incorporated into the cost-effectiveness model.

b) Please explain what is exactly informed by the ESMO guideline and how this would differ if it would be based on the BSH guideline.

As information on disease management in the BSH guidelines was insufficient to serve as inputs for the cost-effectiveness model, it is not possible to infer the differences between the resource use specified between the ESMO and BSH guidelines.^{2, 17} The model was developed based on the assumption that medical resource use differs between the treatment options as well as on and off treatment. Table 7 of the ESMO guidelines was transferred into values per treatment phase as well as on and off treatment. These values were subsequently validated as appropriate in the March advisory board meeting.¹²

As the information on disease management provided in the BSH guidelines lacked the required levels of granularity to serve as inputs for the cost-effectiveness model, a scenario analysis based on the BSH guidelines has not been conducted. Johnson & Johnson would however like to highlight that, as demonstrated by the scenario analysis results presented in the response to Question B22c), changes in resource use assumptions do not have a significant impact on the cost-effectiveness results. As such, use of a different source of resource use data is highly unlikely to impact cost-effectiveness conclusions of the base case analysis.

c) Please update the health economic model, based on the BSH guidelines.

As detailed in the response to Question B21b) above, the information in the BSH guidelines did not have the granularity required to be leveraged as inputs in the cost-effectiveness model, therefore the requested updates have been unable to be conducted.

B 22. CS Tables 67 and 70 show the per year frequency of medical resource use in FF 1L, and PF 2L and PD, respectively. There seem to be some discrepancies with

clinical expert input (Ibrutinib Advisory Board Report_March 2025) the EAG would appreciate clarification on.

- a) During maintenance, only full-blood count and infection prophylaxis were included. However, the CS states maintenance phase for both intervention and comparator can last up to 2-3 years. In comparison, clinical experts stated that routine follow-up during PFS (on and off treatment) should include 4 haematologist visits per year, as well as either a CT (50%) or PET (50%) once a year (Ibrutinib Advisory Board Report_March 2025). Please clarify and update the health economic model if needed.**

As noted at the start of Section B, Johnson & Johnson acknowledge the discrepancies in medical resource use during the maintenance phase between the health economic model and UK clinical expert opinion.¹² As such, the economic model has been updated accordingly to include four haematologist visits per year (per cycle frequency of 0.23) as well as either a CT scan (50% of patients) or PET scan (50% of patients) once a year (per cycle frequency of 0.03) in the 'active' maintenance phase. Resource use estimates for patients not receiving active maintenance treatment have also been updated to align with clinician estimates (50% receiving a CT scan and 50% receiving a PET scan once per year [per cycle frequency of 0.03], as opposed to the 100% for both scans utilised in the original CS [per cycle frequency of 0.06]).

These updates, combined alongside the updates in response to Question B22c) below, as well as Question B11a), reflect the updated Company base case presented alongside this clarification question response and detailed in full in Appendix D 4. Details on the impact on results of this resource use change is provided in Question B22c) below.

- b) When off active treatment, annual frequencies of 0.06 for PET scan and 1.00 for CT scan were reported yet could not be retrieved in the 'Ibrutinib Advisory Board Report_March 2025'. Please clarify and update the health economic model if needed.**

Johnson & Johnson can confirm that the PET scan annual frequency of 0.06 is a typographical error in the CS, reflecting per-cycle rather than per-year frequencies. As noted in response to Question B22a), however, the model has been updated as part of this clarification question response to account for UK clinical expert estimates that 50% of patients would receive a CT scan and 50% of patients would receive a PET scan once a year, resulting in a per cycle frequency of 0.03 for each resource use.

- c) CT and PET scan frequencies seem to diverge with those provided by clinical experts for PF 2L an PD (Ibrutinib Advisory Board Report_March 2025). Please clarify and update the health economic model if needed.**

Johnson & Johnson acknowledge the slight discrepancy in CT and PET scan frequencies included in the economic model and those provided at the March advisory board. As such, Johnson & Johnson have updated the economic model to ensure alignment between the modelled resource use and clinical expert feedback received at the March 2025 advisory board.¹² Specifically, when considering parts a)–c) of this question in totality, the following updates were made to the economic model:

- 50% of patients each receive a PET scan and CT scan once per year in 1L active maintenance treatment (per cycle frequency of 0.03)
- Four haematologist visits per year are applied in 1L active maintenance treatment (per cycle frequency of 0.23)
- 50% of patients each receive a PET scan and CT scan once per year in 1L off active maintenance treatment (per cycle frequency of 0.03; original submission applied per cycle frequency of 0.06)
- 50% of patients each receive a PET scan and CT scan once per year in 2L PF and PD health states (per cycle frequency of 0.03; original submission applied per cycle frequency of 0.06)

The updated cost-effectiveness results based solely on the above changes to the modelling of resource use frequencies are presented alongside the original base case results included in the original submission in Table 5 in the introduction to Section B above. The results show that the direct impact of this modelling update on incremental costs and QALYs (compared to the original base case results) is negligible.

B 23. For clarity, the fully updated Company base case results presented alongside this clarification question response (which also incorporates the updates to the AEs related to blood abnormality values; see response to Question B11a)) are presented in Appendix D 4. Adverse reaction and transplant complication unit costs. The company costed ICU events for 5% of ASCT patients.

a) Please report the findings from TRIANGLE as well as additional evidence on the frequency of ICU events, separately for all three trial arms.

Due to the investigator-initiated nature of TRIANGLE, some key data points, such as the frequency of ICU events, were not captured in the trial. As such, it is not possible to report ICU frequencies for the three arms of TRIANGLE, as requested by the EAG. Additionally, as noted in response to Question A2a), Johnson & Johnson reiterate the A+I arm of TRIANGLE is not of relevance to UK decision-making given that the use of ibrutinib in combination with ASCT in this indication is not licensed for use in UK clinical practice.¹

However, as validated by five UK clinical experts at the November 2025 advisory board, the ASCT regimen imparts a substantial economic burden on the NHS, with experts emphasising that the considerable resource use and cost associated with regimen.⁸ Due to the toxicity of the ASCT regimen and the fact that patients are immunocompromised for several weeks following procedure, patients receiving the ASCT regimen are at high risk of infections and therefore it is known that a

non-insubstantial proportion of patients receiving the ASCT regimen require admission to ICU.²⁸ Of note, clinical experts at the November 2025 advisory board emphasised that the introduction of the ibrutinib regimen into UK clinical practice would be hugely cost saving in terms of reducing resource use compared to the ASCT regimen, including through the reduction of ICU stays.⁸ As such, to ensure the economic model provides an accurate reflection of the potential resource savings associated with the ibrutinib regimen it is critical that ICU stays (and their substantial costs to the NHS) are captured within the economic model.

Given the absence of ICU data collected in TRIANGLE (an inherent limitation of the investigator-initiated nature of the trial), Johnson & Johnson reviewed available literature and sought clinical expert opinion to inform the frequency of ICU events in the economic model. As detailed in the CS, a 10-year retrospective observational study of all patients admitted to the ICU within 3 months after HDT/ASCT for lymphoma was identified as a suitable source of literature to inform the proportion of requiring ICU following ASCT; this study identified that among the 532 patients treated by HDT/ASCT, 27 (5%) required admission to ICU. Thus, the model includes 5% of patients receiving the ASCT regimen to require an admission to ICU. Notably, to ensure the model was reflective of UK clinical practice specifically, UK clinical experts were also consulted on the most appropriate proportion of ICU events to include in the cost-effectiveness analysis. At the March 2025 advisory board, one clinical expert estimated that 5% of patients undergoing ASCT require ICU admission, whilst a second clinical expert estimated this to range from 5–10%;¹² likewise, at the November 2025 advisory board, a UK clinical expert indicated that, based on their clinical experience, 10% of patients require admission to ICU in UK clinical practice.⁸ Therefore, whilst the 5% included in the model is informed by available evidence in the literature (a large real-world observational study of 532 patients with lymphoma receiving HDT/ASCT), this likely represents a conservative estimate of the true proportion of patients requiring ICU admission following the ASCT regimen in UK clinical practice.^{8, 12} The conservative nature of this estimate is further supported by another retrospective analysis of patients undergoing HDT and ASCT in Cologne, in which of the 738 patients receiving HDT and ASCT, 79 (10.7%) were admitted to ICU between the initiation of HDT and day 30 after ASCT.⁴⁹

As such, whilst it is not possible to report ICU findings from TRIANGLE, Johnson & Johnson emphasise that the modelling approach to the proportion of patients receiving ICU in UK clinical practice is based on published literature and supported by UK clinical expert opinion. Furthermore, it should be acknowledged that in the absence of available data from TRIANGLE, the modelling approach likely represents a conservative assumption of the true proportion of patients requiring ICU admission following the ASCT regimen in UK clinical practice.

b) Please discuss whether identified adverse reactions and related resource use might already include ICU costs, introducing double counting.

Johnson & Johnson do not consider that the application of both AE management costs and ICU costs would introduce double counting of the resource use related to adverse reactions of front-line treatment.

The specific AEs accounted for in the FF 1L health state of the model are based on the Grade ≥ 3 AEs occurring in over 5% of patients in either treatment arm of TRIANGLE (see Table 72 of the CS). These costs are included to capture the direct burden that specific AEs of first-line treatment imparts

on the NHS. The costs incorporated into the model for each specific AE are based on the cost of a non-elective short stay, and thus capture the immediate and short-term costs of managing a given AE. However, as detailed in response to Question B23a), due to the toxicity of the ASCT regimen and the fact that patients are immunocompromised for several weeks following the ASCT regimen, some patients receiving the ASCT regimen experience further complications and require admission to the ICU.²⁸ As discussed above, published values in the literature indicate that 1 in 20 (5%) patients undergoing the ASCT regimen require admission to the ICU, primarily due to sepsis.^{50, 51}

As such, escalated complications of treatment that require further management and care (for example, sepsis) are not captured within the specific AEs costed within the model. The substantial difference in care required for specific transient AEs versus those presenting with complications that require ICU stay is evidenced by the substantial difference in the costs associated with the management of specific AEs (ranging from £520.26 to £750.35) versus the unit the cost of ICU per day (£2,405.64). To note, at the November 2025 advisory board, clinical experts confirmed that ICU costs represent a significant driver of resource use associated with ASCT and should be accounted for within the model.⁸ It is therefore critical that the costs associated with additional care in ICU, which extends beyond the acute, short-term costs of managing adverse reactions, are also captured in the economic model to ensure that the costs associated with both front-line regimens are reflective of the true costs of treatment imparted on the NHS.

B 24. The NICE ‘Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template’ states that drug wastage should be captured. The company detailed that drug wastage was not considered, yet applied an IV wastage in the economic model, counting IV drugs on a per vial basis.

- a) Please justify the assumptions on vial wastage, also considering the option of vial sharing.

Johnson & Johnson can confirm that no vial sharing is included in the base case of the economic model. As such, IV wastage is accounted for in the economic model in line with NICE guidance. The CS reports the assumption on drug wastage incorrectly; this sentence in the CS should state that “drug wastage was considered in the cost-effectiveness analysis”.

- b) The EAG would further appreciate clarification on whether oral treatments dispensed in tablet packs were costed on a per pack basis. If not, please update the economic model accordingly.

The model does not cost oral treatments on a per pack basis and instead the per mg cost of oral treatments included in the model is calculated, and then applied to the relevant dose per cycle. Johnson & Johnson acknowledges that ibrutinib may be dispensed on a per pack basis and as such some wastage may occur as a result of patients progressing to a subsequent line of treatment or dying, and not returning unfinished packs of tablets. It was not possible to update the model to cost oral treatments on a per pack basis due to the set up of the cost schedule calculations. However, the

Company has included an exploratory scenario in the model to explore the impact of oral drug wastage on the results. In this scenario, it is conservatively assumed that on average half a pack of ibrutinib would be wasted when patients experience failure on first-line treatment or death. This is implemented by applying 50% of the pack cost for ibrutinib to the proportion of patients experiencing treatment failure or death in 1L (up until the end of the defined maintenance period for ibrutinib) in each cycle. Wastage costs are also applied in the ASCT arm to the proportion of patients experiencing disease progression or death in 2L, only for the proportion of patients expected to receive ibrutinib at 2L (10%). The scenario was not applied for prednisone (the only other oral treatment included in the model), as the pack cost for this treatment is very low and therefore inclusion of wastage is not expected to have any material impact on the results. The results of this scenario are presented in Table 42 and show that this scenario has a minimal impact on the INHB. Given that this scenario is purely arbitrary it is not considered suitable for inclusion in the updated base case analysis.

Table 42: Deterministic scenario analysis results (ibrutinib PAS price): oral wastage

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case (no wastage of oral packs)</i>	■	■	<i>Dominant</i>	■	-
Assumes 50% of ibrutinib pack is wasted upon failure/death in 1L and progression/death in 2L	■	■	Dominant	■	■

Abbreviations: ICER: incremental cost-effectiveness ratio; PAS: Patient Access Scheme; RDI: relative dosing intensity; QALY: quality-adjusted life year.

B 25. Please provide justification and supporting evidence for the use of administration costs for subcutaneous treatment regimens, as these might be administered after a training session at home or in a primary care setting.

Pegfilgrastim represents the sole subcutaneous treatment in the economic model, and is administered to patients receiving induction treatment with R-DHAP, R-DHAOx, Maxi-CHOP, or R-cytarabine to reduce the risk of infection following chemotherapy.⁵² It is Johnson & Johnson's understanding that in the vast majority of patients who require pegfilgrastim, pegfilgrastim is administered in an inpatient setting by a trained healthcare professionals. This is in line with the SmPC for pegfilgrastim which states that "[pegfilgrastim] therapy should be initiated and supervised by physicians experienced in oncology and/or haematology."⁵² As such, Johnson & Johnson consider the NHS reference cost in the model (N10AF – Specialist Nursing, Cancer Related, Adult, Face to face) to be the most appropriate representation of the cost of pegfilgrastim administration UK clinical practice.

Johnson & Johnson however acknowledge that given the SC method of administration there may be some uncertainty around whether patients may be able to self-administer pegfilgrastim following

training from a healthcare professional.⁵³ As such, to assess the impact modelling pegfilgrastim as a self-administered treatment (and thus associated with no administration costs), a scenario analysis whereby the cost of subcutaneous administration (i.e., pegfilgrastim administration) is set to £0 was explored. The results of this scenario analysis are presented in Table 43. Notably, given induction immunochemotherapy represents an integral phase of both the ibrutinib regimen and the ASCT regimen, pegfilgrastim is administered as part of both regimens, and therefore the modelled cost of pegfilgrastim administration has a negligible impact on the conclusions of the cost-effectiveness analysis – the ibrutinib regimen remained a cost-effective option for patients with untreated MCL.

Table 43: Deterministic scenario analysis results (ibrutinib PAS price): subcutaneous administration cost

Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
<i>Base case: subcutaneous administration cost based on NHS Reference Costs 2024/25 N10AF - Specialist Nursing, Cancer Related, Adult, Face to Face⁴⁴</i>	■	■	<i>Dominant</i>	■	■
Subcutaneous administration cost set to £0	■	■	Dominant	■	■

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Results and uncertainty

B 26. Priority question. The EAG requests to update the CS health economic model to adequately address uncertainty in the decision problem.

- a) Please provide a rationale for every parameter omitted from the DSA and/or PSA (such as e.g. transition probabilities, RDI for the comparator arm treatments in the PSA) and update the results as well as the economic model while including all uncertain parameters in uncertainty analyses.

The parameters omitted from the PSA and the corresponding rationale is provided below:

- Starting age (time horizon dependent on this input): the model structure only allows for a time horizon of up to 44.3 years, as such it is not possible to set the starting age to less than 55.7 years whilst also modelling a full lifetime horizon; due to this structural limitation, starting age was therefore excluded from all sensitivity analyses. Nevertheless, it is not anticipated that starting age is a significant model driver, as illustrated by the scenario analysis results presented in response to Question B3, where switching between median and mean baseline age from TRIANGLE has a minimal impact on results, with ibrutinib remaining dominant.

- Discounting rates: a discounting of 3.5% has been applied in line with NICE guidelines and therefore not further explored as part of the sensitivity analyses
- Costs sourced from the NHS reference costs, PSSRU or BNF (including drug acquisition costs, ASCT costs, treatment administration costs and end of life costs): these unit costs are not associated with any uncertainty and have therefore not been included in the PSA
- Relative dose intensities for 1L and subsequent treatments that are assumed 100%: as these values represent the categorical assumption of no RDI for the treatments in question, they were not varied as part of the PSA

For the reasons provided above, these parameters have not been included in the PSA. The parameters that are included in the PSA can be specified in column J of the 'Parameters' tab in the model.

The following parameters were omitted from the DSA:

- Starting age: omitted for the same reason as the PSA
- Discount rates: omitted for the same reason as the PSA
- Drug acquisition costs (including ASCT costs): omitted for the same reason as the PSA
- Survival parameters for 1L TTF and 2L PFS: survival parameters for each endpoint are correlated and therefore varying them independently can yield implausible or internally inconsistent survival curves. Including them in the DSA would not preserve the joint distribution or the logical constraints of the survival models, and therefore it is not appropriate for these to be included. Survival parameters have been included in the PSA using the associated covariance matrices and Cholesky distribution to test the impact of varying the survival inputs in a manner which maintains any correlation and logical constraints of individual parameters.
- Subsequent treatment RDIs: these have all been assumed to be 100% in the model and have therefore not been varied for the same reason as the PSA

b) The CS detailed that $\pm 10\%$ of the deterministic value was used to capture uncertainty in the absence of CIs or published ranges.

i. Please perform a SLR to inform model input parameters and their standard errors.

ii. If unavailable, please use standard errors calculated as 30% of the mean, for obtaining 95% confidence intervals (in line with the respective distributions) and uncertainty assessment, i.e. DSA and PSA.

It has not been feasible to conduct an SLR to inform input parameters and their standard errors. However, in line with the request in Question B26c), a scenario analysis has been implemented in

the model in which a 30% standard error is utilised for the DSA and PSA. This can be selected in cell I89 on the Settings tab.

- c) The convergence plot (CS Figure 25) leaves doubt whether sufficient iterations inform the PSA. Please explore higher numbers of iterations, alongside with separate convergence plots for incremental costs and QALYs.

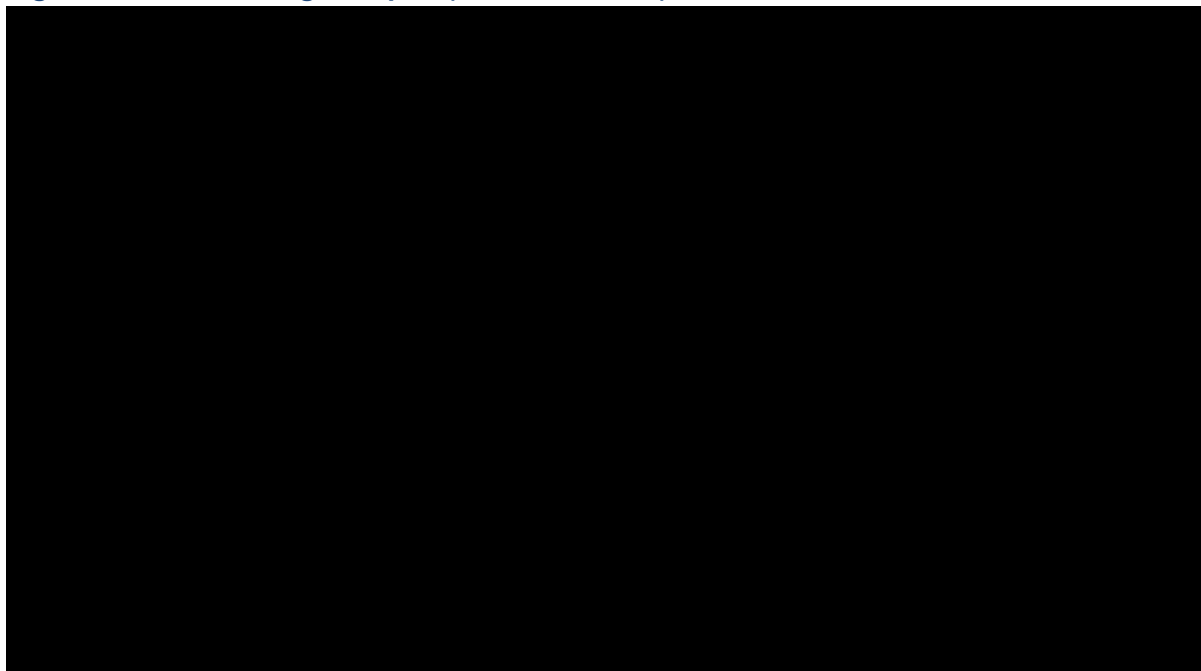
In the CS, 500 iterations were used to run the PSA due to time constraints of running this analysis. A convergence plot for a PSA run at 2,000 iterations is presented in Figure 4, which shows that the ICER converges at approximately 1,200 iterations. Convergence plots for incremental costs and QALYs have also been added into the model and are presented below (for 2,000 iterations; Figure 5 and Figure 6). The deterministic base case ICER and probabilistic base case ICERs for the PSA run at 500 and 2,000 iterations are presented in Table 44, and show that overall the results are closely aligned. These results illustrate that the base case probabilistic ICER run with 500 iterations is suitable for decision-making.

Table 44: Deterministic and probabilistic base case results at different iterations (ibrutinib PAS price)

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000
<i>Base case deterministic</i>	████	██	<i>Dominant</i>	██
Base case probabilistic (500 iterations)	████	██	Dominant	██
Base case probabilistic (2,000 iterations)	████	██	Dominant	██

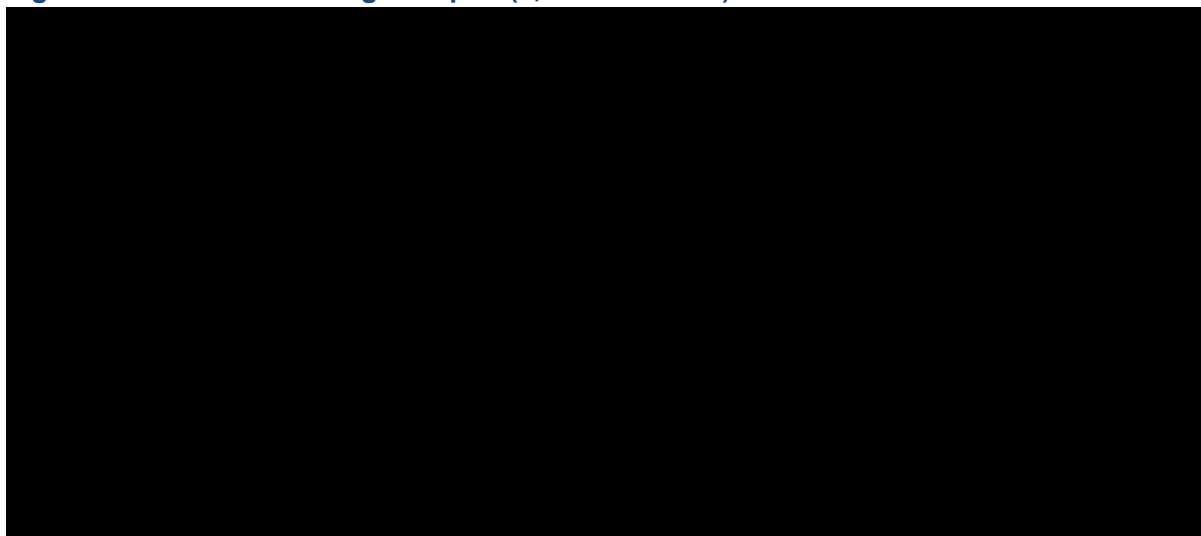
Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

Figure 4: ICER convergence plot (2,000 iterations)



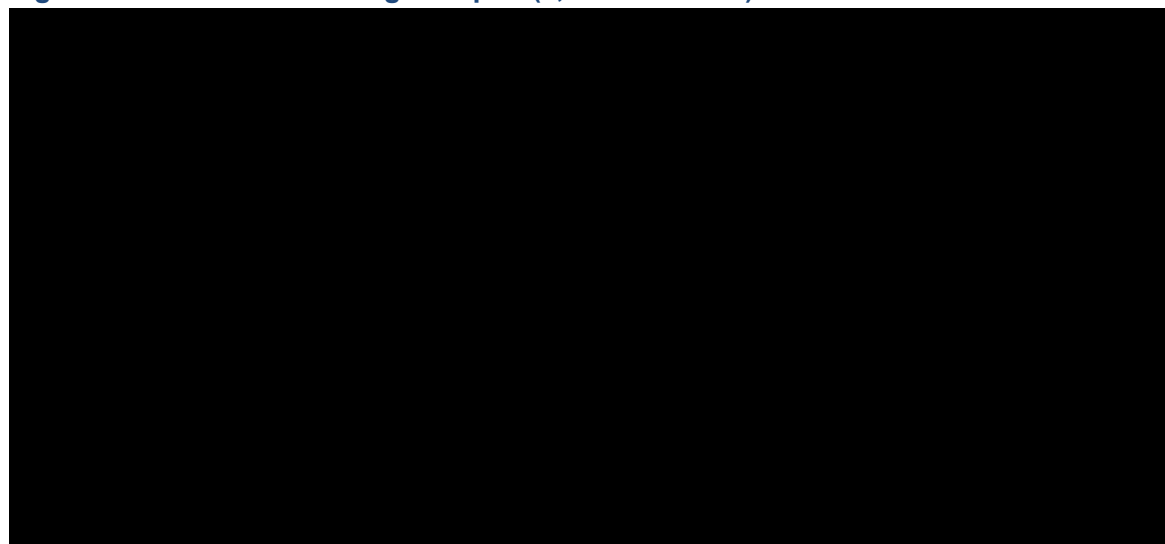
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year.

Figure 5: Inc. costs convergence plot (2,000 iterations)



Abbreviations: Inc.: incremental; QALY: quality adjusted life year.

Figure 6: Inc. QALYs convergence plot (2,000 iterations)



Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; QALY: quality adjusted life year.

B 27. Please report results presented in CS Section 3.10 also for a willingness-to-pay threshold of £20,000.

Given the upcoming changes to the NICE willingness-to-pay threshold, and after clarification from NICE and the EAG on the 18th February 2026, INHB results have been presented at a willingness-to-pay threshold of £25,000 and £35,000 in Table 45 and Table 46 for ibrutinib at PAS and list price, respectively.

Johnson & Johnson would like to highlight that given the availability of head-to-head data from TRIANGLE and the high unmet need for an alternative treatment in this setting, a willingness-to-pay threshold of £35,000 is most appropriate for the appraisal of ibrutinib in this setting. As described in detail in Section 1.3 of the CS, the ASCT regimen is associated with significant physical and psychological burden, which is consistently highlighted by patients, carers and UK clinical experts.⁸ ⁵⁴ As such, there remains a high unmet need for new, efficacious and tolerable front-line treatment options for patients with MCL which removes the need for toxic and costly ASCT. The high unmet need in this setting is evidenced by the investigator-initiated nature of TRIANGLE which clearly demonstrates the clinical community's desire for an alternative treatment to the ASCT regimen. Furthermore, the primary evidence source demonstrating the benefits of the ibrutinib regimen compared to the ASCT regimen, TRIANGLE, is a high quality head-to-head trial. This negates the requirement for an indirect treatment comparison, thereby minimising uncertainty regarding the relative efficacy of the ibrutinib regimen compared to the ASCT regimen.⁵

In line with the conclusions of the base case analysis presented in the original submission, with the PAS price, the ibrutinib regimen was found to be a cost-effective use of NHS resources when compared with the ASCT regimen at a willingness-to-pay (WTP) threshold of £35,000/ QALY.

Table 45: Probabilistic base-case results (ibrutinib PAS price)

Intervention	INHB at £35,000	INHB at £25,000
Ibrutinib regimen versus ASCT regimen	■	■

Abbreviations: ASCT: autologous stem cell transplant; INHB: incremental net health benefit.

Table 46: Probabilistic base-case results (ibrutinib list price)

Intervention	INHB at £35,000	INHB at £25,000
Ibrutinib regimen versus ASCT regimen	■	■

Abbreviations: ASCT: autologous stem cell transplant; INHB: incremental net health benefit.

Validation and transparency

B 28. Priority question. In the submitted health economic model, the ‘Parameters’ sheet does not act as a single source of parameters for model inputs, as parameter values are instead defined and updated across multiple sheets. This limits transparency, increases the risk of implementation errors and makes systematic interrogation challenging. In addition, the EAG observed that deterministic and probabilistic uncertainty analyses were computationally slow, limiting efficient model validation and exploration of uncertainty.

- a) Please provide an updated health economic model that adheres to good modelling practice by clearly defining all model input parameters and their associated distributions in a single ‘Parameters’ sheet, from which all calculations in the model are directly linked. Please also ensure that both deterministic and probabilistic analyses draw exclusively from this ‘Parameters’ sheet.

With the exception of survival parameters, all model inputs are fed into and varied in the ‘Parameters’ sheet in the model. The distributions used to vary all inputs included in the DSA and PSA are outlined in column O.

Survival parameters and their associated covariance matrices and Cholesky distributions are stored in the relevant ‘Stored’ tabs in the backend of the model (orange tab colour). PSA sampling calculations take place on these tabs, before the varied survival parameters are fed into subsequent model calculations (all survival parameters are also fed through the ‘Parameters’ sheet, with the exception of 2L PFS and PPS from RAY-3001 [‘Stored_RAY3001_PFSPPS’ tab] which feed directly into the model engine.

The model has also been updated with additional labelling and formatting changes, to improve transparency and clarity regarding which inputs are being used in the calculations. Model tabs have also been relabelled/reformatted to facilitate navigation. A summary of where all model inputs are stored is provided below:

- Drug/treatment acquisition and administration costs, resource use and AE inputs/costs, utility inputs and subsequent treatment distributions/treatment costs are all stored in the front-end input tabs (light blue shading)
- HRs used for subsequent treatments are stored in the 'Data – HRs' tab (green shading)
- Life tables used to inform GPM are stored in the 'Life tables' tab (green shading)
- AMRs used to inform mortality at 1L and 2L PF health states are stored in the 'Parametric fits' tab (orange shading)

- b) Survival parameters used to inform 1L TTF, 2L PFS and PPS are stored in the relevant 'Stored_' tabs (orange shading) Please improve computational efficiency such that deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) can be run in a timely and practical manner.

An updated version of the model has been provided in which the requirement to run a macro to obtain results has been removed. This has improved the computational and efficiency of the DSA and PSA. The DSA can now be run in under 10 minutes and 1,000 iterations of the PSA can be run in 1 hour.

B 29. The results of the validity assessments are not described in detail in CS section 3.14.1 nor is a comprehensive overview provided of performed validation exercises (i.e., specific black-box tests).

- a) Please provide a detailed description of the validity assessment performed as well as the results.

As part of the development of the cost-effectiveness model for the ibrutinib regimen in patients with untreated MCL, a comprehensive and rigorous quality check was fulfilled, including validating the logical structure of the model, mathematical formulas, sequences of calculations, and the values of numbers supplied as model inputs. Unexpected model behaviour, implementation, and typing errors were all identified by this review. The process involved checking the intermediate calculations for references (whether they are linked to the correct cells, etc.), implementation (whether correct signs for the parameters are used, etc.) and evaluation of the face validity of predicted results. The expected function of parameters was checked with extreme value sensitivity analysis. The process also involved checking the functionality of any built in VBA macros. For further information on the process and results of the validity assessment performed, please refer to 'Ibrutinib in MCL CEM – verification v1.0' included within the reference pack accompanying this submission.

Additionally, the appropriateness of distributions used in the probabilistic analysis of the model was checked, and the model survival predictions were checked against data observed in the clinical trials used as data sources. Any updates made in preparation for the NICE CS were quality controlled by an independent health economist not involved in the model development. This included a quality check of any new inputs added against their original source and a cell-by-cell check of new/updated calculations. The impact of each adaptation on the ICER was recorded and reviewed, to ensure all updates impacted the results as expected. For further information on the process and results of the quality check performed during the adaptation of the model for the NICE CS, please refer to 'ID6596_NICE CEM Adaptations Log' included within the reference pack accompanying this submission.⁵⁵

- b) Please provide complete the TECH-VER checklist (Büyükkaramikli et al. 2019, <https://pubmed.ncbi.nlm.nih.gov/31705406/>) and provide the results.

Given the model structure aligns with prior models within MCL and other NHLs, has been validated at an advisory board with health economists and clinical experts, and has undergone in-depth technical validation plus quality control (see response to Question 29a), Johnson & Johnson consider the model has gone through appropriate and extensive validation.^{8, 40, 41} Therefore, given the limited timeframe for response to questions and the fact that this checklist is not part of the guidance to manufacturers prior to submission, the checklist has not been retrospectively completed.

- B 30. Please provide cross validations, i.e., comparisons with other relevant NICE TAs, including but not limited to those focusing on the broader (non-eligible ASCT) MCL population, as well as health economic models focussing on 2nd/3rd line, and elaborate on the identified differences regarding:

a) Model structure and assumptions

b) Input parameters related to:

- i. Clinical effectiveness
- ii. Health state utility values
- iii. Resource use and costs

c) Estimated (disaggregated) outcomes per comparator/ intervention

- i. Life years
- ii. QALYs

iii. Costs

As noted by the EAG, there are limited prior appraisals that are relevant to the population informing this submission. Given that no prior NICE appraisals were identified by the economic SLR in patients with previously untreated MCL eligible for ASCT, the most relevant economic evaluations to inform the model structure and key model features for this submission were deemed to be TA891 (assessing fixed-duration ibrutinib plus venetoclax for patients with untreated chronic lymphocytic leukaemia [CLL]) and TA502 (assessing ibrutinib for patients with r/r MCL; both of which were accepted by NICE as appropriate for decision making in B cell lymphoma indications of the same intervention which also used a Markov approach.^{40, 41} As discussed in Section 3.2.2 of the NICE submission, as an evaluation of a fixed-duration ibrutinib regimen in a first-line indication, TA891 is the most relevant prior appraisal to this submission. NICE TA502 for the reimbursement of ibrutinib in r/r MCL also used a three-state Markov model. A comparison of the key features of the model compared with the economic analyses presented in TA891 and TA502 is provided in Table 29, Section 3.2.2 of the Company Submission. Together, these two appraisals demonstrate that the model utilised in this submission is appropriate for decision making.

Furthermore, the economic SLR, which searched for economic evaluations in patients with untreated MCL, regardless of transplant eligibility status, identified only one relevant cost-effectiveness analysis in patients with untreated MCL: the analysis of VR-CAP versus R-CHOP in patients with untreated MCL who are ineligible for HSCT. Key details of this appraisal are summarised in Appendix E.1.3 of the Company Submission. Due to the key differences between ASCT-eligible and ASCT-ineligible patient populations, as confirmed by clinical experts who reviewed the unadjusted SHINE data used to inform the HSUVs at the November 2025 advisory board, a side by side comparison has not been provided as this analysis is not relevant to the population addressed within this submission.⁸

Justification for the selected base case inputs and the relevant sources informing them is provided throughout Section 3 of the original CS as well as detailed throughout the responses to the above set of clarification questions. Furthermore, key model inputs and assumptions were validated as generalisable to UK clinical practice by feedback received from UK clinical experts. Finally, any uncertainty surrounding the selected base case inputs was explored via numerous sensitivity and scenario analyses, the results of which are presented in Section 3.11 of the CS and demonstrate that the base case results were robust to uncertainty surrounding key model inputs and assumptions. As such, no additional comparisons have been presented within this clarification question response.

B 31. Further face validity assessment and external validation of the health economic model would be desirable.

- a) Please perform and report on the face validity assessment of the model structure, model assumptions, model inputs, intermediate outcomes as well as final outcomes in more detail (including what aspects were assessed and what were the considerations as well as conclusions).**

Extensive validation was sought from both UK clinical and health economic experts during the November 2025 advisory board in order to validate the model structure presented in the CS and to inform inputs and assumptions.⁸ As discussed in Section 3.2.2 of the CS, a semi-Markov model with four mutually exclusive health states was deemed the most appropriate model structure to robustly and transparently capture the costs and benefits associated with the ibrutinib regimen in patients with untreated MCL. This was driven by several key considerations, but most notably the following:

- To allow additional external data sources (e.g. RAY-3001) to robustly estimate long-term OS estimates
- To align with model structures previously accepted by NICE as appropriate for decision making in the appraisal of ibrutinib in B cell lymphoma indications, which both also used a Markov approach (TA502 and TA891)^{40, 41}
- To appropriately capture the disease course of MCL

At the November 2025 advisory board, UK health economic and clinical experts were presented with a summary of the proposed model structure and were asked the following questions:

- Do you consider the use of a semi-Markov model, as opposed to a partitioned survival model, to be appropriate?
- Does the proposed model structure accurately represent the disease course of MCL?

In response to these questions, the health economic expert agreed that the use of a semi-Markov model was appropriate. They noted that the ability of the model to incorporate external data and allow flexibility in how OS is captured were key strengths of the model structure. All clinical experts agreed that the model structure accurately captured the disease course of MCL, demonstrating the model's face validity.⁸

At the same advisory board, UK clinical and health economic expert opinion was sought to inform and validate key model assumptions and inputs relating to model transition probabilities, utilities, subsequent treatment efficacies and distributions, and costs and resource use. For each topic, experts were either asked to validate and offer opinion on Johnson & Johnson's proposed approach, or to choose between two or more alternative options.⁸ Following these discussions, the cost-effectiveness model was updated to ensure inputs and assumptions were as robust as possible and aligned with clinical expectations. A full summary of questions asked, and expert responses can be found in the November 2025 advisory board report, provided in the reference pack accompanying the original CS.

To inform intermediate and long-term clinical outcomes, ahead of the November 2025 advisory board, clinical experts were asked to provide long-term estimates for FFS and OS at key timepoints (10, 15 and 20 years) for patients receiving either a) the ibrutinib regimen or b) the ASCT regimen at first-line. The average (mean) of the values provided are summarised in Table 47 below. As detailed extensively throughout Section 3.3 of the CS, the clinical plausibility of the curve(s) for each transition, and thus the resulting reconstructed FFS and OS curves, was the primary consideration for the selection of the base case curves. This is reflected in the fact that clinical expert estimates and model-predicted estimates were closely aligned at all landmark estimates for both first-line

regimens for the reconstructed FFS curves and reconstructed OS curves, as detailed in Section 3.14 of the CS.

Additionally, predicted OS estimates for the ASCT regimen were closely aligned to values reported in the literature for patients with untreated MCL. The predicted median OS of patients receiving the ASCT regimen in the model (12.5 years) is closely aligned with the landmark survival estimate of the MCL2 trial assessing the Nordic regimen (alternating cycles of maxi-CHOP and cytarabine), followed by ASCT in 159 patients with previously untreated MCL (median OS of the Nordic regimen: 12.7 years).³² Similarly, the 7-year generated OS for those receiving the ASCT regimen within the model (70.0%) aligned closely with the landmark estimates of the 120 MCL patients receiving rituximab maintenance therapy following ASCT in the LyMA trial where the 7-year OS was 69.5%.^{24, 56}

Table 47: Clinical expert estimates and model-predicted landmark estimates for OS

Distribution	Median OS (years)	10 year (%)	15 year (%)	20 year (%)
Ibrutinib regimen				
Clinical expert estimates ^a	NA	67.0	53.0	37.0
Model predicted estimates ^b	15.8	69.2	52.5	37.8
ASCT regimen				
Clinical expert estimates ^a	NA	56.0	44.4	30.4
Model predicted estimates ^b	12.5	58.3	43.0	31.4

Footnotes: ^aThe mean of the clinical experts' most likely values. ^bLandmark survival estimates for OS at 10, 15 and 20 years based on the reconstructed OS curve when all standard parametric models/AMRs informing transition probabilities in the model were fixed on their base case settings.

Abbreviations: ASCT: autologous stem cell transplant; OS: overall survival.

Source: J&J IM Data on File. November 2025 Advisory Board.⁸

b) Please provide the presentation slides of any meetings held with clinical or health economic experts to inform the current CS.

The slides presented to clinical and health economic experts at the March and November 2025 advisory boards have been included within the reference pack accompanying this clarification question response.^{57, 58}

c) Please assess the external validity of model inputs, intermediate outcomes as well as final outcomes using:

- i. evidence used to develop the economic model. Additionally, please investigate and visualise whether the model can reproduce the observed TTF/FFS curve from TRIANGLE when the transitions are recombined.

Efficacy data for the first-line setting in the model were sourced from TRIANGLE, a high-quality, methodologically robust Phase III RCT in the patient population of interest to this evaluation, providing robust, direct comparative evidence on the efficacy and safety of the ibrutinib regimen versus existing SoC in UK clinical practice (the ASCT regimen). As detailed throughout the response

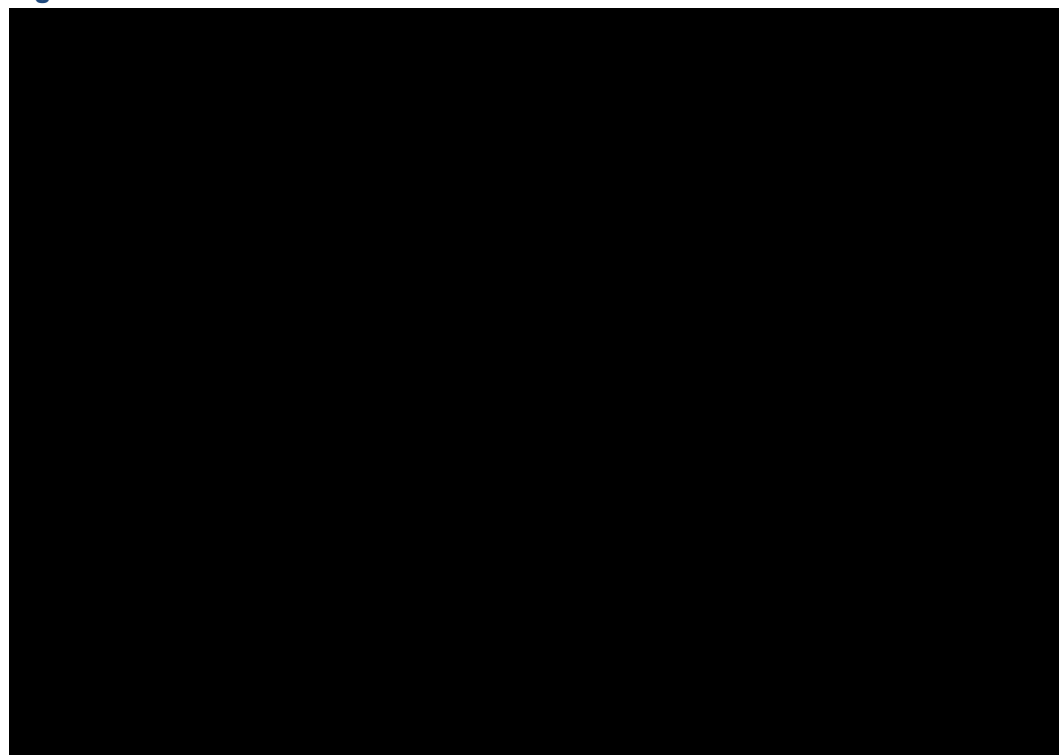
to the above questions, the ibrutinib arm of RAY-3001 (one prior line subgroup) provided efficacy data for transitions from later-line settings and was considered by UK clinical experts to be a suitable data source to inform these transitions given the paucity of published literature in this setting.⁸

Clinical feedback was also used to validate other key inputs and assumptions utilised in the model, including health state utility values, subsequent treatment distributions and efficacy, as well as monitoring frequencies. Crucially, at the November 2025 advisory board, UK clinical experts agreed that key model inputs and assumptions were aligned with UK clinical practice and reflective of the evidence base available.⁸

Model outcomes (FFS and OS for the ibrutinib and ASCT regimen, respectively) were also validated against estimates provided by UK clinical experts for the November 2025 advisory board.⁸ As detailed in Section 3.3.2 of the CS, the Company's base case settings resulted in a reconstructed FFS extrapolation that predicted landmark estimates of FFS that were highly aligned with the clinical expert estimates of FFS.⁸ Likewise, as detailed in Section 3.3.4 of the CS, the reconstructed OS extrapolation (based on the Company's base case settings) also resulted in estimates of OS at landmark timepoints that were highly aligned with clinical expert estimates.⁸ This reflects that, based on the modelled inputs, the long-term predictions of survival from the model align closely with expected outcomes in UK clinical practice.⁸ Specifically, any difference between clinical expert estimates and model-predicted estimates of OS remained less than <2.5% across all landmarks. The results of the economic analysis are therefore considered highly relevant to UK decision-making.

Lastly, Johnson & Johnson highlight that the ability of the model to reproduce the observed FFS data in TRIANGLE is presented in Section 3.14 of the CS. However, for completeness, and to re-highlight that the modelled inputs and assumptions resulted in model survival predictions for FFS (on first-line treatment) that were highly aligned with the observed FFS data from TRIANGLE, Figure 29 of the CS is reproduced below (Figure 7). As shown, the model-predicted FFS curve is highly aligned with the observed FFS KM data from TRIANGLE, clearly demonstrating that the base case modelling approach produced clinical efficacy estimates that accurately reflect the empirical data informing the model.

Figure 7: Reconstructed FFS curves vs observed TRIANGLE FFS KM



Abbreviations: FFS: failure-free survival; KM: Kaplan-Meier.

- ii. evidence not used to develop the economic model. Additionally, please investigate the use of data from the Haematological Malignancy Research Network, mentioned in CS Section 1.3.1. to validate survival in the economic model.

The Haematological Malignancy Research Network (HMRN) is an ongoing population-based UK cohort of patients with haematological cancers and related disorders. As cited in Section 1.3.1 of the CS, a large analysis of patients in the HMRN with lymphoid cancer diagnosed between 2005 and 2019 (n=22,414) determined that the 5-year OS rate for patients with MCL (n=501) was 47.3% (95% CI: 35.5–58.2).⁵⁹ It is however important to acknowledge that the HMRN dataset captures all patients with MCL, rather than first-line patients with untreated MCL who are ASCT-eligible. As such, the HMRN cohort likely represents, on average, a more frail and elderly population with poorer prognoses than that of relevance to this submission.⁵⁹ This is evidenced by the considerable difference in median age between the HMRN cohort (median age: 72 years) and patients in TRIANGLE (median age: 57 years).^{59,5} Whilst the treatments received by patients in the HMRN cohort are not specified, given the elderly nature of the cohort, it is anticipated that treatment with the ASCT regimen (which is typically given to younger [≤ 65 years], fitter patients) is not widespread within the cohort of patients.^{2, 5} This is further supported by the fact this 5-year OS rate reported in this cohort is considerably lower than the 60-month (5-year) OS observed in TRIANGLE which assessed the efficacy of the ASCT regimen in the relevant population (85.6% for Arm I, and 75.3% from Arm A).^{59,5} For these reasons, the overall HMRN cohort cited in Section 1 of the CS is not considered an appropriate source of data to assess the external validity of the model-predicted

survival outcomes. To clarify, reference to this HMRN cohort was made in Section 1.3.1 of the CS to provide context on MCL in the UK more broadly; in this Section, the CS also caveats that MCL is a heterogeneous disease, with a variable clinical course and prognosis depending on a number of factors. It is additionally noted that prognosis data specific to the target population of relevance to the submission is provided in Section 1.3.3 of the CS.

While the large HMRN study detailed above is not relevant to the CS, an HMRN report by Smith *et al.* published in 2018 does report relevant survival information for the patient population of relevance to this submission: patients with untreated MCL eligible for ASCT who received the ASCT regimen.⁷ In this report, 22 patients received chemotherapy and ASCT between September 2014 and August 2015. Smith *et al.* reported that the 1-year and 3-year OS for these patients was 95.5% and 85.5%, respectively.⁷ This is highly aligned to the predicted OS estimates for the ASCT regimen in the model, which reported a 1-year and 3-year OS of 97.2% and 88.5%, respectively. These comparisons demonstrate that the modelled outcomes for survival are externally valid based on available RWE for patients with MCL in the UK who received first-line treatment with the ASCT regimen.

In addition to the HMRN, as detailed in Section 3.14.1 of the CS, predicted OS estimates for the ASCT regimen were externally validated against data from the MCL2 trial (a Phase II evaluating the efficacy of the Nordic regimen [alternating cycles of maxi-CHOP and cytarabine] followed by ASCT for the treatment of previously untreated MCL patients aged <66 years [N=159]).³² As detailed, the predicted median OS of patients receiving the ASCT regimen in the model (12.5 years) was closely aligned with the landmark survival estimate of the MCL2 trial (12.7 years).³² Likewise, a further comparison of 7-year predicted OS estimates for the ASCT regimen in the model with landmark estimates of the 120 MCL patients receiving rituximab maintenance therapy following ASCT in the LyMA trial revealed close alignment between model-predicted 7-year OS (70.0%) and 7-year OS from the LyMA trial (69.5%).^{24, 56} These comparisons further demonstrate that the modelled outcomes (based on the Company's base case inputs and assumptions) are externally valid, in addition to clinically plausible.

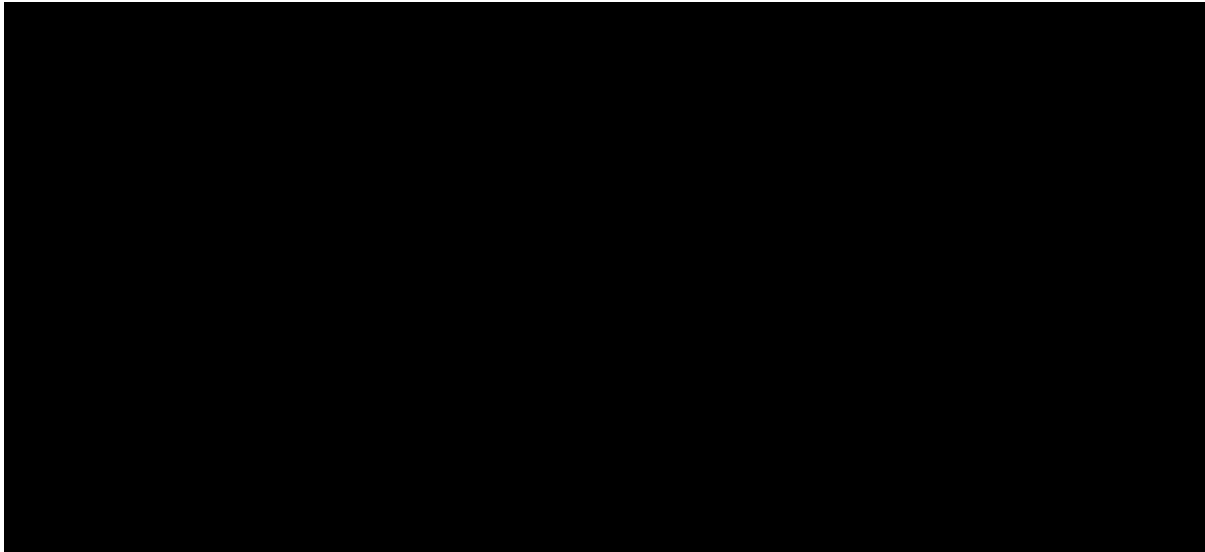
Section C: Textual clarification and additional points

C 1. The EAG noted that the exponential curve in CS Figure 17 seemed missing.

Please provide an updated Figure 17 including the exponential curve.

Johnson & Johnson thank the EAG for flagging this inconsistency, an updated version of Figure 17 in the CS, in which all standard parametric models (including the exponential curve) are presented is provided in Figure 8 below.

Figure 8: TTF: observed vs. predicted for the ibrutinib regimen (TRIANGLE, FAS)



Footnotes: TTF was derived from FFS data, censored for pre-failure mortality, to avoid double-counting.

Abbreviations: FAS: final analysis set; TTF: time to treatment failure

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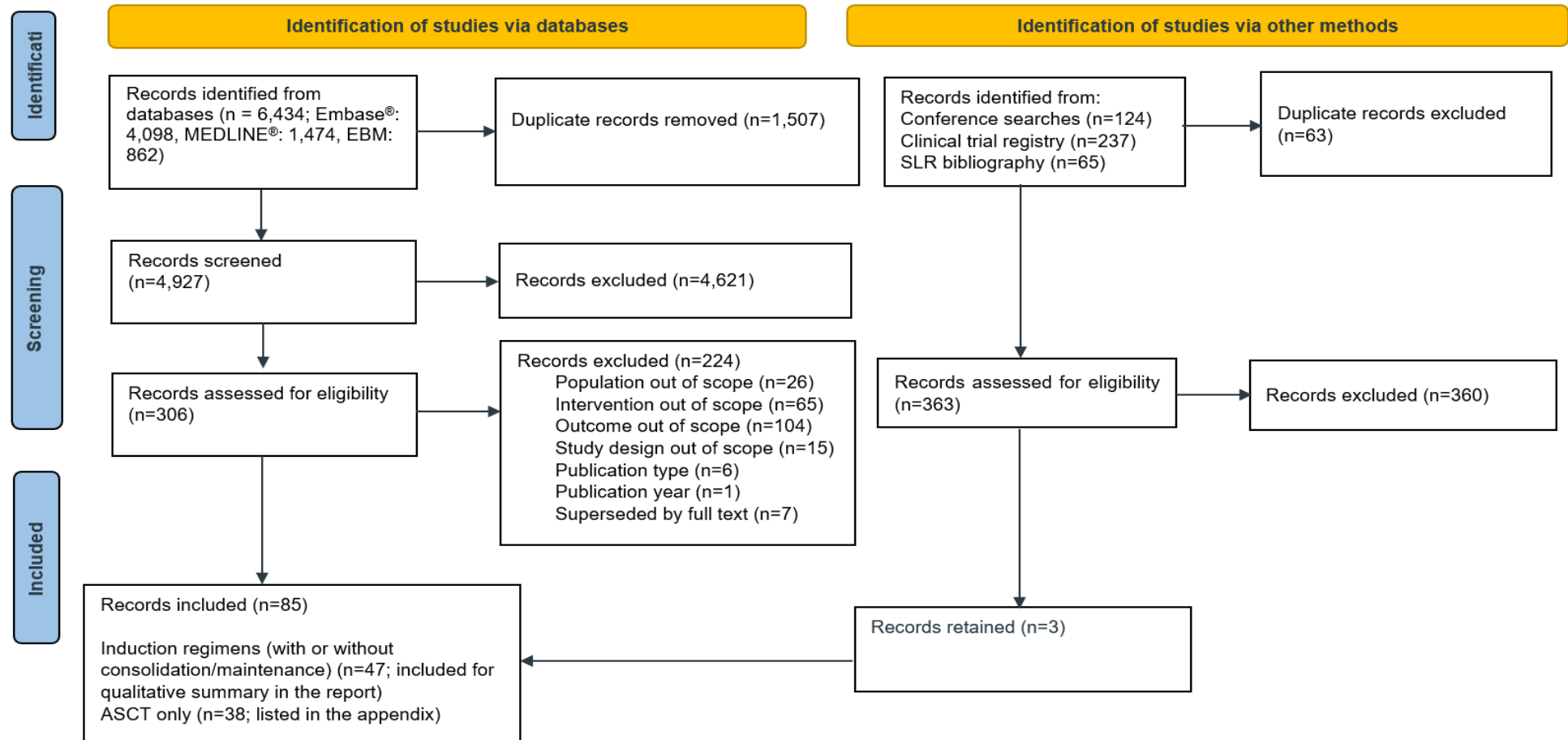
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Section D: Appendix

D 1. Clinical SLR PRISMA

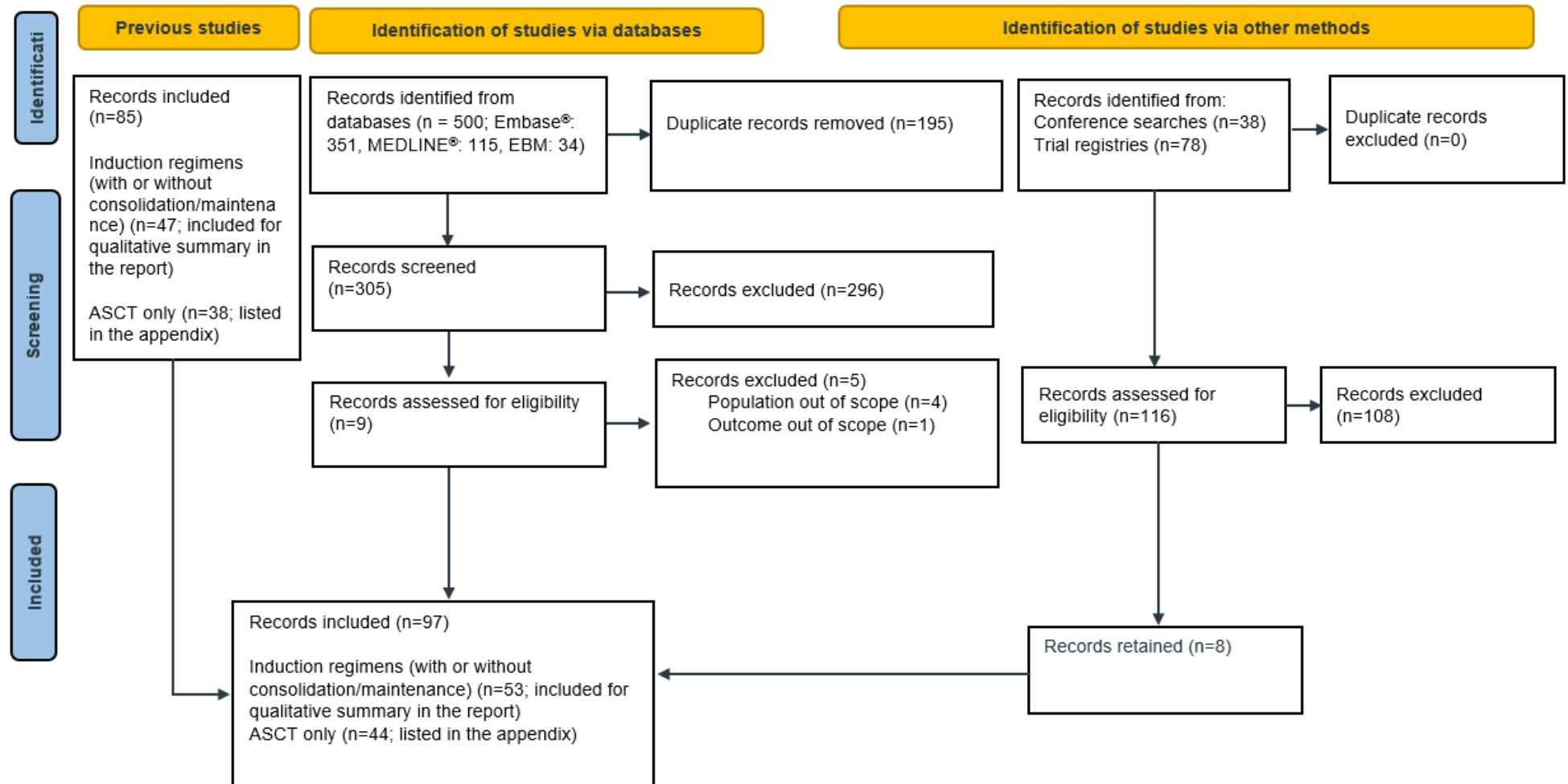
Figure 9: Clinical SLR PRISMA flow diagram (original SLR, September 2024)



Two studies, evaluating zanubrutinib + R-CHOP and R-DHA0x (Yan et al. [2023]) and R-CHOP/R-BAC (Shimizu et al. [2023]), only reporting data for response rates and safety (including discontinuation), were also included in the SLR as these are the only studies identified that evaluate clinical outcomes for these regimens.

Abbreviations: ASCT: autologous stem cell transplantation; SLR: systematic literature review.

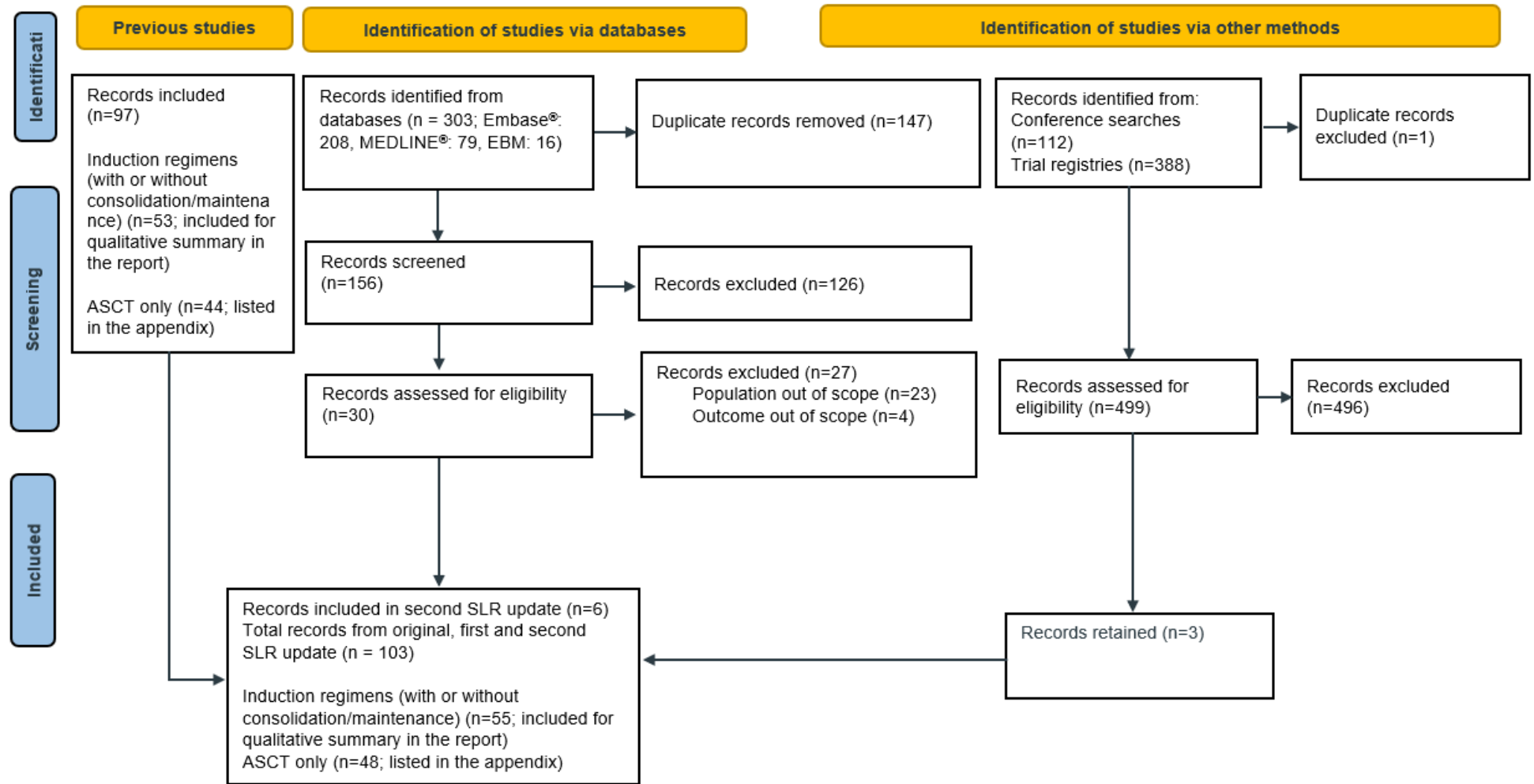
Figure 10: Clinical SLR PRISMA flow diagram (first SLR update, May 2025)



Two studies, evaluating zanubrutinib + R-CHOP and R-DHAox (Yan et al. [2023]) and R-CHOP/R-BAC (Shimizu et al. [2023]), only reporting data for response rates and safety (including discontinuation), were also included in the SLR as these are the only studies identified that evaluate clinical outcomes for these regimens.

Abbreviations: ASCT: autologous stem cell transplantation; SLR: systematic literature review.

Figure 11: Clinical SLR PRISMA flow diagram (second SLR update, October 2025)

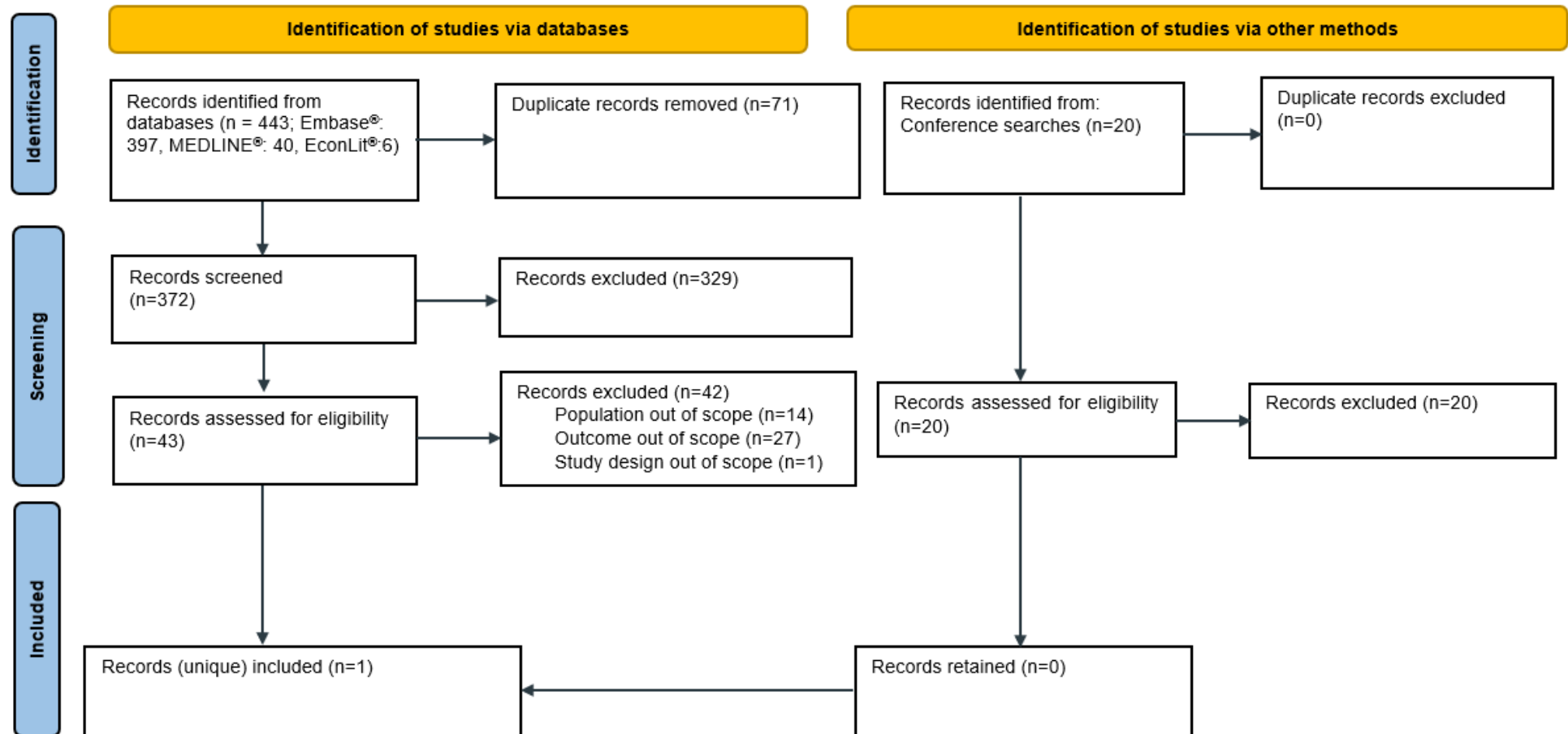


Two studies, evaluating zanubrutinib + R-CHOP and R-DHA0x (Yan et al. [2023]) and R-CHOP/R-BAC (Shimizu et al. [2023]), only reporting data for response rates and safety (including discontinuation), were also included in the SLR as these are the only studies identified that evaluate clinical outcomes for these regimens.

Abbreviations: ASCT: autologous stem cell transplantation; SLR: systematic literature review.

D 2. Economic SLR PRISMAs

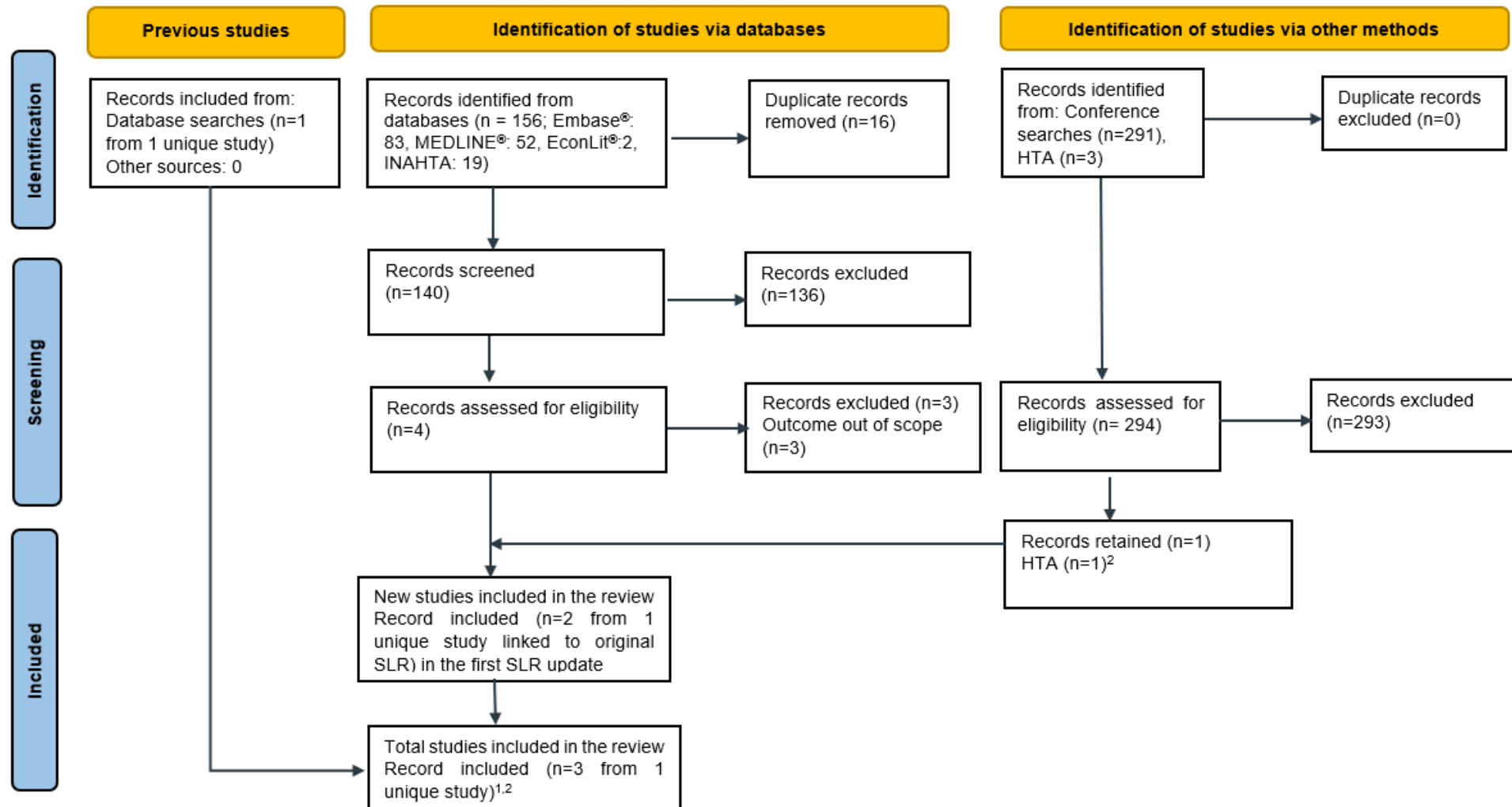
Figure 12: Economic SLR PRISMA flow diagram (original SLR, December 2023: economic evaluations)



A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: SLR: systematic literature review.

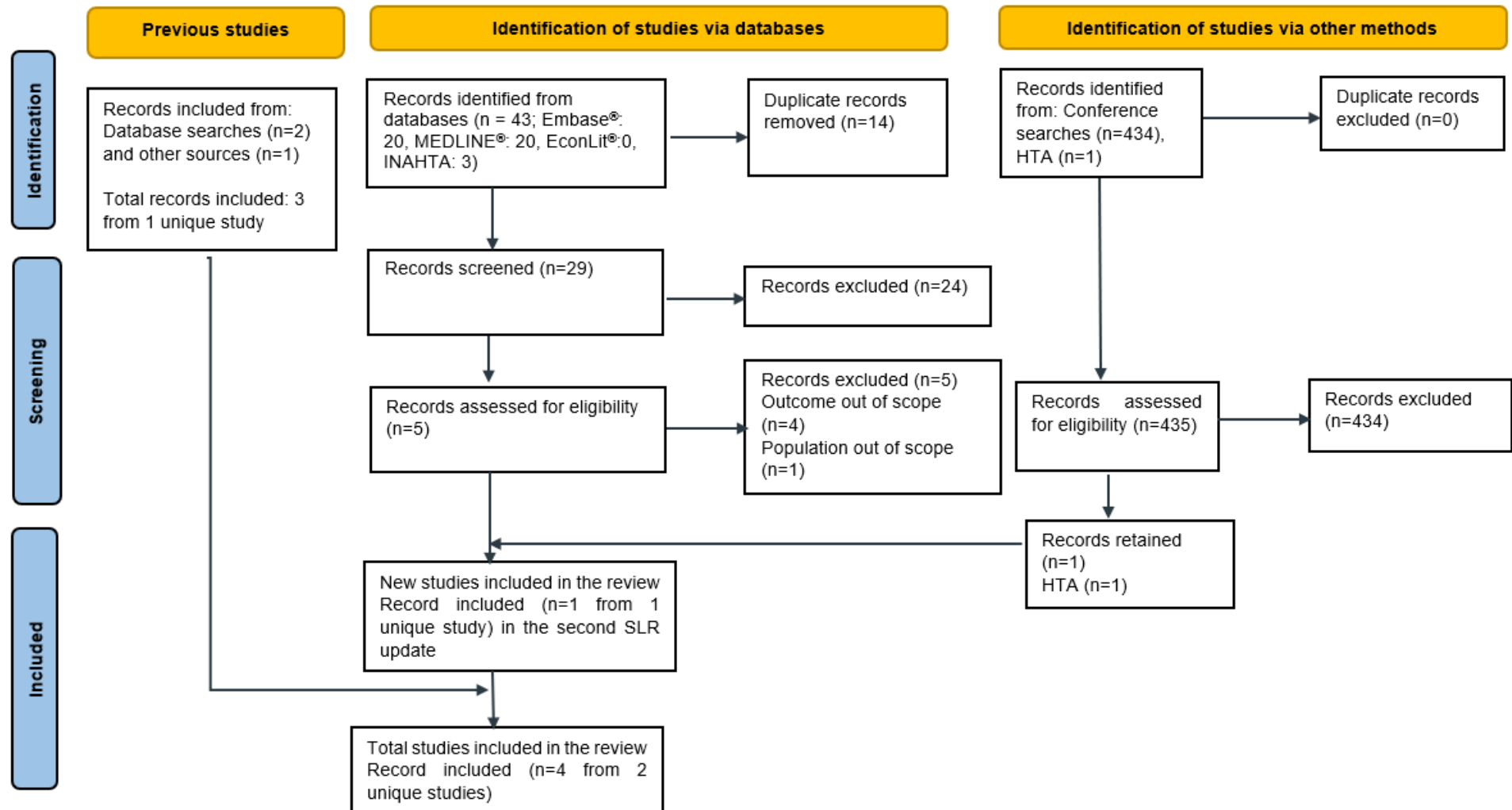
Figure 13: Economic SLR PRISMA flow diagram (first SLR update, May 2025: economic evaluations)



A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: SLR: systematic literature review.

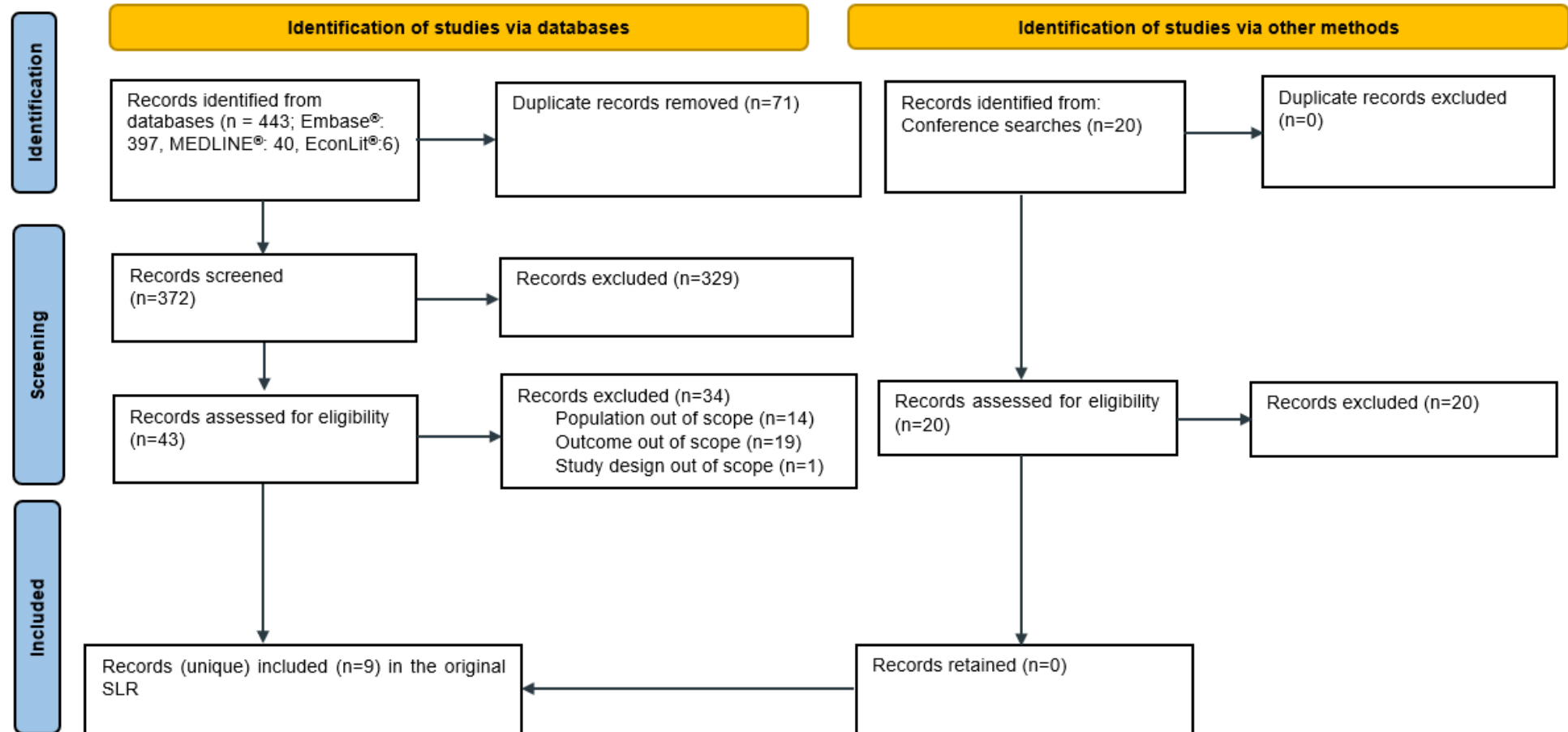
Figure 14: Economic SLR PRISMA flow diagram (second SLR update, October 2025: economic evaluations)



A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: SLR: systematic literature review.

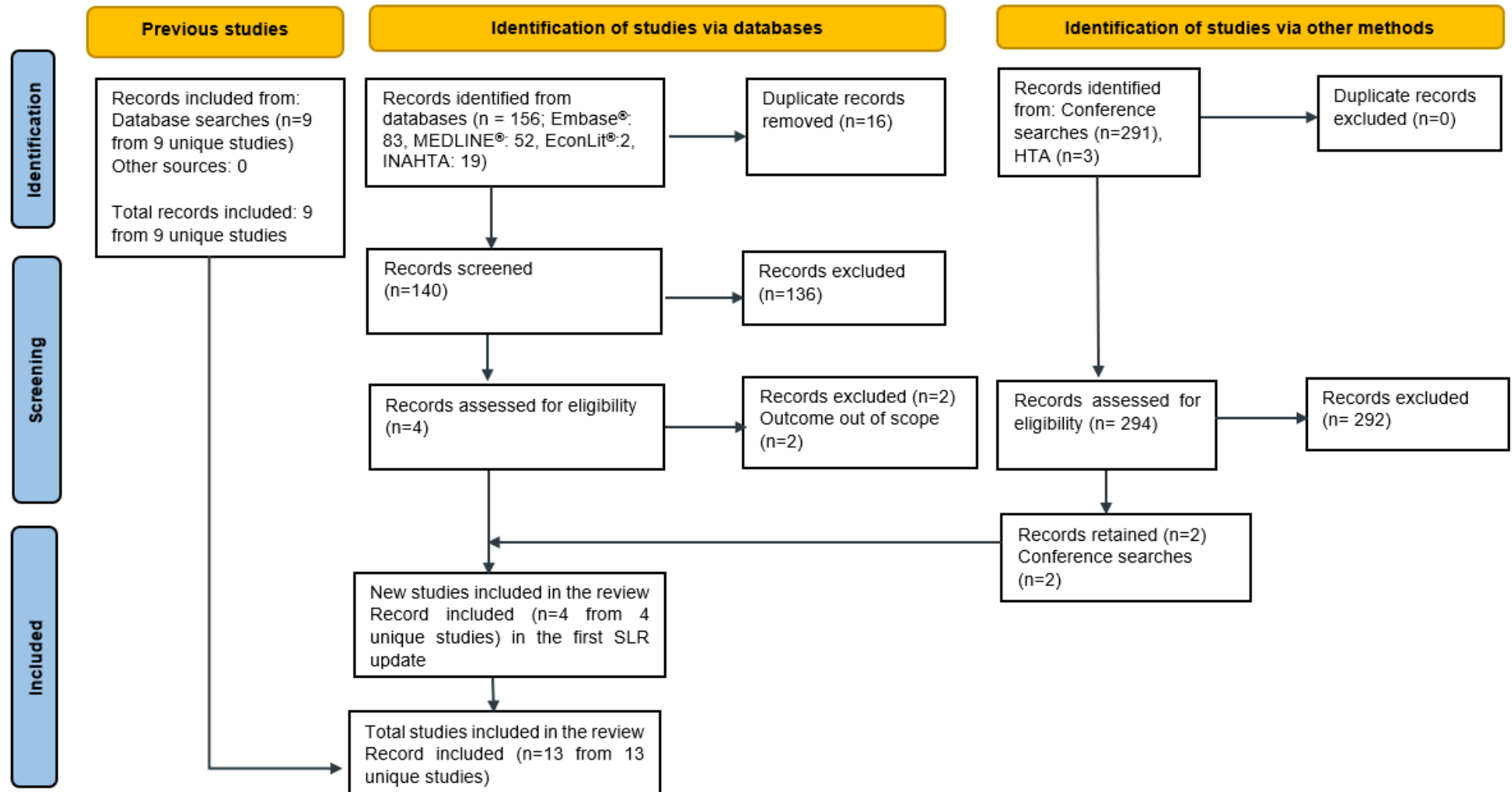
Figure 15: Economic SLR PRISMA flow diagram (original SLR, December 2023: cost and HCRU)



A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: HCRU: healthcare resource use; SLR: systematic literature review.

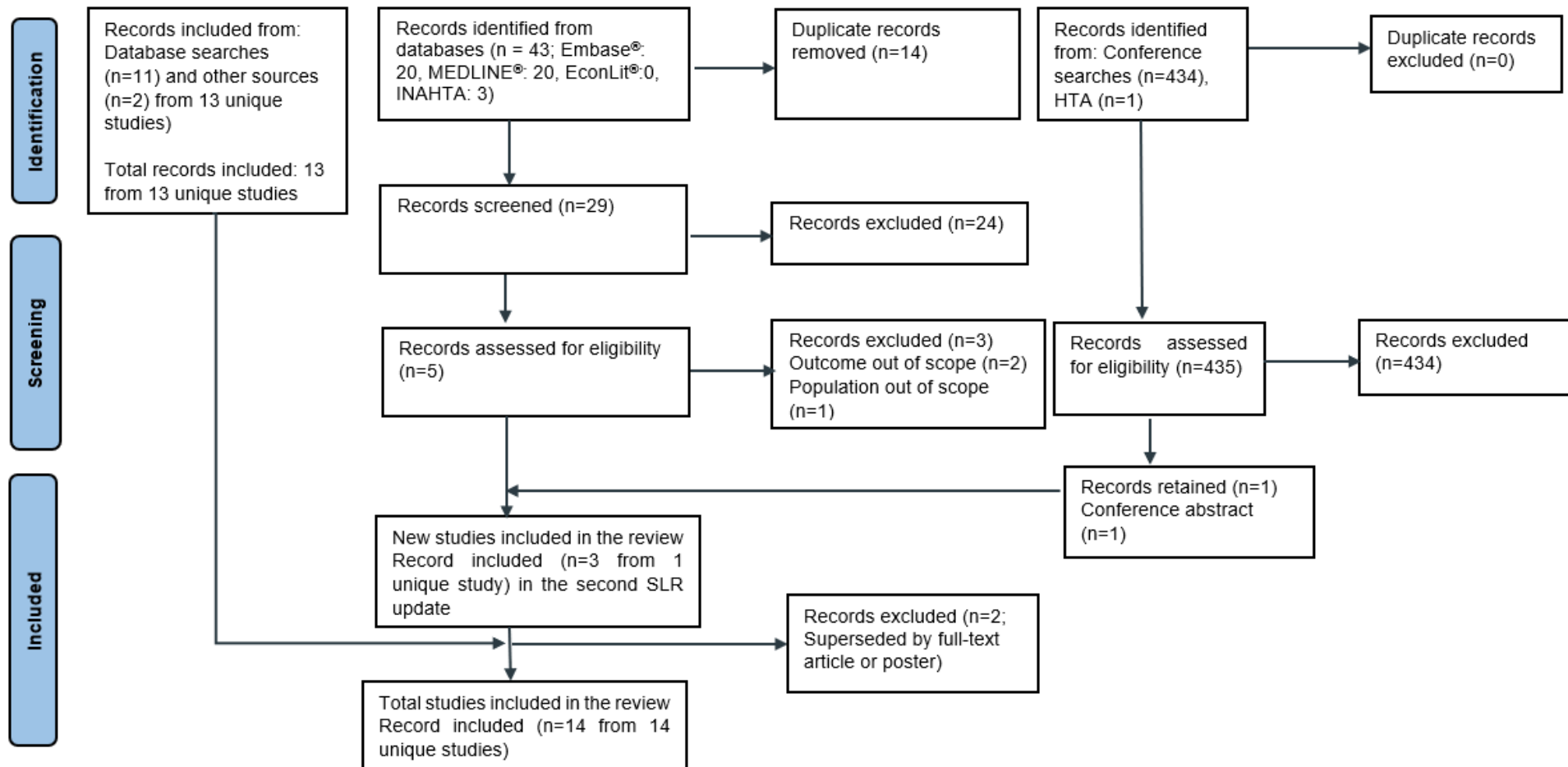
Figure 16: Economic SLR PRISMA flow diagram (first SLR update, May 2025: cost and HCRU)



A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: HCRU: healthcare resource use; SLR: systematic literature review.

Figure 17: Economic SLR PRISMA flow diagram (second SLR update, October 2025: cost and HCRU)

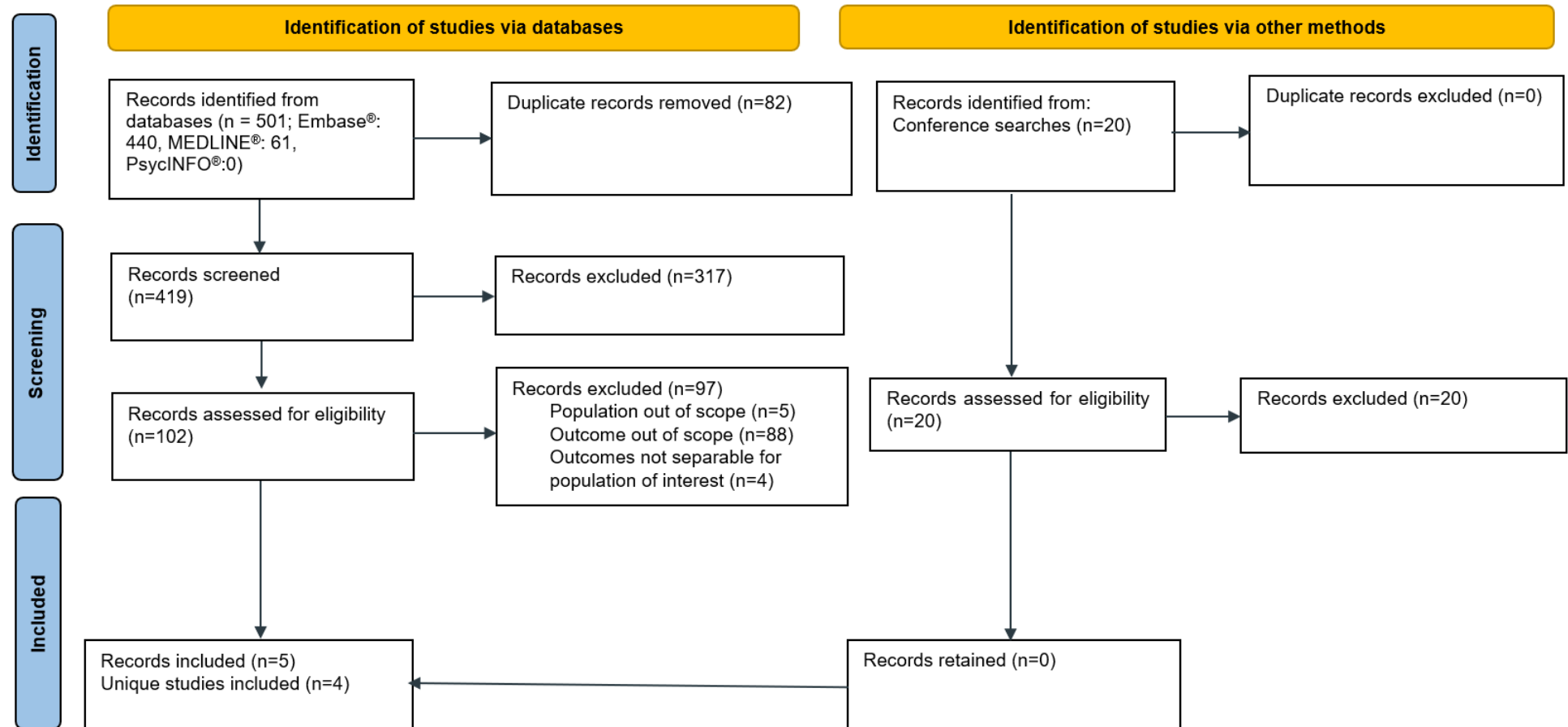


A single comprehensive search was run for both “economic evaluation” and “cost and HCRU” SLRs, and screening was also conducted together. PRISMA for economic evaluation and cost and HCRU SLRs differ only at full-text exclusion stage and at final inclusion.

Abbreviations: HCRU: healthcare resource use; SLR: systematic literature review.

D 3. HRQoL SLR PRISMAs

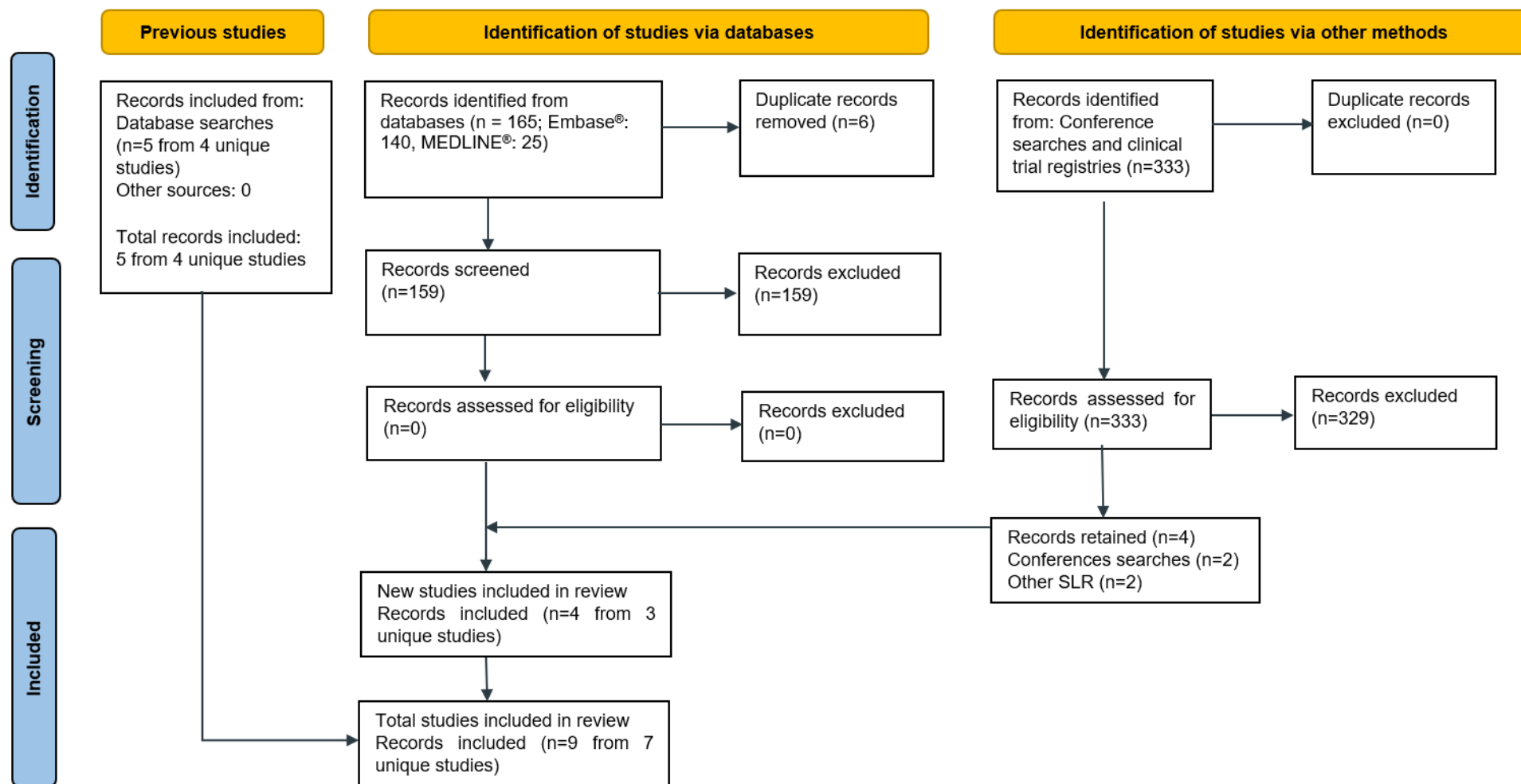
Figure 18: HRQoL SLR PRISMA flow diagram (original SLR, December 2023)



Additionally, four studies from the original SLR on broader lymphoma patients were included in which outcomes specific to the 1L MCL patients were not reported.

Abbreviations: HRQoL: health-related quality of life; SLR: systematic literature review.

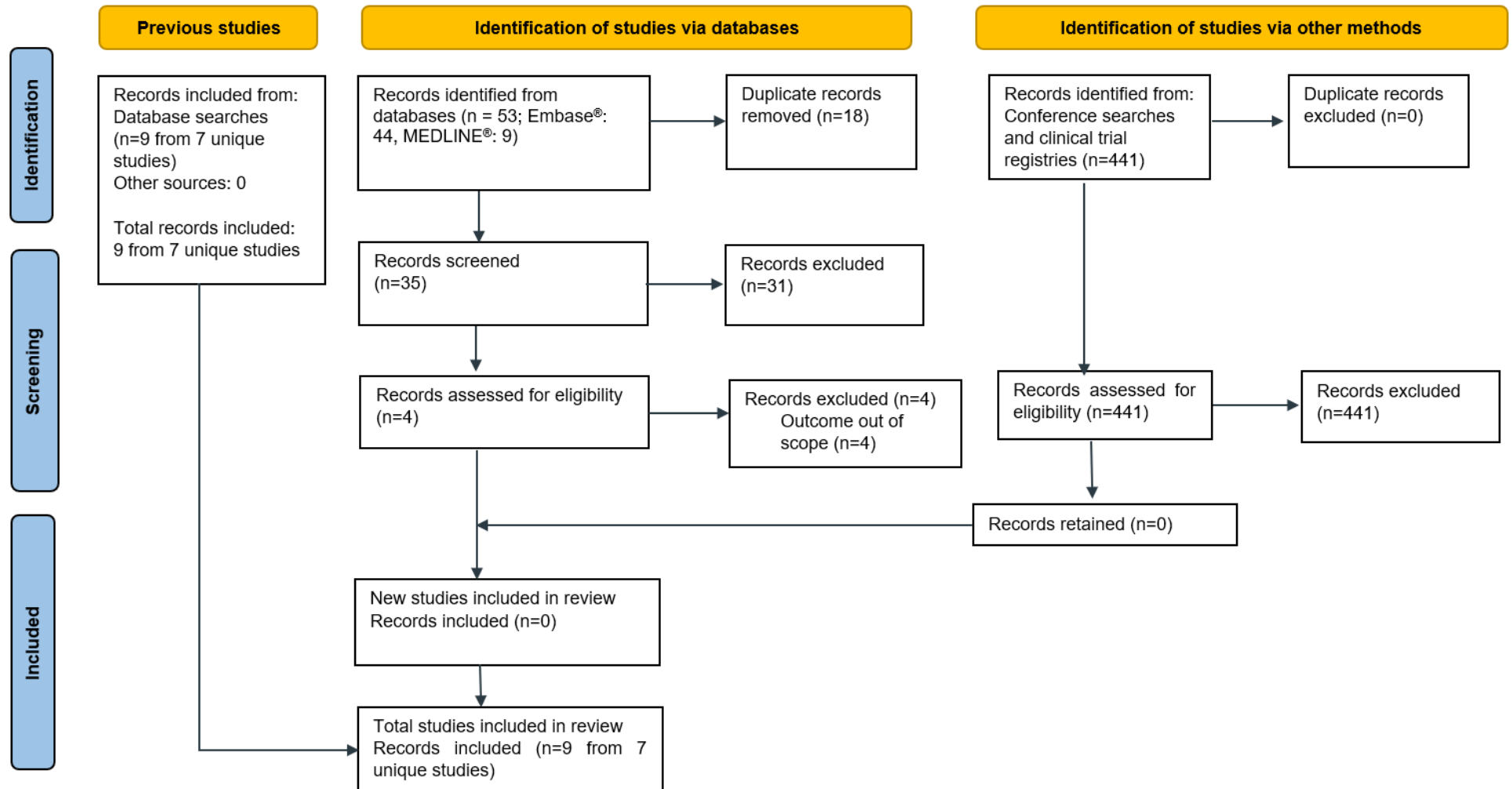
Figure 19: HRQoL SLR PRISMA flow diagram (first SLR update, May 2025)



Additionally, five studies (four from the original SLR and one from the SLR update) on broader lymphoma patients were included in which outcomes specific to the 1L MCL patients were not reported.

Abbreviations: HRQoL: health-related quality of life; SLR: systematic literature review.

Figure 20: HRQoL SLR PRISMA flow diagram (second SLR update, October 2025)



Additionally, five studies (four from the original SLR and one from the SLR update) on broader lymphoma patients were included in which outcomes specific to the 1L MCL patients were not reported.

Abbreviations: HRQoL: health-related quality of life; SLR: systematic literature review.

D 4. Updated base case results

The AE and resource use changes resulting in the updated base case accompanying this clarification question response are detailed at the start of Section B. For completeness, the updated base case probabilistic and deterministic cost-effectiveness results for the ibrutinib regimen (with PAS) vs. the ASCT regimen are presented in Table 48 and Table 50, respectively, with results at the ibrutinib list price presented in Table 49 and Table 51. These results are highly aligned with the original base case results included in the CS and therefore demonstrate that the impact of the changes detailed at the start of Section B are negligible.

Table 48: Probabilistic base-case results (ibrutinib PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	████████	12.13	████	-	-	-	-	-
ASCT regimen	£207,249.07	10.75	████	████████	1.38	████	Dominant	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 49: Probabilistic base-case results (ibrutinib list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	£248,257.17	12.13	████	-	-	-	-	-
ASCT regimen	£212,480.05	10.75	████	£35,777.11	1.38	████	████████	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

Table 50: Deterministic base-case results (ibrutinib PAS price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	████████	12.11	████	-	-	-	-	-
ASCT regimen	£205,523.75	10.77	████	████████	1.35	████	Dominant	████

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

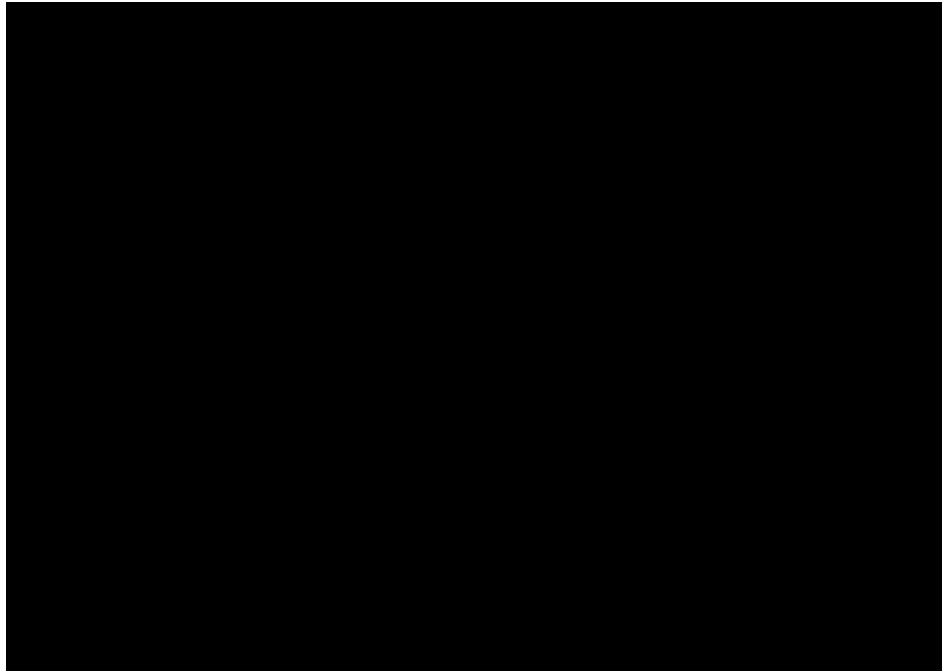
Table 51: Deterministic base-case results (ibrutinib list price)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER	INHB at £30,000
Ibrutinib regimen	£247,188.63	12.11	■	-	-	-	-	-
ASCT regimen	£210,669.14	10.77	■	£36,519.49	1.35	■	■	■

Abbreviations: ASCT: autologous stem cell transplant; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; LY: life years; QALYs: quality-adjusted life years.

D 5. Updated base case DSA results

Figure 21: DSA tornado diagram for ibrutinib regimen vs. ASCT regimen; INHB (ibrutinib PAS price)



Abbreviations: AE: adverse event; AMR: annual mortality rate; ASCT: autologous stem cell transplant; FF: failure free; HR: hazard ratio; INHB: incremental net health benefit; IV: intravenous; PAS: patient access scheme; PD: progressed disease; PF: progression free.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Clarification questions

March 2026

File name	Version	Contains confidential information	Date
ID6596_ibrutinib_clarification question_B15_B16_CON	V1.0	Yes	4 th March 2026

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section B: Clarification on cost-effectiveness data

B 15. The company used EQ-5D-5L data from the SHINE trial (progression-free patients in the ibrutinib arm), mapped to EQ-5D-3L and analysed using a mixed-model repeated measures (MMRM) approach to inform FF 1L health state utilities.

a) Please justify the choice of an MMRM framework with reference to:

i. the longitudinal structure of the SHINE EQ-5D data

A mixed-model repeated measures (MMRM) approach is well suited to the longitudinal structure of the SHINE EQ-5D data because it accounts for the correlation between repeated patient-reported outcomes (PROs) collected from the same individuals over time. Unlike analyses that assume independence between observations, MMRM appropriately models within-patient correlation and enables estimation of mean utility values at each assessment time point. It also facilitates examination of the relationship between patient characteristics and PRO outcomes, which was necessary to apply baseline characteristics from the TRIANGLE population to estimate failure-free first line (FF 1L) utilities for the relevant patient population.

To inform the FF 1L utility values in the model, an MMRM was fitted to EQ-5D-derived utilities from progression-free patients in the SHINE ibrutinib arm. The model incorporated key covariates, including sex, adverse event (AE) status, Eastern Cooperative Oncology Group (ECOG) performance status, baseline disease stage, presence of B-symptoms, creatinine clearance <30 mL/min, and bone marrow involvement. Coefficients from this MMRM were then applied to the corresponding baseline characteristics of TRIANGLE patients to estimate failure-free utility values for the TRIANGLE population.

ii. the extent and pattern of within-patient repeated measurements

Table 1 below shows the extent and pattern of within patient repeated measures in ibrutinib arm of SHINE trial, in the progression free health state. A total of 100 subjects contributed data to the MMRM estimated from SHINE.

Table 1: Extent and pattern of within-patient repeated measurements (ibrutinib arm of SHINE)

Number of visits	Number of within-patient repeated measurements
1	1
2	2
3	1
4	1
5	1
6	2
7	2
8	1
9	2
10	2
11	2
12	1
13	1
14	1
15	1
16	1
17	2
18	1
19	1
20	1
21	1
22	2
23	1
24	1
25	2
26	2
27	2
28	1
29	1
30	1
32	1

Source: J&J Data on File

b) Please provide a concise summary of the EQ-5D data used, including:

i. number of patients and observations

The number of progression-free patients with available utility data in the ibrutinib arm of SHINE are summarised in Table 2, as well as the number who remained progression-free and uncensored for progression and the proportion of missing observations at each assessment point. Although utility data were collected up to 441 weeks, the sample size became increasingly limited at later time points. Therefore, for the MMRM analysis, it was considered more appropriate to restrict the dataset to observations collected up to and including week 361. Beyond this point, uncertainty in the estimates increased, as reflected by the widening confidence intervals shown in Figure 1, although mean utility point estimates remained stable across the time horizon.

Table 2: Summary of EQ-5D data included in the MMRM

Week	Number of patients progression-free and not censored for progression at the PRO collection time point	Number of progression-free respondents in the ibrutinib arm of SHINE Trial	% missing
0	■	■	■
4	■	■	■
8	■	■	■
12	■	■	■
16	■	■	■
20	■	■	■
33	■	■	■
45	■	■	■
57	■	■	■
73	■	■	■
89	■	■	■
105	■	■	■
121	■	■	■
137	■	■	■
153	■	■	■
169	■	■	■
185	■	■	■
201	■	■	■
217	■	■	■
233	■	■	■
249	■	■	■
265	■	■	■
281	■	■	■
297	■	■	■
313	■	■	■
329	■	■	■
345	■	■	■

361	■	■	■
377	■	■	■
393	■	■	■
409	■	■	■
425	■	■	■
441	■	■	■

Abbreviations: MMRM: mixed-model repeated measures; PRO: patient-reported outcomes.

Source: J&J Data on File

ii. assessment time points

PRO assessments in SHINE were performed on Day 1 of the first six cycles. From cycle 7 onwards, PRO assessments were performed every 12 weeks in the first 12 months and, following that, every 16 weeks. PRO assessments were scheduled at the End of Treatment Visit and during the survival follow-up. The End of Treatment Visit was scheduled within 30 days after the last dose of the last study treatment for all subjects, including those discontinuing treatment for any reason, except for those lost to follow-up, death, or withdrawal of consent for study participation. Following disease progression, sites administered the EQ-5D-5L every 16 weeks (up to three times) during the survival follow-up period, unless death or study end occurred first. Importantly, PROs collected after disease progression or after patients were censored for PFS were not used in the estimation of the MMRM model from SHINE. This is because the MMRM was used to estimate utility values for patients using TRIANGLE baseline characteristics data, to inform FF 1L health state utility estimate in the model.

iii. proportion of missing data over time

The proportion of missing data over time is reported in Table 2.

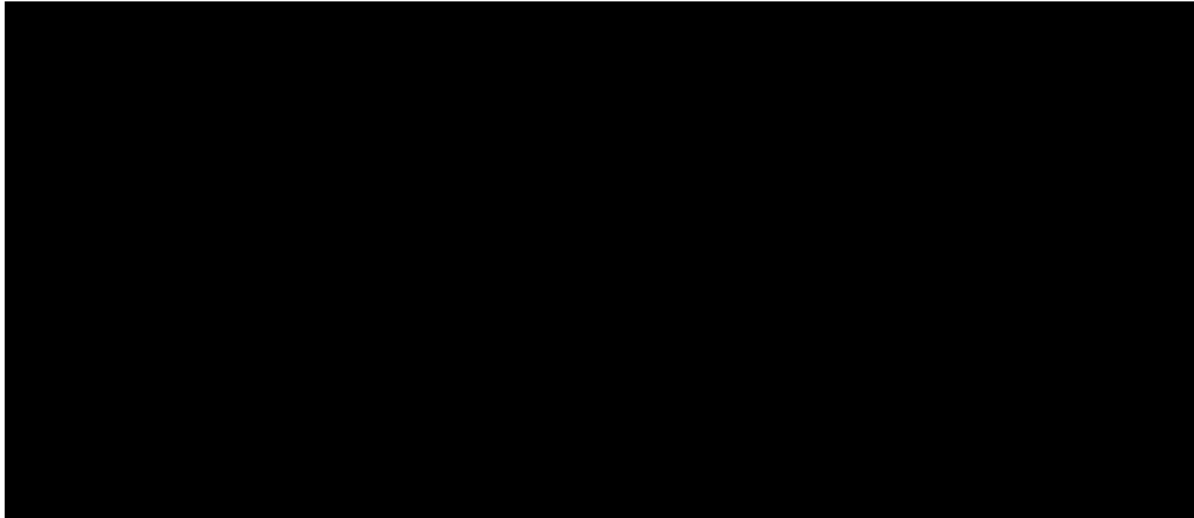
iv. assumptions made regarding missingness (e.g. MAR)

Missing PRO values were not imputed, and the analysis relied on the assumption that data were Missing at Random (MAR). Under this assumption, conditional on observed patient characteristics and PRO assessments at other time points, the expected value of the unobserved PRO/utility outcomes is assumed to be the same as it would have been had those outcomes been observed.

- c) Please present the estimated mean EQ-5D utility profile over time from SHINE, and comment on whether utilities appear stable, improving, or declining within the FF 1L period.

Observed progression-free (non-MMRM) mean utilities in the ibrutinib arm of the SHINE trial are shown in Figure 1. As noted in the response to Question B15b), data were restricted to week 361, as the number of observations dropped to ■ beyond this point, resulting in substantially wider confidence intervals. A total of ■ observations were included in the MMRM. Across the period evaluated, the mean utility values remained stable over time within the progression free population.

Figure 1: SHINE Trial, Ibrutinib Arm, Observed progression-free (non-MMRM) Mean Utilities and the Accompanying 95% CIs (UK weights)



Abbreviations: 3L: third-line; CI: confidence intervals; MMRM: mixed model for repeated measures.

Source: J&J Data on File

- d) Please clarify the final model specification (fixed effects included, random intercept and/or slope) and justify why this structure was selected.

In the final model specification, an MMRM was fitted to EQ-5D-derived utilities from progression-free patients in the ibrutinib arm of SHINE. The model incorporated key covariates based on clinical expert feedback and included sex, adverse event (AE) status, Eastern Cooperative Oncology Group (ECOG) performance status, baseline disease stage, presence of B-symptoms, creatinine clearance <30 mL/min, and bone marrow involvement. Coefficients from this MMRM were then applied to the corresponding baseline characteristics of TRIANGLE patients to estimate failure-free utility values for the TRIANGLE population.

Although age was recognised as clinically relevant and known to differ between the TRIANGLE and SHINE populations, it was excluded from the MMRM. Applying the baseline age–utility relationship from SHINE to the younger TRIANGLE population produced unrealistically high utility values. Excluding age therefore represents a conservative modelling approach, as including it would have generated greater QALY gains for patients receiving the ibrutinib regimen, who spend more time in the FF 1L health state.

In addition to baseline covariates, scheduled visit time points were included as fixed effects. The MMRM was fitted using [REDACTED] observations from [REDACTED] patients, with up to [REDACTED] repeated measurements per individual. Within-patient correlation was addressed through the correlation structure rather than a random effects approach. An autoregressive (1) correlation structure, which produced the lowest Akaike Information Criterion (AIC), was selected.

- e) Please provide the following scenario analyses to assess robustness:
- i. FF 1L utility estimated using a pooled mean EQ-5D value (ignoring time)

As demonstrated in Figure 1, the mean EQ-5D utilities observed in the SHINE ibrutinib arm remained highly stable across the full period evaluated. Given this stability, estimating the FF 1L utility using a pooled mean value without explicitly modelling time is not expected to meaningfully affect the utility inputs used in the economic model. Furthermore, because identical utility values are applied to both treatment arms, any minor variation resulting from ignoring time would have a negligible impact on the incremental QALYs and, consequently, on the ICER. For these reasons, Johnson & Johnson consider that a scenario analysis is not warranted and have not provided one in response to this request.

- ii. FF 1L utility estimated using an MMRM including both treatment arms and a treatment indicator (including SHINE trial data from both arms)

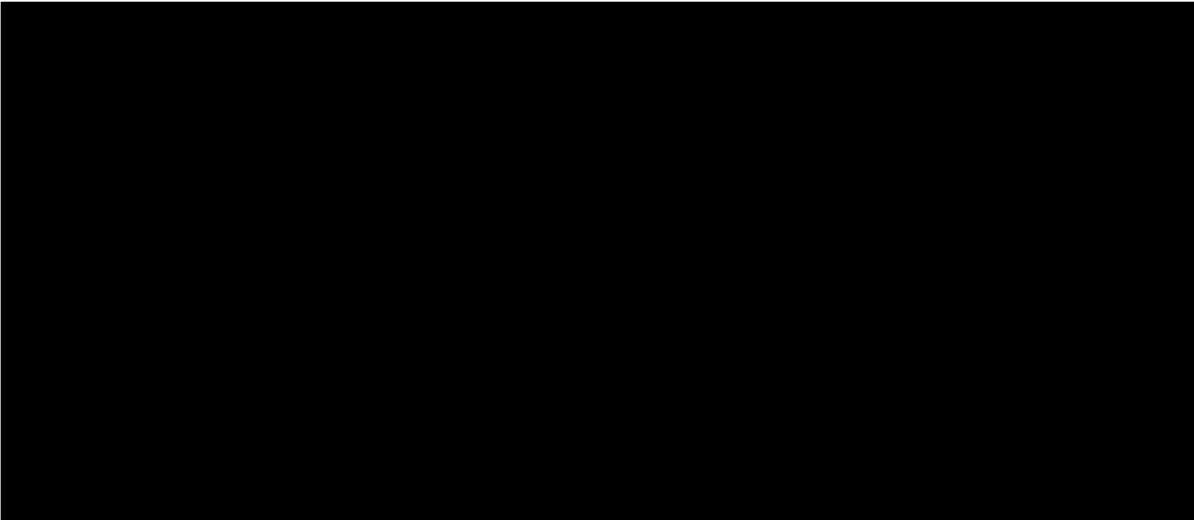
Table 3 presents the observed EQ-5D utility values from the SHINE trial up to week 361 for both the ibrutinib and placebo arms. These values represent directly observed SHINE data rather than modelled estimates from the MMRM. As shown in the Table 3 and further illustrated in Figure 2, there is no discernible difference in utility values between treatment arms over the observed period. Given the clear overlap in utility profiles and the absence of any systematic separation between arms, incorporating both arms into an MMRM with a treatment indicator would not be expected to meaningfully alter utility estimates. Consequently, no additional cost-effectiveness scenario has been conducted.

Table 3: Observed EQ-5D utility values from the SHINE trial

SHINE arm	Area under curve ^a up to week 361 ^b
Ibrutinib	
Placebo	

^a Raw mean observed utilities prior to MMRM model applied to match TRIANGLE characteristics. ^b Given reduced sample size and high uncertainty after this point, remaining observations were left out of the mean calculation.
Source: J&J Data on File

Figure 2: Observed mean utility over time (SHINE trial, progression free)



Abbreviations: 3L: third-line.
Source: J&J Data on File

- iii. FF 1L utility estimated using a progression-adjusted model including progressed disease as a covariate (including SHINE trial data from both progression-free and progressed patients/observations).

The FF 1L utility values used in the model are derived from an MMRM estimated exclusively observations from patients receiving ibrutinib who are progression-free in the SHINE trial, with utilities excluded from the timepoint of progression onwards. This approach was selected because the resulting model coefficients are applied to baseline characteristics of patients in the TRIANGLE study to estimate progression-free utility at baseline. Including observations collected after disease progression from SHINE would have introduced post-progression utility effects into a model intended solely to estimate progression-free health-state utilities (as a proxy for failure-free utility values). For this reason, a scenario analysis incorporating progressed-disease observations as a covariate has not been conducted.

B 15. EQ-5D-5L data from the ibrutinib arms of the RAY-3001 and SPARK trials were pooled and analysed using a mixed model to estimate PF 2L and PD health state utilities.

Johnson & Johnson apologise that owing to the time that has passed since the original analysis was performed, it was not possible to replicate the approach to pooling EQ-5D-5L data from the ibrutinib arms of the RAY-3001 and SPARK trials, as per TA502.¹ Therefore, in response to the EAG's query, a new utility analyses using more recent data cuts was performed.

a) Please describe how EQ-5D data from RAY-3001 and SPARK were combined, including:

- i. alignment of assessment schedules

In both trials, EQ-5D-5L questionnaires were administered on Day 1 of each treatment cycle during the first 6 months, then every 9 weeks up to 15 months after the first dose, and thereafter every 24 weeks until disease progression, death, or study end. As both studies defined a treatment cycle as 21 days, cycle-based assessments correspond to the same nominal time points across trials.

The only notable differences were:

- An additional EQ-5D-5L assessment was available from Cycle 9 in SPARK compared to RAY-3001.
- RAY-3001 included additional post-progression EQ-5D-5L collections during survival follow-up (every 9 weeks, up to three assessments), whereas SPARK did not. These observations were treated as post-progression measurements rather than as part of the pre-progression schedule.

- ii. consistency of EQ-5D instruments and value sets

Across both studies, utility values were derived from EQ-5D-5L questionnaires using UK valuation sets.

iii. any differences in baseline patient characteristics relevant to HRQoL

The baseline characteristics for patients receiving ibrutinib at second-line in RAY-3001 and SPARK are summarised in Table 4.

Overall, the two populations were similar with no statistically significant differences across the baseline characteristics identified (as assessed by chi-square tests), with the exception of geographic region. SPARK enrolled patients in Europe and the United States, whereas RAY-3001 enrolled patients in Europe, Asia, and other regions. This regional difference was not considered clinically or prognostically relevant for the utility estimation, as region was not identified as a key prognostic factor for HRQoL/utility in the set of prognostic factors validated with clinical experts (see Question d)

Table 4: Baseline characteristics of 2L patients in the ibrutinib arm in RAY study and in SPARK study

Baseline characteristic	SPARK (MCL3001) (N=20)	RAY (MCL2001) (N=57)	P-value
Age			
Mean (SD)	65.6 (10.1)	65.8 (8.91)	0.926
Median [Min, Max]	71.0 [43.0, 77.0]	67.0 [39.0, 84.0]	
Age category			
<65	7 (35.0%)	22 (38.6%)	0.986
>=65	13 (65.0%)	35 (61.4%)	
Baseline ECOG			
>=1	11 (55.0%)	31 (54.4%)	1
0	9 (45.0%)	26 (45.6%)	
Sex			
Female	3 (15.0%)	23 (40.4%)	0.0738
Male	17 (85.0%)	34 (59.6%)	
Region			
Europe	8 (40.0%)	44 (77.2%)	<0.001
United States	12 (60.0%)	0 (0%)	
Asia	0 (0%)	9 (15.8%)	
Other	0 (0%)	4 (7.0%)	
Blastoid History			
No	20 (100%)	53 (93.0%)	0.528
Yes	0 (0%)	4 (7.0%)	
Prior Lenalidomide			
No	19 (95.0%)	57 (100%)	0.581
Yes	1 (5.0%)	0 (0%)	

Bulky disease (≥ 10 cm vs. <10 cm)			
< 10 cm	19 (95.0%)	53 (93.0%)	1
≥ 10 cm	1 (5.0%)	4 (7.0%)	
Stage of disease (IV vs. I-III)			
I-III	8 (40.0%)	18 (31.6%)	0.682
IV	12 (60.0%)	39 (68.4%)	
Race			
Unknown	1 (5.0%)	3 (5.3%)	0.252
White	19 (95.0%)	44 (77.2%)	
Asian	0 (0%)	9 (15.8%)	
Other	0 (0%)	1 (1.8%)	
Simplified MIPI Score Category			
High Risk	6 (30.0%)	11 (19.3%)	0.61
Intermediate Risk	8 (40.0%)	26 (45.6%)	
Low Risk	6 (30.0%)	20 (35.1%)	
Extranodal Disease			
No	8 (40.0%)	31 (54.4%)	0.397
Yes	12 (60.0%)	26 (45.6%)	

Abbreviations: ECOG: Eastern Cooperative Oncology Group; MIPI: Mantle Cell Lymphoma International Prognostic Index.

iv. statistical methods used

Data were combined using an MMRM approach. Within-patient correlation was addressed through the correlation structure between observations at fixed timepoints. An autoregressive (1) correlation structure, which produced the lowest AIC, was selected.

- b) Please justify the pooling of these trials for utility estimation and explain how potential between-trial heterogeneity was addressed (e.g. trial indicator, random effects, or adjustment for baseline covariates).

The pooling of EQ-5D-5L data from RAY-3001 and SPARK was discussed with clinical experts at the November 2025 advisory board and considered clinically appropriate because both trials evaluated patients with relapsed/refractory MCL, had similar inclusion/exclusion criteria and broadly comparable study designs.² Prior bortezomib exposure was identified as a difference between the trials; however, this was not considered prognostic for utility.

Potential between-trial heterogeneity was assessed by comparing baseline patient characteristics in the second-line ibrutinib arms (Table 4). No statistically significant differences were observed across the characteristics examined, except for geographic region (SPARK enrolled in Europe and the United States, whereas RAY-3001 enrolled in Europe, Asia, and other regions). Based on the prognostic factors for utility validated with MCL clinical experts (see Question d)), this regional difference was not considered relevant for utility estimation.

Given the high similarity of the trial populations and the absence of differences considered prognostically relevant for HRQoL, the pooled MMRM was fitted without additional adjustment for baseline covariates or an explicit trial indicator/random effect

c) Please summarise the EQ-5D data used, including:

i. number of patients and observations per trial

■ and ■ second-line patients participated in the RAY-3001 and SPARK studies, respectively. The total number of pre-progression utility observations across both trials is ■ (Table 5) and the total number of observations post-progression is ■ (Table 6).

Table 5: Timing and number of pre-progression utility observations

Study	Cycle	Number of Observations
SPARK (MCL2001)	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	II	■
	II	■
	III	I
	IV	I
RAY (MCL3001)	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	I	■
	II	■
	II	■
	II	■
	II	■
	V	I

	■	■
	■	■
	■	■

Table 6 Timing and number of post-progression utility observations

Study	Cycle	Number of Observations
SPARK (MCL2001)	■	■
	■	■
	■	■
	■	■
	■	■
RAY (MCL3001)	■	■
	■	■
	■	■
	■	■
	■	■
	■	■
	■	■
	■	■
	■	■
	■	■

ii. distribution of observations across PF 2L and PD

After data from the RAY-3001 and SPARK studies were combined, there are ■ observations from progression-free second-line patients (Table 5) and ■ from progressed second-line patients (Table 6).

iii. extent and handling of missing data

The proportion of missing observations at each assessment point from pooled second-line patients in the ibrutinib arm in RAY-3001 study and from second-line patients in SPARK study are summarised in Table 7. Missing utility data relative to the proportion of progression-free patients was generally low across timepoints.

Table 7: Proportion of missing observations (ibrutinib arm in RAY-3001 and second-line patients in SPARK)

Analysis Visit	Expected ^a	Compliance n (%) ^b	Missing n (%)
Baseline	■	■	■
Cycle 2	■	■	■
Cycle 3	■	■	■

Cycle 4	■	■■■■■	■■■■■
Cycle 5	■	■■■■■	■■■■■
Cycle 6	■	■■■■■	■■■■■
Cycle 7	■	■■■■■	■■■■■
Cycle 8	■	■■■■■	■■■■■
Cycle 9 ^c	■	■■■■■	■■■■■
Cycle 11	■	■■■■■	■■■■■
Cycle 14	■	■■■■■	■■■■■
Cycle 17	■	■■■■■	■■■■■
Cycle 20	■	■■■■■	■■■■■
Cycle 28	■	■■■■■	■■■■■
Cycle 36	■	■■■■■	■■■■■
Pre-progression Follow-Up 1	■	■■■■■	■■■■■
Pre-progression Follow-Up 2	■	■■■■■	■■■■■
Pre-progression Follow-Up 3	■	■■■■■	■■■■■

^a Expected: N progression free (PF) patients. ^b Compliance: N progression-free patients with observed utility. ^c Cycle 9 is captured only in the SPARK study.

Missing PRO data were treated as Missing at Random. Under this assumption, conditional on observed patient characteristics and PRO assessments at other time points, the expected value of the unobserved PRO/utility outcomes is assumed to be the same as it would have been had those outcomes been observed.

- d) Please describe the final mixed-model specification used and justify why this approach was considered appropriate given the structure of the data.

EQ-5D-5L utilities were analysed using a linear mixed model within a MMRM framework to reflect the longitudinal nature of the data, with multiple utility observations collected per patient over time. This approach was considered appropriate because it explicitly accounts for the correlation between repeated measurements within the same individual and uses all available observed data without imputing missing values, with inference relying on the MAR assumption.

In the final specification, observed EQ-5D-5L utility was the dependent variable. The model included fixed effects to reflect the repeated-measures design and to support estimation of utilities by health state, including health state (PF 2L versus PD) and nominal visit/time (treated as categorical to align with the assessment schedule). Repeated observations were modelled at the patient level using an empirically selected within-patient covariance structure. Candidate covariance structures (including unstructured, compound symmetry, and AR[1]) were compared and the final structure was selected based on AIC, with the selected model providing the best balance of fit and parsimony for these longitudinal data.

Using this approach, the estimated pre-progression (PF 2L) utility from the pooled ibrutinib arms was ■■■ (see Table 8 and Table 9). To assess sensitivity to the weighting of observations over time, time-weighted and area-under-the-curve (AUC) mean utilities were also derived, yielding ■■■ (SE ■■■)

and [REDACTED] (SE [REDACTED]), respectively. These alternative summaries were closely aligned with the primary estimate, indicating that the PF 2L utility estimate was stable and not materially influenced by the distribution or timing of repeated measurements.

It is acknowledged that these values differ slightly from those presented previously in TA502. The original analyses based on earlier RAY-3001 and SPARK data cuts (circa. 2016) were not available for replication, and it was therefore considered preferable to re-run the utility analyses using more recent data cuts. Although small differences are observed (e.g., PF approximately [REDACTED]; PD [REDACTED] in the current analysis versus 0.68 in the previous analysis), these are not expected to materially affect the cost-effectiveness results; cost-effectiveness scenario analyses were therefore included to quantify any potential impact. The results of this scenario analyses are presented in Table 10 and demonstrate that the cost-effectiveness results remain unchanged.

Table 8: Pooled pre-progression utilities comparing the MMRM estimates to the time weighted and area under the curve estimates.

	Model-based		Time-weighted		Area under the Curve	
Treatment	Estimate	Standard Error	Estimate	Standard Error	Estimate	Standard Error
Pooled RAY-3001 and SPARK	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Original submission base case	0.78	0.01	-	-	-	-

Abbreviations: MMRM: mixed models for repeated measures.

The post-progression utility was estimated based on progressed second-line patients from the ibrutinib arms in RAY-3001 and SPARK. The utility estimate is [REDACTED] (SE [REDACTED]), this is slightly higher than the value used in the original submission of 0.68.

Table 9: Pooled post-progression utility estimated from MMRM

	Model based	
Treatment	Estimate	Standard Error
Pooled RAY and SPARK	[REDACTED]	[REDACTED]
Original submission base case	0.68	0.02

Abbreviations: MMRM: mixed models for repeated measures.

Table 10 Deterministic scenario analysis results (ibrutinib PAS price): RAY & SPARK re-estimated utilities

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (utility values aligned with those used in TA502)	[REDACTED]	[REDACTED]	Dominant	[REDACTED]	-

Updated RAY & SPARK PF 2L and PD utilities	████	██	Dominant	██	████

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

e) Please provide the following scenario analyses:

- i. separate utility estimates for PF 2L and PD derived independently from each trial

Utilities for progression-free second-line and post-progression were estimated independently from the ibrutinib arms from RAY-3001 and SPARK and are presented in Table 11. The utility estimates were consistent between both studies when assessed separately by health state. In the PF 2L health state, both trials reported similar utility values (████ in SPARK and █████ in RAY-3001). Likewise, second-line post-progression utilities were comparable between the two trials (████ in SPARK and █████ in RAY-3001). When incorporated into the economic model, scenario analyses demonstrated that using separate RAY-3001 or SPARK utilities had a nominal impact on cost-effectiveness results, as shown in Table 12.

Table 11 Utility estimates from MMRM model applied to RAY-3001 (MCL2001) and SPARK (MCL3001) separately

Study	Status	Estimate	Standard Error
SPARK (MCL2001)	Pre-Progression	████	████
SPARK (MCL2001)	Post-Progression	████	████
RAY (MCL3001)	Pre-Progression	████	████
RAY (MCL3001)	Post-Progression	████	████

Abbreviations: MMRM: mixed models for repeated measures.

Table 12 Deterministic scenario analysis results (ibrutinib PAS price): RAY & SPARK individually estimated utilities

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case (utilities derived from pooled EQ-5D data from RAY-3001 and SPARK)	████	██	Dominant	██	I
SPARK PF 2L and PD utilities used	████	██	Dominant	██	████
RAY-3001 PF 2L and PD utilities used	████	██	Dominant	██	████

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

- ii. utility estimates based on pooled mean EQ-5D values without longitudinal modelling

Mean utility values were calculated for the PF 2L and the PD health states using the pooled RAY-3001 and SPARK datasets, without longitudinal modelling. The mean utilities for PF 2L and PD are [REDACTED] and [REDACTED], respectively. Inclusion of pooled mean EQ-5D utility values without longitudinal modelling into the economic model has a nominal impact on cost-effectiveness results, as shown in Table 14.

Table 13: Pooled RAY-3001 (MCL 3001) and SPARK (MCL2001) utility estimates without longitudinal modelling

Study	Health state	Mean Utility	Standard Error
Pooled RAY-3001 (MCL3001) and SPARK (MCL2001)	PF 2L	[REDACTED]	[REDACTED]
Pooled RAY-3001 (MCL3001) and SPARK (MCL2001)	PD	[REDACTED]	[REDACTED]

Abbreviations: PD: progressed disease; PF 2L: progression-free at second-line.

Table 14 Deterministic scenario analysis results (ibrutinib PAS price): RAY-3001 & SPARK utility estimates without longitudinal modelling

Scenario	Incr. (£)	Incr. QALYs	ICER (£/QALY)	INHB at £30,000	Δ from Base Case INHB
Base case	[REDACTED]	[REDACTED]	Dominant	[REDACTED]	I
SPARK PF 2L and PD utilities without longitudinal modelling	[REDACTED]	[REDACTED]	Dominant	[REDACTED]	[REDACTED]

Abbreviations: ICER: incremental cost-effectiveness ratio; Incr: incremental; INHB: incremental net health benefit; PAS: Patient Access Scheme; QALY: quality-adjusted life year.

- iii. a model including an explicit trial effect to test sensitivity to cross-trial differences

Separate mixed effects models for the PF 2L and the PD utilities were estimated that included a fixed effect for study (SPARK vs RAY-3001). RAY-3001 was used as reference category in both analyses.

In the PF 2L analysis (Table 15) the estimated study effect for SPARK was not statistically significant ($p=[REDACTED]$) indicating there is no trial effect due to cross-trial differences.

Table 15: MMRM estimates on pre-progression utilities - significance tests to check the impact of cross-trial differences

Effect	Study	Estimate	SE	DF	t-value	Pr > t
Intercept		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Study	MCL2001	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: DF: degrees of freedom; MMRM: mixed models for repeated measures; SE: standard error.

In the corresponding analysis for post-progression utility estimate (Table 16), the estimated study effect for SPARK was not statistically significant ($p=[REDACTED]$) indicating there no trial effect due to cross-trial differences.

Table 16: MMRM estimates on post-progression utilities - significance tests to check the impact of cross-trial differences

Effect	Study	Estimate	SE	DF	t-value	Pr > t
Intercept		■	■	■	■	■
Study	MCL2001	■	■	■	■	■

Abbreviations: DF: degrees of freedom; MMRM: mixed models for repeated measures; SE: standard error.

These results illustrate that utility estimates derived from RAY-3001 and SPARK studies are broadly comparable, and that the pooled estimates are not influenced by between-trial heterogeneity. Therefore, Johnson & Johnson considers the pooled EQ-5D utilities across trials as used in the base-case setting as appropriate.

References

1. NICE. Ibrutinib for treating relapsed or refractory mantle cell lymphoma [TA502], 2018. Available at: <https://www.nice.org.uk/guidance/ta502>. Last accessed: July 2025.
2. Johnson & Johnson Innovative Medicine. Advisory Board Meeting Report (November 2025).

Single Technology Appraisal
**Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem
cell transplant is suitable [ID6596]**
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Lymphoma Action
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the most common blood cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the leading charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Lymphoma Action is not a membership organisation. We are funded from a variety of sources, predominantly fundraising activity with some limited sponsorship and commercial activity. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. The total amount of financial support from healthcare companies will not exceed 20% of our total budgeted income for the financial year (this includes donations, gifts in kind, sponsorship etc) and there is a financial cap of £50,000 on support from individual healthcare companies per annum (excluding employee fundraising), unless approval to accept a higher amount is granted by the Board of Trustees.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	• Pfizer (rituximab) £4,000 for sponsorship of our Lymphoma Information Days • Roche (rituximab) £25,000 towards our information provision and peer support days as well as sponsorship of our Lymphoma Management course
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We used information from members of our community to understand their experiences of living with the types of non-Hodgkin lymphoma mentioned in this appraisal. We combined the information gathered from this, along with our experiences of working with these patients and their carers.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Lymphoma is the 5th most common type of cancer in the UK. It is a type of blood cancer, where white blood cells known as lymphocytes grow out of control. There are two main types: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). NHL is the most common type, with around 14,200 people diagnosed each year in the UK. There are many different types of NHL, which can be classified in two main ways. Firstly, they can be grouped into low-grade and high-grade based on how fast they grow. Secondly, they can be grouped depending on the type of lymphocyte the cancer develops from: B cells or T cells. B-cell lymphomas are much more common, accounting for 90% of cases. Mantle cell lymphoma (MCL) is a type of B-cell non-Hodgkin lymphoma affecting B-cells found in the mantle zone of lymph nodes. It mainly affects lymph nodes but can also spread to other parts of the body such as bone marrow, spleen, bowel and liver. MCL is a rare cancer with around 600 people being diagnosed each year in the UK. It can occur at any age but is very rare in young people and tends to be a cancer of later years, with most people diagnosed being middle-aged or older. Unlike most other types of lymphoma, MCL has features of both a high-grade lymphoma as it grows very quickly, and a low-grade lymphoma as it is highly likely to relapse. Due to the fact MCL often grows very quickly, symptoms can develop fast. These can include swollen lymph nodes, abdominal pain or a feeling of fullness due to an enlarged spleen, or symptoms arising from lymphoma cells invading the bone marrow. This can include bruising or bleeding, being more prone to infections, or symptoms of anaemia. Some people also have what are known as B-symptoms which can include weight loss, night sweats or fever. Fatigue is also a common symptom of mantle cell lymphoma, but one which is often overlooked. It can be particularly burdensome and have a profound impact on how a person can function; as one patient described, <i>"I also had to accept the tiredness and the limitations that imposed"</i>. The psychological impact of a diagnosis of lymphoma is enormous. We have heard people describe insomnia, anxiety and a constant fear of dying along with many other symptoms. MCL usually responds well to treatment but is likely to relapse after treatment. This obviously adds to the psychological impact of the diagnosis as patients and those close to them live with this fear. This can sadly have a significant impact on a patient's mental health as described by this patient: <i>"The fact of having incurable lymphoma is in the back of my mind at times but I try to live a day at a time and make the most of what I have"</i>.

The family and friends of people with MCL also have their lives turned upside down and can struggle with the diagnosis given to their loved one. They have to be there emotionally but also practically, often taking on the burden of day-to-day activities: *“My husband had to do a lot of driving me to hospital etc, and he was constantly uncertain”*.

Carers can often feel powerless to help, as summed up by these patients when talking about their family:

“I think it is worse for carers. The patient is taken care of, but the carers can feel a bit helpless to do anything”.

“It is very hard for my wife as we always have the fact it will come back hanging over us”.

“I think he (my son) worried about me but there was nothing he could do at the time”.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The treatment for MCL varies according to several factors, including the stage at diagnosis and the patient's prognostic score, along with the patient's age and overall health. If a patient has very few symptoms, or their lymphoma is growing slowly, no active treatment may be initially required. This is called active monitoring, or 'watch and wait'. This is not as easy as it may seem, as even though patients don't have to endure any side effects from treatment, they do have to deal with the constant worry that their lymphoma may get worse and wondering when that will happen, <i>"Getting the diagnosis and understanding that it was treatable but not curable – therefore being placed on Watch and Wait was challenging!"</i>. In most cases, if treatment is required this is chemotherapy in combination with immunotherapy such as rituximab. If patients are fit enough, they will be given an intensive regimen including cytarabine. This can be very effective and helps to prevent the MCL from spreading, but it can be incredibly difficult to endure. If people respond to this treatment they may then go on to have high-dose chemotherapy and a stem-cell transplant. Again, this is very intense and not a suitable treatment for everyone. As MCL primarily affects older people many patients sadly do not meet the criteria, <i>"I was offered and had to decide if a stem cell transplant would be appropriate for my first treatment. I opted against this because of my age."</i> For these patients who are not able to endure more intense treatments they may be offered an alternative chemotherapy regimen such as R-CHOP (rituximab, cyclophosphamide, doxorubicin (or hydroxydaunorubicin), vincristine (Oncovin®) and prednisolone), bendamustine plus rituximab or VR-CAP (a version of R-CHOP which includes a targeted drug called bortezomib). In almost all cases, despite treatment MCL will unfortunately relapse. This can happen on multiple occasions, requiring many different treatment regimens. Our patients were very complimentary of the treatment they received and as one patient told us, <i>"I would be dead now without it"</i>. However, the treatments can be very difficult to endure, with even the gentler regimens having numerous short and long-term side effects. Some of the short-term side effects experienced are described by these patients: <i>"The side-effects (of chemotherapy) were insomnia and extreme tiredness plus hair loss"</i>.

	<i>“Chemotherapy appeared to be the best plan for me personally. I did get into serious trouble with immune system failure during my rituximab maintenance and had recurrent pneumonias”.</i> There are many longer-term effects that have a significant impact on a patient’s ability to resume to a normal way of life. These can be fatigue, peripheral neuropathy or mental health problems: <i>“The tiredness and the uncertainty about the future still impacts on my life e.g. it is difficult to plan things more than 6 months ahead and I do not feel safe enough to travel long distances on a plane”.</i> <i>“The chemotherapy saved my life but has left me with tinnitus, peripheral neuropathy, and also sciatica which greatly affect my quality of life...I cannot sleep without a sleeping tablet, and even then I only sleep for 4 hours a night and am constantly tired. This affects my mood and has impact on the people around me”.</i> <i>“Long term effects are lowered immunity to infections”.</i>

8. Is there an unmet need for patients with this condition?	The fact that MCL can act like a high-grade lymphoma by growing quickly and causing significant symptoms, but also like a low-grade lymphoma, often relapsing after treatment and requiring various treatment regimens, makes it very difficult to experience, <i>“It is very hard to live with this type of lymphoma, as although I am in remission I know it will come back at some point”</i>. With this in mind patients and their carers want multiple treatment options open to them, especially ones which can be tolerated by most patients. They feel that there is currently an unmet need for this, as they fear that the treatment options that they are offered will either not provide a long-term remission, or will cause intolerable side effects: <i>“I think the more options for treatment for this condition there are the better, so that clinicians can help patients decide which treatment is best tailored to their personal life at the time”</i>. <i>“Obviously we’d all hope for a cure with a treatment that did not endanger life and had fewer side effects”</i>. <i>“Yes there is an unmet need. The perfect treatment would be something with relatively little side effects”</i>. These views were confirmed by the 2024 Lymphoma Coalition survey, which shows that 72% of patient respondents and 80% of carer respondents (total respondents 1204; 3% MCL) rated fewer side effects/more tolerable side effects during treatment as important, or very important.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	As already stated, patients struggle with the side effects of the current treatment options open to them. Ibrutinib may give them another option with a better side effect profile. Having treatments with fewer or more tolerable side effects contributes to better mental health overall.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	None were identified by our patients.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Mantle cell lymphoma is a complex condition which often relapses after treatment • Current treatment options have significant short and long term side effects • Another treatment option would provide hope to patients and their carers • •

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Single Technology Appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Clinical expert statement

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In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

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Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

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Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Part 1: Treating mantle cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

1. Your name	David Lewis
2. Name of organisation	Plymouth Hospitals NHS Trust
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with mantle cell lymphoma? ☒ A specialist in the clinical evidence base for mantle cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

8. What is the main aim of treatment for mantle cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To induce remission of the lymphoma, for as long as is possible. Where possible to reduce the toxic side effects of treatment. Length of progression free survival and ultimately overall survival are the most important endpoints
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Remission has well defined criteria by CT or PET assessment. Any treatment that maximises progression
10. In your view, is there an unmet need for patients and healthcare professionals in mantle cell lymphoma?	Yes.
11. How is mantle cell lymphoma currently treated in the NHS? • What proportion of patients have the 'NORDIC' regimen (R-maxi-CHOP) for induction? • What proportion of patients have rituximab maintenance? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	NORDIC (or variations) are used by approximately 70% of UK trusts. There are variations in that some sites use R-Cytarabine + dexamethasone The majority of patients (I would estimate 90%) will receive rituximab maintenance (assuming eligibility ie at least a partial response to induction chemotherapy) BCSH guideline for MCL published in 2023 https://b-s-h.org.uk/guidelines/guidelines/diagnosis-and-management-of-mantle-cell-lymphoma Pathway: Yes it is well defined. The pathway is dependent on whether a patient is eligible for autologous Stem cell transplant (generally <65 yo and no comorbidities that preclude intensive treatment). If they are fit for this approach then offering an intensive regimen such as NORDIC MCL2 + auto SCT would be considered standard of care. This technology would replace the current 1L standard treatment (as it has in other countries where it is reimbursed)

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • What proportion of patients would have rituximab maintenance after ibrutinib? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Yes it will be used as per the trial protocol. It is not currently available outside of a named patient early access scheme. The majority (90-100%) of eligible patients will receive maintenance rituximab TRIANGLE approach will allow an induction approach free of autologous stem cell transplant which will save a significant amount of inpatient healthcare resource and will significantly improve quality of life of the patients under treatment, This will primarily be used in specialist clinics in secondary care The TRIANGLE study is well known amongst haematologists who treat lymphoma. Ibrutinib is also a familiar drug. Minimal investment will be required other than the usual local procedures for adopting a new protocol at sites.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care? In particular, what are the expected differences in health-related quality of life for people who have ibrutinib with R-CHOP versus people who have autologous stem cell transplant?	<i>Length of life:</i> <i>Yes. 4 year OS increased from 80% to 88% in the study (p=0.0036), (comparing Ibrutinib arm to ASCT arm)</i> <i>Health-related quality of life:</i> <i>Autologous stem cell transplant has a significant negative impact on quality of life (eg https://pubmed.ncbi.nlm.nih.gov/41567023/). Most patients require hospitalisation for 3-4 weeks and have negative QOL impacts for at least 3 months. Being able to avoid the stem cell transplant will significantly improve QOL for patients undergoing induction chemo for mantle cell lymphoma</i>

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Potentially patients with known cardiac comorbidities could cause concern due to the cardiac toxicity of ibrutinib.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Overall I would say easier due to the lack of requirement for an autologous stem cell transplant. Each site will need to build an RCHOP+Ibrutinib regimen and then patients will require 2 years ibrutinib post induction, but this will not be any more visits than current care as rituximab maintenance is given every 2 months currently. No extra monitoring will be required.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It is a limited duration ibrutinib treatment for 2 years after induction. So patients will stop if they reach 2 years, or if they have progression of disease on treatment or if they develop toxicity to ibrutinib.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The patients will not need to spend a month in hospital having an autologous stem cell transplant Patients are very well informed and are fully aware of the TRIANGLE study so if it is not available and reimbursed it will cause considerable psychological distress for patients and their families.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	Yes. This is the first randomised study in the first line treatment for MCL with a BTKi that demonstrates a significant improvement in overall survival and it allows us to omit the autologous stem cell transplant. It defines the standard of care approach for mantle cell lymphoma in younger patients. The fact that there is a significant and clinically meaningful overall survival benefit and ability to omit the autologous stem cell transplant represents a step change.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Overall due to the omission of the autologous stem cell transplant I would expect the patients' QOL to be improved.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes this is a patient cohort that we recognise in UK practice. The trial measured both failure free survival and overall survival, and these are clearly the most important endpoints
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	As yet we do not have real world data from this regimen

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

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No patients are particularly disadvantaged

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

RCHOP+ibrutinib in this setting leads to a clinically meaningful improvement in overall survival

The adoption of this protocol will allow us to omit autologous stem cell transplant

The TRIANGLE approach for MCL is now the internationally recognised standard of care for younger patients with MCL

This study will improve the quality of life of MCL patients

There is no significant excess toxicity associated with using this regimen compared with current approaches

Thank you for your time.

Your privacy

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Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Single Technology Appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Clinical expert statement

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Clinical expert statement

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Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Part 1: Treating mantle cell lymphoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Rory McCulloch
2. Name of organisation	Gloucestershire Hospitals NHS Foundation Trust
3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with mantle cell lymphoma? ☒ A specialist in the clinical evidence base for mantle cell lymphoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil.
8. What is the main aim of treatment for mantle cell lymphoma?	Achieve a deep and durable remission that prolongs overall survival, and with treatment that causes minimal toxicity.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Partial response to therapy as defined by Lugano Classification.
10. In your view, is there an unmet need for patients and healthcare professionals in mantle cell lymphoma?	Yes. Young patients currently receive high intensity chemotherapy followed by autologous stem cell transplant. The treatment has high associated toxicity and is very disruptive to a patient's life. For those of working age, they are likely to require several months off work and spend at least 4 weeks as inpatient on ward. Treatment is not curative, although most patients achieve durable response (median PFS ~8 years).
11. How is mantle cell lymphoma currently treated in the NHS? - What proportion of patients have the 'NORDIC' regimen (R-maxi-CHOP) for induction? - What proportion of patients have rituximab maintenance? - Are any clinical guidelines used in the treatment of the condition, and if so, which? - Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) - What impact would the technology have on the current pathway of care?	For younger patients deemed transplant fit: Majority in UK receive Nordic MCL2 protocol (alternating Maxi-CHOP/HD Ara-C) followed by consolidation BEAM autograft (~80%) Some centres use alternative induction regimen (ie alternating R-DHAP/R-CHOP or R-DHAox x4) followed by transplant. In older patients R-Bendamustine x6 is standard of care. All patients are generally offered 2-3 years maintenance rituximab unless there are clinical concerns regarding a patient's risk of infection. BSH guidelines from 2024: "Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline" Eyre TA et al. Br J Haematol. Treatment pathway is well defined and there is strong consensus across UK.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

	Current technology would mean that patients would no longer be offered consolidation autologous stem cell transplant (high toxicity, requires ~4 week inpatient stay, and often takes ~6 months for physical recovery), and instead would receive outpatient maintenance ibrutinib + rituximab, which is generally well tolerated and inpatient admissions would be rare.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • What proportion of patients would have rituximab maintenance after ibrutinib? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Maintenance rituximab would be given alongside ibrutinib as per trial protocol. The total treatment would be the same as current practice. Impact on service: No longer need to deliver BEAM autologous stem cell transplant. No need for stem cell collection and cryopreservation. No need for 4 week inpatient admission to deliver treatment. Lower risk of severe infection – reduced rate of ICU admissions. Technology will be delivered in specialist clinics in secondary care. No additional investment, but obvious savings.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care? In particular, what are the expected differences in health-related quality of life for people who have ibrutinib with R-CHOP versus people who have autologous stem cell transplant?	<i>Length of life: Trial showed improved outcomes (both FFS and OS) for patients receiving ibrutinib compared to ASCT. Likely to extend life. Anticipate median OS likely to exceed 10 years.</i> <i>Health-related quality of life: Anticipate marked improvement in quality of life as no longer require autologous stem cell transplant, with high associated toxicity and prolonged hospital inpatient stay (this treatment also carries ~3% treatment related mortality risk).</i>

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is appropriate for younger patients with mantle cell lymphoma regarded fit for autologous stem cell transplant (generally regarded as age ≤ 65 years old).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier to use than current care.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Significant improved quality of life.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This technology will be transformative in how we manage our younger patients. Easier to deliver than current standard of care. Potentially avoid need for any hospital admissions during delivery of care.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

- Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	This will also have less impact financially on patients as the time required off work is likely to be substantially reduced.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Compared to current standard of care the additional side effects of ibrutinib are unlikely to be significant.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Clinical trial was run predominantly in Europe and no sites in UK were included, however one would expect the results to translate across to UK practice. Main outcomes in trial were overall survival and failure free survival (a variant of progression free survival). These represent the most important outcomes. Clinicians have been using ibrutinib at relapse in MCL for over 10 years and so are very familiar with the potential toxicities.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	Not aware of significant data sets. In the UK a Free to access scheme is open meaning clinicians are already gaining experience using this technology. Early experience at my local site has been positive.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	No.

Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

people with this condition are particularly disadvantaged.

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Please state if you think this evaluation could

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Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Ibrutinib incorporated into 1st line therapy in MCL provides excellent patient outcomes

Treatment means autologous stem cell transplant is no longer required without loss of treatment efficacy

This represents a significant improvement in patient experience, with reduced toxicity and time admitted to hospital

This treatment represents an exciting clinical advance in MCL.

Click or tap here to enter text.

Thank you for your time.

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

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Clinical expert statement

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Single Technology Appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with mantle cell lymphoma or caring for a patient with mantle cell lymphoma. The text boxes will expand as you type.

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Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

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Part 1: Living with this condition or caring for a patient with mantle cell lymphoma

Table 1 About you, mantle cell lymphoma, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☒ A patient with mantle cell lymphoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with mantle cell lymphoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Lymphoma Action
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have not completed part 2 of the statement

Patient expert statement

6. What is your experience of living with mantle cell lymphoma? If you are a carer (for someone with mantle cell lymphoma) please share your experience of caring for them	Diagnosed 2013 on routine blood test having had recurrent chest infections and tiredness for 18 mths approx. Put on watch and wait. Developed colitis needing urgent steroids but the colitis was found to be mantle cell driven. Decision to treat with Bendamustine and Rituximab followed by Rituximab maintenance. Developed 2ndry hypogammaglobulinaemia needing IgG replacement for 6 years. Lung infections with pseudomonas identified in 2021, requiring multiple hospital admissions and continuing nebulised and oral antibiotics. I remain in remission – 11 years +
7a. What do you think of the current treatments and care available for mantle cell lymphoma on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	a) Mantle cell lymphoma is a heterogeneous condition with a huge variation in presentation and course of the disease. There are a variety of treatments for various stages of the disease which is changing all the time now that there is more research going on. At the time of my illness, I was given a choice of ASCT or BR and after discussion, BR was felt more appropriate knowing the disease is not curable. I understood that the best approach was one that gave me the longest 1st remission, but I also wanted a reasonable quality of life because of my age and lung problems. Because this disease is considered incurable, it is very difficult for patients to come to terms with, and even more difficult if they are told that certain treatments which have been shown to be effective have been withdrawn – e.g. CAR-T b) People vary in their approach and emotional response to understanding what an incurable but treatable condition is. W&W is difficult to comprehend. Most people I hear, will accept what is offered by their clinician but because there is to a certain extent, 'choice', there is often anxiety about what the best route might be and patients need 'trust' in the clinician the unit where they are being treated .
8. If there are disadvantages for patients of current NHS treatments for mantle cell lymphoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are big advantages to oral treatment taken at home as opposed to IV treatments which need multiple hospital visits. Loss of hair is distressing Minimising side effects and complications is obviously important but all medication carries side effects and therefore it is a balance for patients and clinicians who need to work out individually which treatment may be best at which stage.

Patient expert statement

	Basically my understanding is that the front line treatment is stratified into a) 'strong' chemo/immunotherapy +/- ASCT. b) 'medium' – BR which in my case led to 2ndry hypogammaglobulinaemia and was still quite tough for a week after each dose with tiredness and sickness etc, c) Then there is the milder more tolerable immunotherapy treatments which can keep people in remission without too many side effects. Clearly the length of the 1st remission is crucial as options on relapse are limited and will not last as long as the 1st remission
9a. If there are advantages of Ibrutinib with R-CHOP over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Ibrutinib with R-CHOP help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a) My understanding is that adding ibrutinib to a current front line treatment prolongs the 1st remission and may prevent the need for an ASCT. This would definitely enhance the quality of life for some patients with this disease. Younger patients may well have less time off work etc. and us older ones could enjoy a longer time with the family as well as continue to contribute to society in a variety of ways! b) I think quality of life is probably most important – but that depends on age at diagnosis and patient expectations c) Non chemo drugs like ibrutinib are much more easily tolerable than the chemotherapy drugs especially those required for ASCT
10. If there are disadvantages of Ibrutinib with R-CHOP over current treatments on the NHS please describe these. For example, are there any risks with Ibrutinib with R-CHOP? If you are concerned about any potential side effects you have heard about, please describe them and explain why	There are always side effects for any drug but I understand that infections, bruising and gut problems are more common with ibrutinib. Having been through problems with my immune system, I would be anxious about anything which would impact on my ability to meet in large groups and have contact with grandchildren etc. but if it were to give a longer 1st remission, any additional risks would be tolerable. It's a balance

11. Are there any groups of patients who might benefit more from Ibrutinib with R-CHOP or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Older, less fit patients will find stem cell transplants and/or 'harsher' treatments more difficult to tolerate and given a choice might well refuse ASCT (like myself) especially if the addition of an immunotherapy drug could prolong the 1st remission.
12. Can you comment specifically on the impact of ibrutinib with R-CHOP on your quality of life? How does this differ from the impact on quality of life of current NHS treatments (in particular, stem cell transplant)?	I do not have experience personally of this treatment regime, but did decide that for me, personally , at my age and co-morbidities, ASCT would be too difficult to manage.
13. Are there any potential equality issues that should be taken into account when considering mantle cell lymphoma and Ibrutinib with R-CHOP? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	We, as patients, are all dependent on the specialist team and their ability to give best opinion for a wide range of individuals presenting with this condition and each individual's way of coping with this difficult situation. Many patients presenting with mantle cell lymphoma are in the older age group who may find it difficult to understand the complexities of managing this disease. They need time and support from family and health care professionals....

Patient expert statement

14. Are there any other issues that you would like the committee to consider?	There is no 'one size fits all' for any health care decision and therefore the more treatments that are available for use by a clinician must be of value and enable that discussion and decision making consultation between the clinician and the individual patient. In view of the relatively small numbers of patients and variation in the presentation and the uncertainty around the outcomes of various treatments, could data from every patient with mantle cell lymphoma be shared nationally through an NHS database?

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Because mantle cell lymphoma is a rare, heterogenous disease, which is essentially incurable, the clinicians need to have a wide range of drugs and treatments available to manage each patient individually.
- Any drug or combination of drugs with good effectiveness and lower side effects is valuable.
- Mantle cell lymphoma is relatively rare and complex to manage and as patients we are dependant on highly specialist knowledge of the disease by the treating clinician and their team.
- There is an evolving situation with regard to treatment options for this disease which needs to be recognised when evaluating possible drugs and combinations
- Click or tap here to enter text.

Thank you for your time.

Patient expert statement

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Maastricht University

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Center+ (UMC+)
Authors	Nigel Armstrong, HTA Lead, KSR Ltd, United Kingdom (UK) Bram Ramaekers, Health Economist, Maastricht UMC+, the Netherlands (NL) Willem Witlox, Health Economist, Maastricht UMC+, the NL Teresa Holly, Health Economist, Maastricht UMC+, the NL Kevin McDermott, Systematic Reviewer, KSR Ltd, UK John Franklin, Director of Reviews, KSR Ltd, UK Keith Nockels, Information Specialist, KSR Ltd, UK Manuela Joore, Health Economist, Maastricht UMC+, the NL Huiqin Yang, Reviews Manager, KSR Ltd, UK
Correspondence to	Dr Nigel Armstrong Kleijnen Systematic Reviews Ltd. Unit 6, Escrick Business Park Riccall Road, Escrick York, YO19 6FD United Kingdom
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Confidential (CON) data are highlighted in blue throughout the report.

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Contributions of authors

Nigel Armstrong acted as project lead and health economist on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Huiqin Yang also acted as project lead and systematic reviewer on this assessment and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Willem Witlox, Sabine Grimm, Teresa Holly and Manuela Joore acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott and John Franklin acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Keith Nockels critiqued the search methods in the submission and contributed to the writing of the report. Huiqin Yang and Nigel Armstrong critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BEAC	Carmustine, Etoposide, Cytarabine and Cyclophosphamide
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian Information Criterion
BMI	Body mass index
BNF	British National Formulary
BR	Bendamustine and rituximab
BSA	Body surface area
BSC	Best supportive care
BSH	British Society of Haematology
BTKi	Bruton's tyrosine kinase inhibitor
CADTH	Canadian Agency for Drugs and Technologies in Health
CCO	Clinical cut-off
CE	Cost effectiveness
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHOP	Cyclophosphamide, doxorubicin
CI	Confidence interval
CMH	Cochran-Mantel-Henszal
CNS	Central nervous system
CR	Complete response
CRR	Complete response rate
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
DHAOx	Dexamethasone, high-dose cytarabine and oxaliplatin
DHAP	Dexamethasone, high-dose cytarabine and platinum
DOR	Duration of response
DP	Decision problem
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
EAG	External Assessment Group
EBM	Evidence-based medicine
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EEA	European Economic Authority
EMA	European Medicines Agency
eMIT	Electronic market information tool
EOT	End of treatment
EQ-3D-3L	EuroQol Three Dimensions Three Level
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	EuroQol Five Dimensions Five Level

ESMO	European Society for Medical Oncology
EU	European Union
EUR	Erasmus University Rotterdam
FAS	Full Analysis Set
FE	Fixing errors
FF 1L	Failure-free on first-line treatment
FFS	Failure-free survival
FV	Fixing violations
HCRU	Healthcare resource unit
HDT	High-dose chemotherapy
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ICH	International Conference on Harmonisation
Incr.	Incremental
iNHB	Incremental net health benefit
IPCW	Inverse probability of censoring weighting
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LDH	Lactate dehydrogenase
MA	Marketing Authorisation
mAb	Monoclonal antibody
MCL	Mantle cell lymphoma
MHRA	Medicines and Healthcare Products Regulatory Agency
MIPI	MCL International Prognostic Index
MJ	Matters of judgement
MMRM	Mixed-model repeated measures
MUE	Median unbiased estimate
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not estimable
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
nos	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme

PD	Progressed disease
PF 2L	Progression-free on second-line treatment
PFS	Progression-free survival
PH	Proportional hazards
PICO	Patient Intervention Comparator Outcome Study design
PPS	Post-progression survival
PR	Partial response
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALYs	Quality-adjusted life years
QD	Once daily
QoL	Quality of life
R-	Rituximab
R-BAC	Rituximab, bendamustine and cytarabine
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
RCT	Randomised controlled trial
R-DHAOx	Rituximab, dexamethasone, high-dose cytarabine and oxaliplatin
R-DHAP	Rituximab, dexamethasone, high-dose cytarabine and cisplatin
RDI	Relative dose intensity
R-HDAC	Rituximab, high-dose cytosine arabinoside
RoB	Risk of bias
RR	Relative risk/Risk ratio
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SD	Stable disease
SLR	Systematic literature review
SmPC	Summary of medicinal product characteristics
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TESAE	Treatment-emergent serious adverse event
THAM	Fractionated total body irradiation, cytarabine and melphalan
TSD	Technical Support Document
tSPRT	Truncated sequential probability ratio test
TSE	Two stage estimation
TTF	Time-to-treatment failure
TTP	Time-to-progression
UK	United Kingdom
ULN	Upper limit of normal
UMC+	University Medical Centre+

vs	Versus
WBC	White blood count
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive Summary

This summary provides a brief overview of the Key Issues identified by the External Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the Key Issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem (DP), Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-Key Issues are in the main EAG report, see Sections 2 (DP), 3 (clinical effectiveness) and 4 (CE) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's Key Issues

Table 1.1: Summary of Key Issues

ID1457	Summary of issue	Report Sections
1	Uncertainty as to the percentage of patients who receive rituximab maintenance in clinical practice	2.2, and 2.3
2	Uncertainty as to the comparator induction regimen	2.3
3	Uncertainty in the effect of ibrutinib on HRQoL	2.4, 3.2.4.6 and 3.2.6
4	Uncertainty as to the method of adjustment for rituximab maintenance	3.2.5
5	Model structure: The modelling of ASCT	4.2.2
6	Treatment effectiveness and extrapolation: pre-failure mortality	4.2.6
7	Treatment effectiveness and extrapolation: second-line treatment effectiveness	4.2.6
8	Resource use and costs: subsequent treatment (distributions) for ibrutinib patients	4.2.9
9	Model validation and face validity check: model transparency	5.3
ASCT = autologous stem cell transplant; EAG = External Assessment Group; HRQoL = health-related quality of life		

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves length (overall survival [OS]) and quality of life (QoL) in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by:

- First-line treatment effectiveness

- Distribution and effectiveness of second-line treatment received

Overall, the technology is modelled to affect costs by:

- ASCT costs
- Ibrutinib costs
- Second-line treatment costs

The modelling assumptions that have the greatest effect on the ICER are:

- Assuming an alternative parametric distribution for second-line time-to-progression (TTP) extrapolation (Scenario 4)
- Assuming a time horizon of 20 years (Scenario 9)
- Assuming a disutility for autologous stem cell transplant (ASCT) (Scenario 7)
- Second-line treatment distributions and effectiveness

1.3 The decision problem: summary of the EAG's Key Issues

Table 1.2: Key Issue 1: Uncertainty as to the percentage of patients who receive rituximab maintenance in clinical practice

Report Section	2.2, 2.3
Description of issue and why the EAG has identified it as important	Rituximab maintenance is not mentioned in the NICE scope, but it is assumed to be given to 85% of patients in UK clinical practice, which caused the company to adjust OS and FFS outcomes from the TRIANGLE trial, where a smaller percentage of patient received it. Use of rituximab maintenance is recommended in guidelines and confirmed by the EAG clinical expert, as well as in the licence to support it. However, according to the EAG clinical expert and one of the company experts, the figure might be higher than 85%. This affects both the intervention and the comparator.
What alternative approach has the EAG suggested?	The EAG requested clarification as to the origin of the 85% figure and the consideration of other percentages for OS and FFS adjustment, including 100%, which the company provided.
What is the expected effect on the CE estimates?	Small.
What additional evidence or analyses might help to resolve this Key Issue?	Data and/or further clinical expert opinion as to percentage use of rituximab maintenance.
CE = cost effectiveness; EAG = External Assessment Group; FFS = failure-free survival; NICE = National Institute for Health and Care Excellence; OS = overall survival; UK = United Kingdom	

Table 1.3: Key Issue 2: Uncertainty as to the comparator induction regimen

Report Section	2.3
Description of issue and why the EAG has identified it as important	Alternating R-CHOP and R-DHAP or R-DHAox for induction is the comparator in both the scope and the DP. However, the so-called "NORDIC regimen" is also recommended in guidelines, and according to the company clinical expert opinion, more common in (80% of) UK clinical practice. The guidelines and opinion of the EAG clinical expert, who stated that their department use the NORDIC regimen, suggest that there is no difference in efficacy between the two induction regimens, but there is a cost difference.

Report Section	2.3
What alternative approach has the EAG suggested?	Reducing the percentage use of the NORDIC regimen was shown decrease the cost of comparator.
What is the expected effect on the CE estimates?	Minimal impact on ICER
What additional evidence or analyses might help to resolve this Key Issue?	Further clinical expert opinion.
CE = cost effectiveness; EAG = External Assessment Group; DP = decision problem; UK = United Kingdom	

1.4 The clinical effectiveness evidence: summary of the EAG's Key Issues

Table 1.4: Key Issue 3: Uncertainty in the effect of ibrutinib on HRQoL

Report Sections	2.3, 3.2.4.6, 3.2.6
Description of issue and why the EAG has identified it as important	There is no data on HRQoL data in the pivotal TRIANGLE trial. Nevertheless, the company argues that the avoidance of ASCT by use of ibrutinib is likely to enhance HRQoL, and it is true that ASCT is reserved for fitter patients. However, the evidence of avoidance of ASCT toxicity is unclear with higher treatment duration than Arm A (ASCT only) not only for Arm I, but also Arm I+A, and increased rates of some AEs including infections in Arm I. The EAG clinical expert also made a comparison between ibrutinib and ASCT that appeared to be consistent with what was observed in TRIANGLE i.e. the toxic effects of ASCT are potentially serious and include mortality, but the effects on HRQoL appear to be short-term, whereas the those of ibrutinib appear to be longer term.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this Key Issue?	Further evidence or clinical expert opinion as to the likely relative impact of ASCT and ibrutinib on AEs and HRQoL.
AEs = adverse events; ASCT = autologous stem cell transplant; CE = cost effectiveness; EAG = External Assessment Group; HRQoL = health-related quality of life	

Table 1.5: Key Issue 4: Uncertainty as to the method of adjustment for rituximab maintenance

Report Section	3.2.5
Description of issue and why the EAG has identified it as important	The IPCW method was used to adjust FFS and OS for insufficient rituximab maintenance in the TRIANGLE trial (59.7% in Arm I and 62.5% in Arm A) in comparison to clinical practice (assuming 85% use). Clinical guidelines and some clinical expert opinion, both from the company experts and the EAG clinical expert suggested that percentage use might be higher. The EAG considered the IPCW approach to be appropriate, but without sufficient justification and considered the TSE approach also appropriate.
What alternative approach has the EAG suggested?	In responding to the EAG's clarification request, the company reported the results of adjustment assuming 100% rituximab use,

Report Section	3.2.5
	provided further justification for the IPCW method and also conducted analyses using the TSE approach. The results of IPCW analyses, assuming 100% rituximab maintenance and the TSE analyses showed that these results of HRs for PFS and OS were generally consistent with those results of the IPCW analyses assuming 85% presented in the CS. Therefore, both the IPCW sensitivity analyses with the assumption of 100% rituximab use and the TSE analyses demonstrated that the results of IPCW primary analyses presented in the CS were robust, and that the HRs for FFS and OS might plausibly lie in a range between [REDACTED] and [REDACTED], respectively. The IPCW method assuming 85% use is the most favourable to ibrutinib, causing the FFS HR to decrease slightly to from [REDACTED] to [REDACTED] with no change to the OS HR. Only the analysis using TSE method and assuming an exponential distribution causes any HR reduction and only in FFS. All other analyses, including the IPCW with 100% use cause the HRs to increase. Subgroup analysis shows that the FFS HR does increase with rituximab maintenance, but the effect of rituximab is provably biased due to its choice occurring after induction/consolidation.
What is the expected effect on the CE estimates?	Small.
What additional evidence or analyses might help to resolve this Key Issue?	The EAG cannot think of any further evidence or analyses that would help to resolve this issue.
CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; FFS = failure-free survival; HRs = hazard ratios; IPCW = inverse probability of censoring weighting; OS = overall survival; PFS = progression-free survival; TSE =	

1.5 The CE evidence: summary of the EAG's Key Issues

A full summary of the CE evidence review conclusions can be found in Section 6.4 of this report. The company's CE results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The Key Issues in the CE evidence are discussed below.

Table 1.6: Key Issue 5: Model structure: the modelling of ASCT

Report Section	4.2.2
Description of issue and why the EAG has identified it as important	Long-term benefits of ASCT, in terms of both survival and HRQoL increase, are not (explicitly) captured in the economic model, whereas the short-term mortality risk associated with ASCT was overestimated.
What alternative approach has the EAG suggested?	An updated economic model and scenario analysis including ASCT-specific (tunnel) state(s) to reflect ASCT-related long-term benefits without extrapolating the short-term mortality risk associated with ASCT.
What is the expected effect on the CE estimates?	Explicit inclusion of long-term ASCT benefits will likely decrease the iNMB.
What additional evidence or analyses	An updated economic model and scenario analysis explicitly including ASCT in health or tunnel states, or at least a scenario analysis including more explicit adjustments to the current economic model to

might help to resolve this Key Issue?	reflect the long-term benefits of ASCT (without overestimating the short-term mortality risk associated with ASCT).
ASCT = autologous stem cell transplant; CE = cost effectiveness; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; iNMB = incremental net monetary benefit	

Table 1.7: Key Issue 6: Treatment effectiveness and extrapolation: pre-failure mortality

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG is concerned that long-term pre-failure mortality in the company's base-case is currently overestimated, particularly for the ASCT regimen. Additionally, the constant hazard assumption by using an annual mortality rate is clinically implausible as ASCT-related mortality risk is likely increased short-term and expected to decrease thereafter.
What alternative approach has the EAG suggested?	A scenario analysis in which ASCT-related mortality was modelled separately (from pre-failure mortality). A scenario analysis in which parametric survival modelling was used for the estimation of pre-failure mortality.
What is the expected effect on the CE estimates?	Alternative modelling of ASCT-related mortality will likely decrease the iNMB.
What additional evidence or analyses might help to resolve this Key Issue?	Separate modelling of ASCT-related mortality using parametric survival modelling.
ASCT = autologous stem cell transplant; CE = cost effectiveness; EAG = Evidence Assessment Group; iNMB = incremental net monetary benefit	

Table 1.8: Key Issue 7: Treatment effectiveness and extrapolation: second-line treatment effectiveness

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG questions the suitability of RAY-3001 to inform transitions beyond first-line treatment in the company's economic model, as all patients in RAY-3001 were ibrutinib-naïve at study entry and prior ASCT treatment in RAY-3001 was limited. As a result, the ibrutinib second-line treatment effect is likely overestimated, and the ASCT second-line treatment effect is likely underestimated. Additionally, the EAG questions the company's approach of using HRs from MANTLE-FIRST to inform second-line relative treatment effectiveness.
What alternative approach has the EAG suggested?	Scenario analyses using alternative real-world and/or registry data to inform transitions beyond first-line. Scenario analyses using extrapolated data from TRIANGLE to inform transitions beyond first-line.
What is the expected effect on the CE estimates?	The EAG's scenario analysis exploring alternative HRs to inform second-line relative treatment effectiveness substantially increased the ICER. Moreover, reflecting the impact of first-line ASCT and BTKi treatment in transitions beyond first-line will likely decrease the iNMB.
What additional evidence or analyses	Scenario analyses in which differential second-line treatment effectiveness is not only reflected by the distributions of patients

Report Section	4.2.6
might help to resolve this Key Issue?	receiving different second-line treatments, but also by decreased BTKi efficacy in treatment-experienced versus treatment-naïve patients. Similarly increased treatment effectiveness should be reflected for patients treated with ASCT. Scenario analysis informing the relative treatment effect of ibrutinib versus R-BAC and BR based on different HRs, as indicated by the results of MANTLE-FIRST, as well as for ibrutinib versus BSC. Scenario analysis including second-line treatment efficacy analyses accounting for early and late progressors.
ASCT = autologous stem cell transplant; BR = bendamustine-rituximab; BSC = best supportive care; BTKi = Bruton's tyrosine kinase inhibitor; CE = cost effectiveness; EAG = Evidence Assessment Group; HRs = hazard ratios; ICER = incremental cost-effectiveness ratio; iNMB = incremental net monetary benefit; R-BAC = rituximab, bendamustine and cytarabine	

Table 1.9: Key Issue 8: Resource use and costs: subsequent treatment (distributions) for ibrutinib patients

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	The EAG is concerned that the company's current modelling of subsequent treatments (second-line, third-line) may not be reflective of UK clinical practice. Company clinical experts indicated high variability in subsequent treatment options and distributions (second-line, third-line) for UK clinical practice, and the company's base-case options and distributions do not match with those of the EAG clinical expert. As subsequent treatments drive the majority of costs (Section 5.2c), changes in options and/or distributions are expected to materially affect conclusions about both clinical and CE.
What alternative approach has the EAG suggested?	The EAG has requested supporting evidence for the second-line/third-line estimates in Clarification Question B20 alongside an updated health economic model, to ensure that subsequent treatments reflect UK clinical practice.
What is the expected effect on the CE estimates?	Unclear. Due to the high variability in treatment options and distributions it may increase or decrease the iNMB.
What additional evidence or analyses might help to resolve this Key Issue?	The EAG would appreciate additional evidence on subsequent treatment (distributions) for ibrutinib, sourced from trial data, literature, and clinical experts. Estimates should be updated accordingly in the health economic model. Additionally, a scenario exploring second-line ASCT for patients who did not fully complete the ibrutinib regimen first-line could be informative.
ASCT = autologous stem cell transplant; CE = cost effectiveness; EAG = External Assessment Group; iNMB = incremental net monetary benefit; UK = United Kingdom	

Table 1.10: Key Issue 9: Model validation and face validity check: model transparency

Report Section	5.3
Description of issue and why the EAG has identified it as important	The EAG is concerned about the transparency of the company's economic model, as the parameter sheet was not the source of all input values and the relatively long running time, e.g. the PSA.

Report Section	5.3
What alternative approach has the EAG suggested?	The EAG has requested during clarification to update the health economic model as follows: 1) making the “Parameter” sheet the original source of input values, 2) including all relevant parameters in (uncertainty) analyses (as stipulated by¹), 3) providing additional technical verification such as the TECH-VER checklist,² 4) moving calculations insofar possible from VBAs to the base Excel environment, 5) speeding up the analyses run time.
What is the expected effect on the CE estimates?	Any cost effectiveness estimates produced by the health economic model would become more credible and thus informative to the DP.
What additional evidence or analyses might help to resolve this Key Issue?	Besides the aspects mentioned in alternative EAG suggestions, updating any current methodological shortcomings identified during the review of good practice guidelines and checklists such as by Ades (2011) ¹ and Büyükkaramikli (2019). ²
CE = cost effectiveness; DP = decision problem; EAG = External Assessment Group; PSA = probabilistic sensitivity analysis; VBA = visual basic analysis	

1.6 Summary of the EAG’s view

- The EAG considers that the company’s CE results are subject to substantial uncertainty, primarily related to the modelling of ASCT, treatment effectiveness beyond first-line, and assumptions regarding subsequent treatment pathways.
- Long-term benefits of ASCT in terms of survival and health-related quality of life (HRQoL) were not explicitly modelled, while short-term mortality risks may have been overestimated. This modelling approach may underestimate the value of the ASCT-based treatment strategy.
- Evidence used to inform treatment effectiveness beyond first-line was drawn from clinically different populations, which may overestimate second-line effectiveness for patients previously treated with ibrutinib and underestimate effectiveness for patients previously treated with ASCT.
- Assumptions regarding subsequent treatment distributions and treatment costs had a substantial impact on results and were associated with considerable uncertainty due to limited empirical evidence and variability in UK clinical practice.
- Overall, substantial uncertainty remains regarding the CE of the ibrutinib regimen compared with the ASCT regimen. Further analyses explicitly incorporating ASCT-related long-term benefits, more appropriate evidence to inform treatment effects beyond first-line, and stronger evidence on subsequent treatment distributions would help reduce decision uncertainty.

Table 1.11: Deterministic EAG base-case

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Deterministic CS base-case (updated as per clarification response)							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_1: Use NHS Reference Costs 2024/25 for ASCT							

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Ibrutinib			-	-	-	-	-
ASCT							
EAG_2: Assume equal pre-failure mortality between ibrutinib and ASCT regimens (set pre-failure mortality of ASCT equal to ibrutinib)							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_3: Set RDI of all drug treatments (incl. ibrutinib) to 100%							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_4: Drug wastage: add scenario on ibrutinib wastage received during clarification to current CS vial wastage							
Ibrutinib			-	-	-	-	-
ASCT							
Deterministic EAG base-case							
Ibrutinib			-	-	-	-	-
ASCT							
ASCT = autologous stem cell transplantation; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; NHS = National Health Service; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness-to-pay							

Table 1.12: Probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Probabilistic CS base-case (updated as per clarification response)							
Ibrutinib			-	-	-	-	-
ASCT							
Probabilistic EAG base-case							
Ibrutinib			-	-	-	-	-
ASCT							
ASCT = autologous stem cell transplantation; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness-to-pay							

Table 1.13: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Deterministic EAG base-case							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_5: Second-line treatment efficacy: HR of 1.00 for ibrutinib versus R-BAC, HR of 1/1.77 for ibrutinib versus BR and ibrutinib versus BSC							
Ibrutinib			-	-	-	-	-

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
ASCT							
EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma"							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_7: Use exponential for extrapolation of TTP: set to "Exponential" from "Log-logistic"							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_8: Exclude ICU stays for ASCT							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_9: Use subsequent treatment distributions informed by EAG clinical expert							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_10: Use subsequent treatment distributions from ibrutinib for ASCT							
Ibrutinib			-	-	-	-	-
ASCT							
ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; Incr. = incremental; NHB = net health benefit; NHS = National Health Service; QALY = quality-adjusted life-year; R-BAC = rituximab, bendamustine and cytarabine; RDI = relative dose intensity; TTF = time-to-failure; TTP = time-to-progression; WTP = willingness-to-pay							

Table 1.14: Probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Probabilistic EAG base-case							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_5: Second-line treatment efficacy: HR of 1.00 for ibrutinib versus R-BAC, HR of 1/1.77 for ibrutinib versus BR and ibrutinib versus BSC							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma"							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_7: Use exponential for extrapolation of TTP: set to "Exponential" from "Log-logistic"							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_8: Exclude ICU stays for ASCT							
Ibrutinib			-	-	-	-	-
ASCT							
EAG_9: Use subsequent treatment distributions informed by EAG clinical expert							

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Ibrutinib	████	████	-	-	-	-	-
ASCT	████	████	████	████	████	████	████
EAG_10: Use subsequent treatment distributions from ibrutinib for ASCT							
Ibrutinib	████	████	-	-	-	-	-
ASCT	████	████	████	████	████	████	████
ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; Incr. = incremental; NHB = net health benefit; QALY = quality-adjusted life-year; TTF = time-to-failure; TTP = time-to-progression; WTP = willingness-to-pay							

2. Critique of company's definition of decision problem

Table 2.1: Statement of the DP (as presented by the company)

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
Population	Adults with untreated MCL when an ASCT is suitable.	Adults with untreated MCL when an ASCT is suitable.	N/A	No comment.
Intervention	Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, with or without ASCT, followed by ibrutinib monotherapy.	Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, followed by ibrutinib monotherapy. ^a	N/A	The intervention differs from the scope in that ASCT is removed as an optional addition (note that “with or without ASCT” was not included in the CS). The company have argued that the license is for without ASCT, but the SmPC does not explicitly state this, and the EAG clinical expert indicated that the option of ASCT for some patients could be valuable. It also differs by the inclusion of rituximab maintenance according to clinical practice, although the precise percentage who get maintenance rituximab in clinical practice is uncertain.
Comparator(s)	Induction phase: - Alternating R-CHOP and R-DHAP or R-DHAOx - Acalabrutinib with bendamustine and rituximab (subject to NICE evaluation) Consolidation phase: - ASCT	Induction phase: - Alternating R-CHOP and R-DHAP or R-DHAOx Consolidation phase: - ASCT Maintenance phase: - Rituximab	At the time of this submission, acalabrutinib with bendamustine and rituximab has not undergone NICE evaluation. Furthermore, acalabrutinib with bendamustine and rituximab is only licensed as an induction regimen for patients who are not eligible for ASCT. This positioning was clarified by the manufacturer in ID6155 and is in accordance with the most recent ESMO and BSH guidelines. Acalabrutinib with	It does seem to be the case that acalabrutinib is not an appropriate comparator given that it only has MA and is recommended for those ineligible for ASCT. Just as for the intervention, the percentage of patients who receive rituximab maintenance in clinical practice is uncertain.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	Maintenance phase: Rituximab		bendamustine and rituximab would therefore not represent a relevant comparator to the ibrutinib regimen, even if it was recommended by NICE.	
Outcomes	- OS - FFS - PFS Response rates: - Adverse effects of treatment - HRQoL	- OS - FFS - PFS Response rates: - CRR - ORR - Conversion rate of PR to CR during follow-up after end of induction therapy - AEs and SAEs	In line with the NICE scope, all requested outcomes (key survival, response, safety and HRQoL data) are presented within this submission. Of note, TRIANGLE was an investigator-initiated trial and as such, J&J IM did not have any input into the trial design or endpoints selected. HRQoL data were not collected as part of the TRIANGLE trial; utility values informing the CE model were therefore informed by values from alternative sources.	The outcomes reported are in line with the NICE scope.
Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and CE should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The	The economic analysis has been conducted as per the final scope and in line with the NICE reference case.	N/A	Consistent with NICE reference case.

	Final scope issued by NICE	DP addressed in the CS	Rationale if different from the final NICE scope	EAG comments
	availability and cost of biosimilar and generic products should be taken into account.			
Subgroups to be considered	If evidence allows, subgroups based on baseline clinical disease characteristics, cytology of mantle cell lymphoma, p53 expression and receipt of rituximab maintenance may be considered.	Subgroup analyses for the clinical endpoint of FFS, based on baseline clinical disease characteristics, cytology of MCL, p53 expression and receipt of rituximab maintenance are presented.	Subgroup data for the primary endpoint of TRIANGLE (FFS) are presented in the CS). However, subgroups are not considered in the CEA given that they are not anticipated to be important for decision-making in UK clinical practice.	The EAG has identified the proportion receiving rituximab maintenance as a key issue, although the effect that it has on FFS and OS appears to be small.
Special considerations including issues related to equity or equality	None specified.	No special considerations including issues related to equity or equality are relevant to this submission.	N/A	

Source: Table 1, CS.³

^a Rituximab may be added to ibrutinib maintenance treatment. The addition of rituximab to ibrutinib maintenance treatment is in line with the UK license for ibrutinib in this indication, which notes that: “*rituximab may be added [to ibrutinib maintenance treatment] as per national treatment guidelines*”.

AE = adverse event; ASCT = autologous stem cell transplantation; BSH = British Society of Haematology; CE = cost effectiveness; CEA = cost-effectiveness analysis; CHOP = cyclophosphamide, doxorubicin; CR = complete response; CRR = complete response rate; CS = company submission; DHA0x = dexamethasone, high-dose cytarabine and oxaliplatin; DHAP = dexamethasone, high-dose cytarabine and platinum; DP = decision problem; ESMO = European Society for Medical Oncology; FFS = failure-free survival; HRQoL = health-related quality-of-life; MA = Marketing Authorisation; MCL = Mantle cell lymphoma; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PSS = Personal Social Services; R- = rituximab; SAEs = serious adverse events; SmPC = summary of medicinal product characteristics; UK = United Kingdom

2.1 Population

The population defined in the scope is the same as in the decision problem (DP), i.e. Adults with untreated Mantle cell lymphoma (MCL) when an autologous stem cell transplant (ASCT) is suitable.^{3,4}

EAG comment: No comment.

2.2 Intervention

The intervention in the scope is the same as in the DP, i.e. ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), alternating with rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin (R-DHAox) without ibrutinib, followed by ibrutinib monotherapy, except for:

- the possibility of including ASCT
- the inclusion of maintenance rituximab according to clinical practice.^{3,4}

EAG comments: The EAG notes that the intervention in the DP excludes ASCT, and Table 1 in the company submission (CS) excludes it from the National Institute for Health and Care Excellence (NICE) scope. However, the NICE scope states: “...with or without ASCT”.⁴ The CS states in Section 2.3.1 on the TRIANGLE trial design: “As ibrutinib is licensed in the UK in combination with R-CHOP alternating with R-DHAP (or R-DHAox) without ibrutinib, followed by ibrutinib monotherapy^c, the use of ibrutinib in combination with ASCT is off-label.” The EAG can confirm that the term ‘monotherapy’ is used, and the European Society for Medical Oncology (ESMO) and British Society of Haematology (BSH) guidelines do recommend ibrutinib for the relevant population only without ASCT.^{5,6} However, the summary of medicinal product characteristics (SmPC) does not explicitly state that ASCT is not to be used.⁷ Therefore, the EAG requested clarification as to whether ibrutinib is used or might be used with ASCT in United Kingdom (UK) clinical practice, to which the company responded:⁸ “As detailed in the SmPC on the MHRA [Medicines and Healthcare Products Regulatory Agency] website, and in Section 1.2 of the Company Submission (CS), the use of ibrutinib in combination with ASCT in this indication is not licensed for use in UK clinical practice. As such, the use of ibrutinib in combination with ASCT represents off-label treatment and is not relevant for UK decision making. This is supported by the fact that the BSH guidelines recommend the usage of ibrutinib explicitly in place of ASCT if licensed and reimbursed. The use of ibrutinib in combination with ASCT is therefore not expected in UK clinical practice.” This does seem to indicate that the company considers that ASCT would not be used, but the EAG clinical expert, when asked: “What might be the percentage use of ibrutinib + R-CHOP followed by ASCT in UK clinical practice if ibrutinib + R-CHOP were recommended by NICE?”, responded: “I don’t know. But if the data were equivalent to the outcomes with ASCT we would start to move away from ASCT because of the long-term side effects, probably particularly in our younger patients.” To seek clarification, the EAG asked the clinical expert: “Are you saying that you would still like the option to be able to continue using ASCT after ibrutinib + R-CHOP alternating with DHAP at least for some patients?”, to which they replied: “I suspect yes: having options taken away from our clinical decision making are never good.” A further response from the EAG clinical expert was: “In fact, looking again at the TRIANGLE data, we would move away from ASCT in all patients in whom RCHOP/RDHAP + Ibrutinib could be delivered – so vast majority of patients would not get ASCT. However, were a patient to be ibrutinib intolerant during induction chemotherapy, it would be useful to be able to offer them ASCT instead in order to try to maintain a chance of longer-term disease-free survival”. This suggests that perhaps without a clear exclusion of

ASCT in the NICE recommendation for this appraisal, some clinicians might still want to use it, the license notwithstanding. It should be noted that the company only provided a comparison between Arms A (ASCT without ibrutinib) and I (ibrutinib without ASCT) and not the third Arm, A+I (ibrutinib with ASCT) of the TRIANGLE trial (see Section 3.2). However, the Clinical Study Report (CSR) did conclude “no meaningful differences in the hazard rates of the primary outcome failure-free survival (FFS) (1-sided [REDACTED] % confidence interval [CI]: [REDACTED]), overall survival [OS] [Cox regression hazard ratio [HR] [(REDACTED)]) or progression-free survival [PFS] HR [(REDACTED)])”.⁹

The intervention also differs by the addition of rituximab maintenance, which the company states is permitted according to by the license, citing the MHRA: “*rituximab may be added [to ibrutinib maintenance treatment] as per national treatment guidelines*”.⁷ Although the link in this reference is broken, the SmPC found by the EAG on the MHRA website confirms the use of maintenance rituximab.¹⁰ The company made an adjustment to the outcomes OS and FFS from the TRIANGLE trial in order to simulate the effectiveness with a higher percentage use of rituximab maintenance (85%, see also Section 3.2), although it is unclear what the percentage use in clinical practice is. Therefore, the EAG requested clarification as to the source of the 85%, as well as to consider other values, including 100% (see also Section 3.2), to which the company responded that the value of 85% was a product of consensus between clinical experts in the March 2025 Advisory Board meeting.^{8, 11} The company also stated that the clinical experts stated that it would not be 100% because of infections or inability to travel. The EAG can confirm that this was the figure reported for Arm A, and ‘NORDIC’ in the Advisory Board report, although a figure of 90% was reported for Arm I, and one expert stated that all patients in Arm I would receive rituximab maintenance, which was supported by the EAG clinical expert. Nevertheless, the company have provided the results assuming 100% rituximab maintenance (see Section 3.2).

In conclusion with regards to ASCT, the EAG acknowledge that NICE does not make recommendations for products that are contrary to the license, and the results of the TRIANGLE trial suggest equal efficacy. Also, the EAG clinical expert, after careful consideration, suggested that the main place of ASCT in those treated with ibrutinib would be in those who are intolerant. With regards to rituximab maintenance, the SmPC includes its use according to ‘national guidelines’ and it is recommended in the BSH guidelines. Also, both company and EAG clinical experts believe that it would be used for at least 85% of patients, but the precise percentage is uncertain. Therefore, uncertainty about its use is also a Key Issue.

2.3 Comparators

The comparators in the NICE scope are:⁴

Induction phase:

- Alternating R-CHOP and R-DHAP or R-DHAox
- Acalabrutinib with bendamustine and rituximab (subject to NICE evaluation)

Consolidation phase:

- ASCT

Maintenance phase:

- Rituximab

The company have excluded acalabrutinib because its marketing authorisation (MA) specified only patients who are unsuitable for ASCT, as recommended in the ESMO and BSH guidelines.^{3, 12}

EAG comment: The EAG can confirm that acalabrutinib with bendamustine and rituximab does not have a MA, and is not recommended for patients who are suitable for ASCT.^{5, 6}

With regards to the induction phase, the company also include the “*NORDIC regimen*” in the economic model as the most common treatment in UK clinical practice in an 80:20 split with the comparator as stated in the DP, based on clinical expert opinion.³ The company assume no difference in efficacy, which they state aligns with the BSH and ESMO guidelines. The EAG note that the BSH guidelines mention the comparator in the NICE scope, but also states.: “*No specific induction regimen is clearly superior with overall response rates (ORRs) of >90% and CT-based complete response (CR) rates of >50% reported.*” (p.111) They then recommend that: “*Younger fit patients should receive a first-line induction regimen containing rituximab and high-dose cytarabine (1A).*” (p.113) The ESMO guidelines recommend the comparator in the NICE scope and DP, but also R-maxi-CHOP (cyclophosphamide, doxorubicin, vincristine given at the maximum dose)/R-HD-cytarabine for induction (p.10), which the company refer to as the NORDIC regimen. The EAG are inclined to consider that the two different regimens can be considered to have equal efficacy based on these guidelines, but the precise percentage use in UK clinical practice is uncertain, TRIANGLE did not use the NORDIC regimen (see Section 3.2), and there is a cost difference between the two regimens (see Section 4.2.9). Therefore, the uncertainty as to the comparator is regarded as a Key Issue.

2.4 Outcomes

The outcomes in the NICE scope and DP are aligned except for health-related quality of life (HRQoL), which was not available in TRIANGLE.³

EAG comment: The EAG consider that, although one might be able to infer something from the other outcomes, there is a substantive gap in the trial evidence with the lack of HRQoL data in the pivotal TRIANGLE trial. Nevertheless, the company argues that the avoidance of ASCT by use of ibrutinib is likely to enhance HRQoL, and it is true that ASCT is reserved for fitter patients.^{3, 5, 6} However, the evidence of avoidance of ASCT toxicity is unclear, as discussed in Section 3.2.6. Therefore, uncertainty in the effect of ibrutinib on HRQoL is identified as a Key Issue.

2.5 Other relevant factors

None.

EAG comment: No comment.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.³ The evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) from Canada's Drug Agency (formerly the Canadian Agency for Drugs and Technologies in Health [CADTH]) was used to inform this critique.¹³

The EAG has presented only the major limitations of each search strategy in the report.

Appendix B of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence on the efficacy and safety of ibrutinib with R-CHOP for untreated MCL when an ASCT is suitable.¹⁴

EAG comments:

- Searches were undertaken to identify clinical evidence on the efficacy and safety of ibrutinib with R-CHOP for untreated MCL when an ASCT is suitable. The CS, Appendix B and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{3,8,14} The original searches were conducted on 13 September 2024 and update searches were conducted on 9 May 2025 and 30 October 2025.
- The following databases were searched: MEDLINE and MEDLINE In-Process and Embase from inception, Cochrane Database of Systematic Reviews from 2005 onwards, Cochrane Central Register of Controlled Trials (CENTRAL) from 1991 onwards. No date limits were used in the original search, except for limiting conference abstracts to those published from 2022 to the date of the search.
- The EAG notes the use of a publication date limit in the update search and would prefer the use of a limit to find material added to the database since a specified date, as anything that falls outside the publication date limit, but added to the database since the original search or previous update could have been missed.
- Twelve key conference proceedings were manually searched between 2022 and 2025 where available. The EAG assumes that any dates that were not searched were not available, but this is not stated. There was some inconsistency in the choice of search terms, as the same terms were not used across all the conference proceedings. Including "hematological" in the non-haematology sources is noted, although including variant words, including the UK spellings would perhaps have been advisable too.
- Two trials registries, ClinicalTrials.gov and the European Clinical Trials Registry were searched but the dates searched were not specified. The EAG notes that euclinicaltrials.eu was not searched. This includes trials initiated in the European Union (EU) or European Economic Authority (EEA) since 31 January 2023.
- No health technology agency sources were searched for evidence on clinical effectiveness, and including health technology agency sources may have found useful references not available elsewhere.
- Bibliographies of SLRs and meta-analyses and other selected studies were reference checked.
- The study design filters used were not referenced, so the EAG was unclear whether the filters used were published objectively derived filters. The trial filter used also includes a very limited range of

terms to identify systematic reviews and meta-analyses, presumably to identify publications whose reference lists can be checked, but the database limits or subject headings for those publication types are not included. Overall, the filters contained a combination of subject heading terms and free text terms, and the EAG deemed them to be adequate.

- There is a typographical error in line 99 of the Embase searches, where quasiransom\$ appears instead of quasirandom\$, although the EAG feel this is likely to make little difference to the searches.
- The synonym “poorly differentiated diffuse lymphocytic lymphoma” was not included in the MCL facet in the searches. The EAG added this synonym to the search strategy in the CS and the revised strategy found a further 1,000 references, before other facets were applied to the search, so including it may have found additional references.
- The EAG notes that the MCL terms were searched only in title and abstract, and not in keyword fields using .kf. or .kw.
- Terms in the drug facet were searched only in the title and abstract fields. Searching .tw. in Embase instead of .ti,ab. would also search the drug trade name. Keyword fields (.kw. or .kf.) could also have been included. Some drug synonyms in Emtree are not in the Embase search in line 31.
- The EAG notes the comprehensive list of drug names are included in the search. However, melphalan, a constituent of carmustine, etoposide, cytarabine and melphalan (BEAM) and fractionated total body irradiation, cytarabine and melphalan (THAM), is not included in the search. The abbreviations R-DHAOx and RDHAOx, and the variant abbreviation R-CHOP (with the hyphen) are also not included in the search.
- The database searches for the clinical effectiveness SLR were well structured, transparent and reproducible.¹⁴ They contained a good range of search terms, synonyms and subject headings, although additional searches as described above might have found additional references.

3.1.2 Inclusion criteria

To identify evidence in the SLR, the company employed the following eligibility criteria as presented in Table 3.1.

Table 3.1: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion	Exclusion
Population	Adult patients (≥ 18 years) with previously untreated (first-line) MCL who are eligible for ASCT.^a Studies with mixed population of ASCT-eligible and ineligible patients were eligible for inclusion if they reported outcomes in the population of interest, or the population of interest comprises most ($\geq 80\%$) of the study population.^b	Paediatric patients. Studies that do not include patients with MCL. Studies not including patients with previously untreated MCL. Studies not including ASCT-eligible patients.
Intervention /comparator	Induction regimens (with or without consolidation/maintenance) including, but not limited to those recommended by NCCN, ESMO and BSH: • High-dose Ara-C based regimens including: ○ R- plus maxiCHOP alternating with R plus high dose cytosine arabinoside (Ara-C) (NORDIC regimen)	Regimens not used or studied in the treatment of previously untreated patients with MCL who are eligible for ASCT. Studies assessing non-ASCT-based/non-pharmacological interventions including total body radiation and radioimmunotherapy.

	Inclusion	Exclusion
	○ R plus bendamustine followed by R plus high dose Ara-C ○ Hyper cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) alternating with high-dose methotrexate (MTX) and Ara-C, plus R or another anti-CD20 mAb ○ R-DHAP followed by R-CHOP (LyMA regimen) ○ Alternating R-CHOP and R-DHA(P/Ox) ○ Alternating R-CHOP and R-DHA(P/Ox), with BTKi added to the R-DHA(P/Ox) cycles (TRIANGLE regimen) ○ Rituximab, bendamustine and cytarabine (R-BAC500) ○ VR-doxorubicin, cyclophosphamide and cisplatin (CAP) alternating with R plus high dose Ara-C ○ R-CHOP followed by R-BAC • CHOP in combination with R or another anti-CD20 mAb • Zanubrutinib/obinutuzumab/venetoclax Additional treatments specified in NICE CG PICOS and published SLR: • CALGB 59909 regimen: rituximab, methotrexate and R-CHOP followed by Ara-C and etoposide with rituximab then ASCT • Cyclophosphamide, fludarabine and rituximab (RFC) or RFC with mitoxantrone (RFCM) • CHOP • R-cladribine • Sequential R-CHOP and rituximab with ifosfamide, carboplatin, and etoposide (R-ICE) • Rituximab with mitoxantrone, chlorambucil and prednisolone (R-MCP) Consolidation/maintenance therapy: • Conditioning regimens such as BEAC or BEAM • ASCT • Rituximab • Rituximab + BTKi	
Outcomes	Efficacy: Survival outcomes: • FFS	Outcomes not listed in the inclusion criteria

	Inclusion	Exclusion
	• OS • PFS Treatment response outcomes: • CR • Duration of first remission/response • Minimal response • Minimal residual disease • Overall/objective response • Progressive disease • PR • PR to CR conversion rate • Stable disease • Time to progression Safety: • Overall AEs • TEAEs • TRAEs • Grade 3+ AEs • Grade 3+ TEAEs • Grade 3+ TRAEs • SAEs • Discontinuations due to AEs HRQoL outcomes (measured using generic or disease-specific instruments/questionnaires)	
Study design	• RCTs (any phase) • Single Arm trials • Non-RCTs • Observational studies	Pharmacodynamic/pharmacokinetic studies, genetic studies, cellular/molecular studies, in vitro/ex-vivo studies. Case reports or case-series. Economic evaluations. Reviews including SLRs, meta-analyses and NMAs.^c
limits	Time limit: full text publications – no limit; conference titles/abstracts – from 2022 onwards. Geography: No restriction. Language: English	Time limit: conference abstracts published before 2022.
Source: Adapted from Table 11, CS and Appendices.^{3, 14} ^a The TRIANGLE trial includes patients eligible for high-dose treatment including high-dose Ara-C. ^b IQWiG recommends including the study if the population criterion applies to at least 80% of the patients if analyses of the relevant subpopulation is not available. ^c SLR, meta-analyses and NMAs will be included at abstract review stage to search their reference lists for any missed studies and subsequently excluded during the full text review stage. AEs = adverse events; Ara-C = cytarabine; ASCT = autologous stem cell transplantation; BEAC = carmustine, etoposide, cytarabine and cyclophosphamide; BEAM = carmustine, etoposide, cytarabine and melphalan; BSH = British Society of Haematology; BTKi = Bruton tyrosine kinase inhibitors (ibrutinib, acalabrutinib or zanubrutinib); CALGB 59909 regimen = rituximab, methotrexate and CHOP followed by rituximab, cytarabine, etoposide and filgrastim, followed by carmustine, etoposide and cyclophosphamide, followed by rituximab and ASCT; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CR = complete response; CS = company submission; ESMO = European Society for Medical Oncology; FFS = failure-free survival; HRQoL = health-related quality of life; HyperCVAD = hyper fractionated cyclophosphamide,		

	Inclusion	Exclusion
	vincristine and adriamycin (doxorubicin) and dexamethasone alternating with high-dose methotrexate/cytarabine; maxiCHOP = maximal cyclophosphamide, doxorubicin, vincristine and prednisone; MCL = Mantle cell lymphoma; NCCN = National Comprehensive Cancer Network; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; PICO = Patient Intervention Comparator Outcome; PR = partial response; R-BAC = rituximab, bendamustine and cytarabine; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; RCT = randomised controlled trial; RDHA = rituximab, dexamethasone and cytarabine; RDHA(P/Ox) = rituximab, dexamethasone, cytarabine and platinum (cisplatin, carboplatin or oxaliplatin); RFC = rituximab, fludarabine and cyclophosphamide; RFCM = rituximab, fludarabine, cyclophosphamide and mitoxantrone; RICE = rituximab, ifosfamide, carboplatin and etoposide; RMCP = rituximab, mitoxantrone, chlorambucil and prednisone; SAE = serious adverse event; SLR = systematic literature review; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event	

3.1.3 Critique of Screening and data extraction

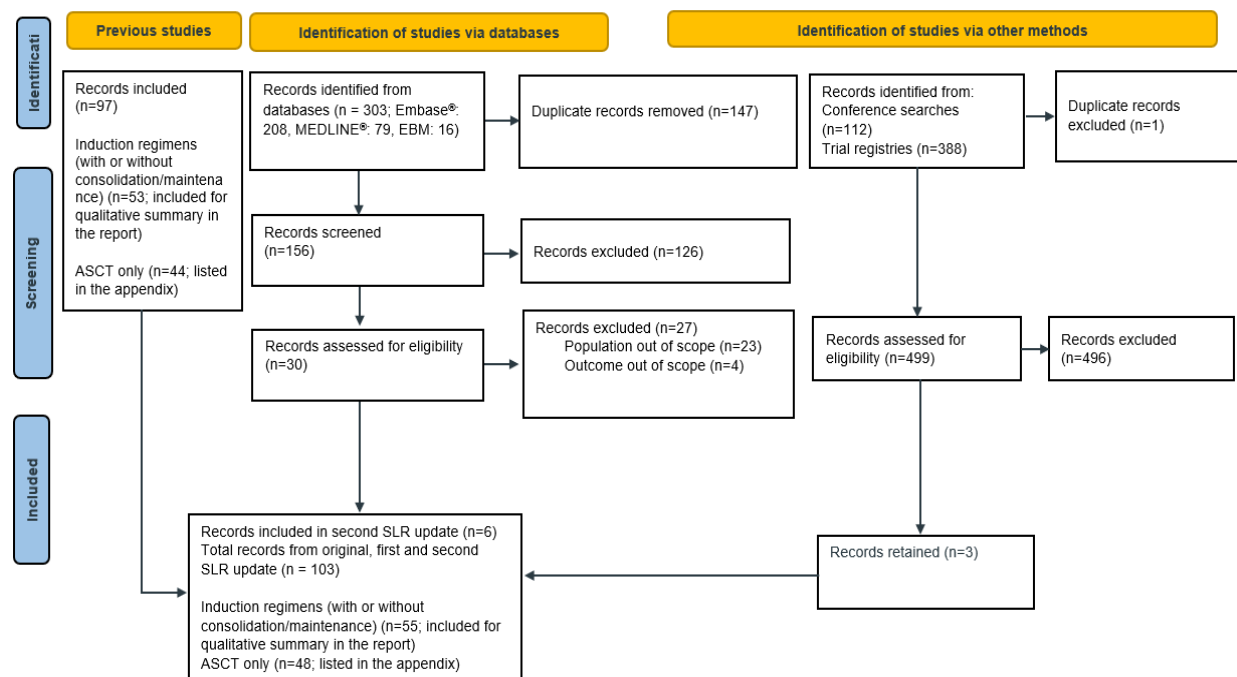
The CS confirms that all screening decisions were documented to ensure the process was transparent and replicable with studies being screened in two stages.¹⁴ The first stage involved two independent reviewers with any discrepancies being resolved by consulting a third reviewer and on reaching consensus. In the second stage all relevant full text publications were independently assessed by two reviewers with any discrepancies were resolved by consulting a third reviewer and on reaching consensus.

For data extraction, one reviewer was involved identifying and extracting the relevant data which was then quality checked by a second reviewer. No further details are provided on this process.

EAG comment: The company have described an optimal method for screening which utilises duplicate processes conducted independently, and with a third independent reviewer resolving any disputes. This approach carries the least risk of error and bias and increases trustworthiness of the SLR. The data extraction, however, was not carried out with the same level of rigour. While the company did use a widely employed method with one reviewer extracting data and this work being checked by a second reviewer, it is not as robust or reliable as duplicate extractions conducted independently. It is more at risk of error and bias. Additionally, they did not describe how any disagreements were resolved between the reviewer who extracted the data and the reviewer who checked it. As a consequence of this, the EAG must assume there is an increased risk of bias (RoB) and error in the SLR. However, given the inclusion of only one trial, TRIANGLE, this is not regarded as a major problem by the EAG.

3.1.1 Study retrieval

Briefly, the original SLR search was conducted on the 13 September 2024 and subsequently updated twice, on the 9 May 2025 and the 30 October 2025.³ After duplicates were removed a total of 5,388 records across all searched were screened. After exclusion of records not meeting the eligibility criteria, 89 records were included in the SLR. An additional 16 records were identified via hand searches including conference, registry and bibliography searches, of which 14 were included based on the eligibility criteria. One hundred and three publications were therefore included in the SLR. Of these 103 publications, 40 unique studies described in 55 publications evaluated induction regimens with or without consolidation/maintenance. The remaining 48 publications assessed the efficacy of ASCT only. An overview of the results of the original SLR and subsequent two updates is provided below and summarised in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram in Figure 3.1. Of the 40 studies identified, only one trial provided evidence on the clinical efficacy and safety of ibrutinib with immunochemotherapy in patients with previously untreated MCL, i.e. TRIANGLE.

Figure 3.1: SLR PRISMA flow diagram

Source: Adapted from figure 1 CS Appendices.¹⁴

Two studies, evaluating zanubrutinib + R-CHOP and R-DHA0x (Yan 2023) and R-CHOP/R-BAC (Shimizu 2023), only reporting data for response rates and safety (including discontinuation), were also included in the SLR as these are the only studies identified that evaluate clinical outcomes for these regimens.

ASCT = autologous stem cell transplantation; EMB = evidence -based medicine; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-analyses; SLR = systematic literature review

EAG comment: The EAG agree that TRIANGLE is the only trial that makes a comparison between the intervention and comparator in the population of interest, as specified in the DP.

3.1.2 Quality assessment

TRIANGLE was critically appraised using the revised Cochrane RoB tool 2.0 based on the Dreyling 2024 study publication.³ This RoB assessment contains five distinct domains, where each domain is judged as having a low RoB, some concerns, or high RoB, with an overall judgment for the study derived from the domain-level evaluations. The company did not detail exactly how many reviewers were involved in assessing the quality of the study, and whether or not appraisals were checked by a second reviewer.

Table 3.2 details the results of the company appraisal of the TRIANGLE trial. The EAG also assessed the trial and where any major disagreements with the company existed, comments are included in the Table below.

Table 3.2: Quality assessment of TRIANGLE

Domain	RoB	Justification	EAG comment if required
Bias arising from the randomisation process	Low	Randomisation was implemented in the electronic data capture system, blocked and stratified according to study groups and MIPI risk groups and used computer-generated random numbers with	N/A

		unpredictable seed. In addition, baseline characteristics were well balanced between the Arms.	
Bias due to deviations from intended interventions	Low	The primary analysis on the FAS was done via ITT principals. Discontinuations due to reasons such as progression, AEs, MCL diagnosis rejection, patient decision, COVID-19 death and suicide were small.	N/A
Bias due to missing outcome data	Low	Efficacy analyses were performed on the FAS via the ITT principal. Outcome data was collected for nearly all randomised patients.	N/A
Bias in measurement of the outcome	Low	Response assessments were performed by the investigator, based on physical examinations, preplanned CT scans, laboratory results, and bone marrow examinations applying the Revised Response Criteria for Malignant Lymphoma. FFS, OS and PFS are objective outcomes, so differential ascertainment is unlikely.	N/A
Bias in selection of the reported result	Low	The outcomes in the trial were reported according to pre-specified analysis plans. The timing of interim analyses was pre-specified in the protocol, and the disclosure of results was permitted after formal decision of each statistical test.	N/A
Source: Adapted from Table 10, CS. ³ AE = adverse event; CS = company submission; CT = computed tomography; FAS = full analysis set; FFS = failure-free survival; ITT = intention-to-treat; MCL = Mantle cell lymphoma; MIPI = MCL International Prognostic Index; OS = overall survival; PFS = progression-free survival; RoB = risk of bias			

EAG comment: It is unclear how robust the critical appraisal process was as it is not detailed how many reviewers were involved or how the reviewers' decisions were checked. The EAG considers that a submission must be sufficiently detailed to describe the processes that were undertaken and to assist in determining likelihood of error or biases. However, the EAG did conduct an appraisal, and no major disagreements were found, and the TRIANGLE trial is therefore considered to be of low bias.

3.1.3 Evidence synthesis

Only one trial, TRIANGLE, was included.

EAG comment: Not applicable.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Summary of TRIANGLE

This Section presents a summarised overview of the relevant trial details as presented in the CS.³

TRIANGLE was the registrational trial supporting the licence application for ibrutinib in the indication of relevance to this submission and therefore forms the principal source of effectiveness data for this submission. The CS emphasises that the data presented is from the primary analysis, which is from the most recent clinical cut-off (CCO) of TRIANGLE (9 May 2024).³ An overview of TRIANGLE is provided in the Table 3.3 below.

Table 3.3: Overview of TRIANGLE

Study design	An investigator-initiated, Phase III, randomised, open-label, international, multicentre, three-Arm, parallel group trial assessing whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT.
Population	Adult patients aged 18–65, with previously untreated, stage II–IV MCL, with at least one measurable lesion (or bone marrow only), ECOG PS ≤ 2 , and suitable for high-dose treatment including high-dose cytarabine-containing therapy
Intervention(s)	Arm I Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAOx (Cycles 2, 4 and 6) - Ibrutinib 560 mg QD on days 1–19 of R-CHOP cycles Maintenance: - Ibrutinib 560 mg QD for 2 years - Rituximab (according to national treatment guidelines)^a
Comparator(s)	Arm A Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAOx (Cycles 2, 4 and 6) ASCT conditioning: - High-dose therapy (THAM [fractionated total body irradiation, cytarabine and melphalan] or BEAM [carmustine, etoposide, cytarabine and melphalan]^b) and ASCT Maintenance: - Rituximab (according to national treatment guidelines)^a Arm A+I^c Induction: - Alternative three cycles of R-CHOP (Cycles 1, 3 and 5) and three cycles of R-DHAP or R-DHAOx (Cycles 2, 4 and 6) - Ibrutinib 560 mg QD on days 1–19 of R-CHOP cycles ASCT conditioning: - High-dose therapy (THAM or BEAM^b) and ASCT Maintenance: - Rituximab (according to national treatment guidelines)^a
Indicate if study supports application for MA	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the DP	- FFS - PFS - OS - Response rates: - ORR - PR - CRR

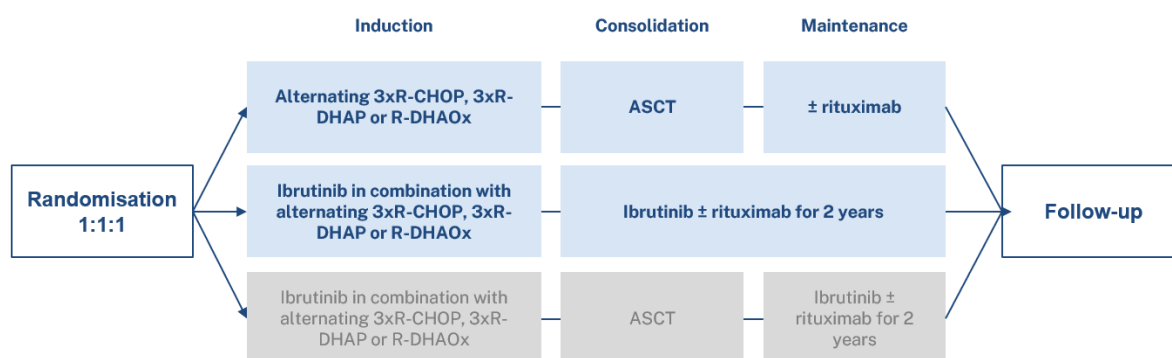
	○ Conversion rate of PR to CR during-follow-up after end of induction therapy ● AEs and SAEs
All other reported outcomes	N/A
Source: Adapted from table 4, CS.³ ^a As evidence supporting rituximab maintenance treatment was not yet established during the development of the study protocol, rituximab maintenance was not considered a study treatment in TRIANGLE. However, upon its implementation in national treatment guidelines, rituximab maintenance therapy was administered to patients across all three study Arms per the recommendations of the site's study group. Rituximab was administered at the end of induction for Arm I and in the case of PR or CR following ASCT in Arm A. ^b Choice of THAM or BEAM was stratified per trial site before trial activation at site. ^c Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib and is therefore not relevant to clinical decision making in the UK. AEs = adverse events; ASCT = autologous stem cell transplant; BEAM = carmustine, etoposide, cytarabine and melphalan; CHOP = cyclophosphamide, doxorubicin; CRR = complete response rate; DHAOx = dexamethasone, high-dose cytarabine and oxaliplatin; DHAP = dexamethasone, high-dose cytarabine, platinum; DP = decision problem; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FFS = failure-free survival; MA = marketing authorisation; MCL = Mantle cell lymphoma; N/A = not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QD = one daily; SAEs = serious adverse events; THAM = fractionated total body irradiation, cytarabine and melphalan; UK = United Kingdom	

TRIANGLE is a Phase III randomised open label three Arm parallel group trial (see Figure 3.2 and Table 3.4) conducted across multiple sites in Europe and Israel. Patients were ≥ 18 years of age and ≤ 65 years of age with untreated MCL. TRIANGLE included patients with previously untreated MCL eligible for ASCT, with patients randomised to the following treatment Arms in a 1:1:1 ratio.³ Patients were stratified according to study group and MIPI risk group (low, intermediate, high). The three Arms were defined in the CS as follows:³

- Arm I: R-CHOP/R-DHAP or R-DHAOX with ibrutinib followed by 2-years of ibrutinib maintenance $\pm$ rituximab
- Arm A: R-CHOP/R-DHAP followed by high-dose chemotherapy (HDT)-ASCT $\pm$ rituximab maintenance
- Arm A+I: R-CHOP/R-DHAP with ibrutinib followed by HDT-ASCT and 2-years of ibrutinib maintenance $\pm$ rituximab

For Arm A and Arm A+I, HDT with THAM or BEAM was only given to patients in complete or partial remission after induction immunochemotherapy. For patients who did not achieve remission at the end of induction immunochemotherapy patients remained in the study for progression and survival follow-up.³ For Arm I and Arm A+I, maintenance therapy with ibrutinib was only given to patients who achieved complete response (CR) or partial response (PR) at the end of induction therapy or following ASCT, respectively. For all treatment Arms, in the event of progressive disease (proven by computed tomography [CT] scan), study treatment was stopped, and patients remained in study for survival follow-up. Any salvage therapy according to individual institutional standard could be used after stopping study treatment.³

The CS states that evidence supporting the use of rituximab in this treatment setting was not established when the protocol was developed for TRIANGLE.³ Therefore, rituximab maintenance was not considered a study treatment in TRIANGLE. Following the publication of evidence supporting rituximab maintenance treatment, and upon its implementation into the national treatment guidelines for a participating country, rituximab maintenance was administered to patients across all Arms per the recommendation of the site's study group.³

Figure 3.2: TRIANGLE trial design

Source: Adapted from figure 4, CS.³

According to the recently completely recruited LyMa trial, rituximab maintenance could have been added to all three study Arms depending on national guidelines.

ASCT = autologous stem cell transplant; CHOP = cyclophosphamide, doxorubicin; CS = company submission; DHAP = dexamethasone, high-dose cytarabine, platinum

The Arms were administered as follows:³

- Arm I: 18 weeks induction therapy, 2 years ibrutinib maintenance, observation until progression and follow-up until the end of the trial
- Arm A: 18 weeks induction therapy, 6 weeks ASCT, observation until progression and follow-up until the end of the trial
- Arm A+I: 18 weeks induction therapy, 6 weeks ASCT, 2 years ibrutinib maintenance, observation until progression and follow-up until the end of the trial

The company stated that as ibrutinib is licensed in the UK in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy, the use of ibrutinib in combination with ASCT is off-label. The CS emphasises that Arm A+I of TRIANGLE is therefore not relevant to decision-making in the UK and as such the study methodology and results presented for the remainder of this submission are for the Arm I and Arm A only.³

Table 3.4: Overview of TRIANGLE methodology

Location	165 sites across 13 European countries (Czech Republic, Germany, Italy, Portugal, the Netherlands, Belgium, Denmark, Finland, Norway, Sweden, Poland, Spain, and Switzerland) and Israel ^a
Trial design	A Phase III, randomised, open-label, multicentre, three-Arm, parallel group, trial assessing whether the addition of ibrutinib results in a superior clinical outcome compared with the pre-trial immunochemotherapy standard with ASCT or an ibrutinib-containing treatment without ASCT All patients were randomised in a 1:1:1 ratio to one of three treatment Arms: • Arm I • Arm A • Arm A+I Further details of the treatment regimens included in each Arm are provided within the 'method of study drug administration' row below.
Key eligibility criteria for patients	The key inclusion and exclusion criteria for TRIANGLE are summarised below. A full list of inclusion and exclusion are provided within the CSR. Inclusion criteria:

	• Histologically confirmed diagnosis of MCL according to WHO classification • Suitable for high-dose treatment including high-dose cytarabine-containing therapy • Stage II-IV disease (Ann Arbor) • Age ≥ 18 years and ≤ 65 years • Previously untreated MCL • At least 1 measurable lesion (or bone marrow only) • ECOG PS/WHO ≤ 2 • The following laboratory values at screening (unless related to MCL): ◦ Absolute neutrophil count ≥ 1000 cells/μL ◦ Platelets $\geq 100,000$ cells/μL ◦ Transaminases (AST and ALT) ≤ 3 x ULN ◦ Total bilirubin ≤ 2 x ULN unless due to known Morbus Meulengracht (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 • Sexually active men and women of child-bearing potential must agree to use one of the highly effective contraceptive methods together with one of the barrier methods while on study; this should be maintained for 90 days after the last dose of study drug and 12 months after the last dose of rituximab Exclusion criteria: • Known CNS involvement of MCL • Previous lymphoma therapy with radiation, cytostatic drugs, anti-CD20 antibody or interferon
Method of study drug administration	Arm I: R-CHOP: • Induction: IV rituximab 375 mg/m² on day 0 or 1, IV cyclophosphamide 750 mg/m² on day 1, IV doxorubicin 50 mg/m² on day 1, IV vincristine 1.4 mg/m² on day 1, and oral predniso(lo)ne 100 mg on days 1–5 R-DHAP or R-DHAox induction: • Induction: IV rituximab 375 mg/m² on day 0 or 1, IV or oral dexamethasone 40 mg on days 1–4, IV cytarabine 2 $\times$ 2 g/m² for 3 hours every 12 hours on day 2, and IV cisplatin 100 mg/m² over 24 hours on day 1 (alternatively IV oxaliplatin 130 mg/m² on day 1), SC G-CSF 5 μg/kg daily from day 6 until recovery of WBC > 2.5 G/l (alternatively pegfilgrastim may be applied once on day 6) Ibrutinib: • Induction: 560 mg (4 $\times$ 140 mg capsules) orally QD on days 1–19 of R-CHOP cycles • Maintenance: 560 mg (4 $\times$ 140 mg capsules) orally QD for 2 years ◦ Ibrutinib maintenance was only given to patients who achieved CR or PR after induction immunochemotherapy Rituximab:^b • Maintenance: rituximab maintenance was only given to patients who achieved CR or PR after induction immunochemotherapy Arm A: R-CHOP: • Induction: IV rituximab 375 mg/m² on day 0 or 1, IV cyclophosphamide 750 mg/m² on day 1, IV doxorubicin 50 mg/m² on day 1, IV vincristine 1.4 mg/m² on day 1, and oral prednisone 100 mg on days 1–5 R-DHAP or R-DHAox: • Induction: IV rituximab 375 mg/m² on day 0 or 1, IV or oral dexamethasone 40 mg on days 1–4, IV cytarabine 2 $\times$ 2 g/m² for 3 hours every 12 hours on day 2, and IV

	cisplatin 100 mg/m² over 24 hours on day 1 (alternatively IV oxaliplatin 130 mg/m² on day 1), SC G-CSF 5 µg/kg daily from D6 until recovery of WBC > 2.5 G/l (alternatively pegfilgrastim may be applied once on day 6) ASCT: - Stem cell mobilisation and harvest 5-10 µg/kg G-CSF on day 6 of DHAP cycle 3 until completion of stem cell harvest - Conditioning THAM - Total body irradiation with a total of 10 Gray (day -7, to day -5), IV cytarabine 2x1.5 g/m², every 12 hours for 30 minutes (day -4 and day -3), and IV melphalan 140 mg/m² (day -2) for 1 hour - Peripheral stem cells (2.0 x 10⁶/kg body weight CD34+ cells) transfused on day 0 (2 days after melphalan) - Conditioning BEAM - Combined chemotherapy with IV carmustine 300 mg/m² (day -7) for 1 hour,^c IV cytarabine 2 x 200 mg/m², every 12 hours for 30 minutes (day -6 to day -3), IV etoposide 2 x 100 mg/m², every 12 hours for 1 hour (day -6 to day -3) and IV melphalan 140 mg/m² (day -2) for 1 hour - Peripheral stem cells (2.0 x 10⁶/kg body weight CD34+ cells) transfused on day 0 (2 days after melphalan). - Only one of THAM or BEAM conditioning prior to ASCT was applied to patients who achieved complete or partial remission after induction immunochemotherapy Rituximab^b - Maintenance: rituximab maintenance was only given to patients who achieved CR or PR after induction immunochemotherapy
Primary endpoint	The primary endpoint of TRIANGLE was FFS, defined as the time from randomisation to SD at end of induction immunochemotherapy, PD, or death from any cause, whichever came first.
Secondary endpoints	- OS - PFS - ORR - CRR - PR to CR conversion rate - TEAEs - SAEs - AESIs - Other significant AEs
Pre-planned subgroups	Pre-specified subgroup analyses of the key TRIANGLE trial endpoints were performed for FFS. The following subgroups were considered: - MIPI risk group (low, intermediate, high) - Ki-67 index (≥30%, <30%) - Cytology of MCL (blastoid or pleomorphic, classic or small cell, not done) - p53 expression (>50%, ≤50%) - Remission status (CR, PR) at end of induction immunochemotherapy (for DOR) - Remission status after ASCT months after end of induction immunochemotherapy (for DOR from ASCT) - Sex - Rituximab maintenance^b
Duration of study and follow-up	The study was initiated on 25 July 2016 (which corresponds to the date the first patient signed the informed consent form). At the latest CCO the median time on study was ■■■ months and ■■■ months for Arm I and Arm A, respectively.
Source: Adapted from Table 5, CS. ³	

^a The FAS does not include patients from the ITT in the Israeli study group as it was not possible to re-consent these patients due to the ongoing geopolitical situation.

^b As evidence supporting rituximab maintenance treatment was not yet established during the development of the study protocol, rituximab maintenance was not considered a study treatment in TRIANGLE. However, upon its implementation in national treatment guidelines, rituximab maintenance therapy was administered to patients across all three study Arms per the recommendations of the site's study group. Rituximab was administered at the end of induction for Arm I and in the case of PR or CR following ASCT in Arm A.

^c The availability of carmustine could be challenging at some sites. Instead, TEAM (Thiotepa 5 mg/kg twice a day on Day -7) could be considered based on a retrospective EBMT comparison.

ALT = alanine aminotransferase; AE = adverse event; AESI = adverse event of special interest; ASCT = autologous stem cell transplant; AST = aspartate aminotransferase; BEAM = chemotherapy regimen (carmustine, etoposide, cytarabine, melphalan); CCO = clinical cut off; CNS = central nervous system; CR = complete response; CRR = complete response rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EU = European Union; FAS = full analysis set; FFS = failure-free survival; ICH = International Conference on Harmonisation; ITT = intention-to-treat; IV = intravenous; MCL = Mantle cell lymphoma; MIPI = MCL International Prognostic Index; OS = overall survival; ORR = overall response rate; PD = progressed disease; PFS = progression-free survival; PR = partial response; QD = once daily; SAE = serious adverse event; SD = stable disease; TEAEs = treatment-emergent adverse events; THAM = total body irradiation; ULN = upper limit of normal; WHO = World Health Organization

EAG comment: As stated in Section 2.2, the EAG raised the question as to whether there should be a comparison with the ibrutinib induction followed by ASCT, which would be represented by Arm A+I in TRIANGLE, which the company stated in the CS and reiterated in the clarification response was irrelevant because this combination treatment would be outside of the license. Since this is discussed in full in Section 2.2, there is nothing further to add here.

3.2.2 Baseline characteristics

The CS presented the baseline demographics and disease characteristics based on the full analysis set (FAS) from the 9 May 2024 CCO.³ These are detailed in Table 3.5.

Table 3.5: Baseline demographics and disease characteristics in TRIANGLE (FAS)

Baseline Characteristic	Arm I (N=268)	Arm A (N=269)
Age, years		
Mean (SD)	██████████	██████████
Median (range)	57.0 (27, 65)	57.0 (31, 65)
≥65 years, n (%)	8 (3.0%)	17 (6.3%)
Sex, n (%)		
Female	54 (20.1%)	64 (23.8%)
Male	214 (79.9%)	205 (76.2%)
Race, n (%)		
White	268 (100%)	264 (98.1%)
Other	0	5 (1.9%)
Weight, kg		
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████
BMI, kg/m²		
Mean (SD)	██████████	██████████
Median (range)	██████████	██████████

Baseline Characteristic	Arm I (N=268)	Arm A (N=269)
MIPI risk group		
Low risk	152 (56.7%)	153 (56.9%)
Intermediate risk	76 (28.4%)	75 (27.9%)
High risk	40 (14.9%)	41 (15.2%)
ECOG PS		
0	187 (70.0%)	191 (71.8%)
1	75 (28.1%)	71 (26.7%)
2	5 (1.9%)	4 (1.5%)
Rituximab maintenance		
Yes	160 (59.7%)	168 (62.5%)
No	108 (40.3%)	101 (37.5%)
Ann Arbor stage		
I	0	1 (0.4%)
II	16 (6.0%)	8 (3.0%)
III	26 (9.7%)	22 (8.2%)
IV	226 (84.3%)	236 (88.4%)
Source: Adapted from table 6, CS. ³ BMI = body mass index; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAS = full analysis set; MIPI = MCL International Prognostic Index; SD = standard deviation		

The CS emphasises that baseline demographics such as sex, weight and body mass index (BMI) were well balanced and reflective of UK clinical practice.³ Additionally, The CS makes clear that patients had a median age of 57 years (range 27, 65) across both treatment Arms; which is consistent with UK clinical practice in which ASCT is only suitable for patients ≤ 65 years.³

Furthermore, the CS states that MCL most commonly occurs in men, the higher proportion of males in TRIANGLE is in line with UK clinical practice.³

The CS continues³ to state that various disease characteristics disease characteristics, including the MCL International Prognostic Index (MIPI) risk group, the Eastern Cooperative Oncology Group Performance Status (ECOG PS) and Ann Arbor stage of MCL, were highly aligned across treatment Arms and that the majority of patients presented with low risk disease as measured by MIPI, and an ECOG PS of either 0 or 1. Again the CS emphasises that this is aligned with the population of patients who would be fit enough to receive HDT-ASCT in UK clinical practice and that the majority of patients presented with stage IV disease which is reflective of the UK patient population, as the majority (up to 95%) of patients with MCL are diagnosed at an advanced stage of disease with multiple nodal and/or extra nodal sites of involvement³.

EAG comment: The EAG considers that overall, baseline demographic characteristics were well balanced across treatment Arms. Typically, those differences beyond 5% or above are highlighted by the EAG as those which may be of note either clinically or statistically. In the case of the data provided, no such differences existed.

The EAG requested that their clinical expert provide additional input on the generalisability of the patient population in TRIANGLE to what would be observed in UK clinical practice. The EAG clinical

expert stated that: “the population in the trial are generalisable to the UK population with MCL currently considered for intensive chemo + ASCT (age, stage etc)”.¹⁵

3.2.3 Summary of statistical methods

The protocol-specified primary analysis used a one-sided 5% overall significance level across three pairwise comparisons, corresponding to a one-sided 1.67% significance level per comparison after Bonferroni correction for multiple comparisons.³ A one-sided hypothesis test using the log-rank test statistic for FFS was performed for each comparison: Arm A versus Arm I, Arm A+I versus Arm A, and Arm A+I versus Arm I. The CS confirms that considering the hypothesis testing of Arm A versus I was one sided to detect superiority of A versus I, superiority of I versus A could not be concluded from the protocol-specified analyses.³

The CS confirms that the CSR includes not only the results of the original pre-specified (one-sided tests at 0.05/3 significance level for each test), but also supplementary analyses based on two-sided alpha at 5% significance level (i.e., two-sided test at 1.667% significance level for each pairwise test). These two-sided tests were used to analyse the efficacy data presented in this submission, given they are powered to detect superiority of either the ASCT regimen or the ibrutinib regimen and are described in Table 3.6 below. However, as this significance test was not pre-specified, results deemed significant through the two-sided tests are referred to as nominally significant throughout the submission.³

Table 3.6: Statistical methods for the primary analysis of TRIANGLE

Hypothesis objective	Primary - The primary objective of the trial was to establish one of three study Arms, R-CHOP/R-DHAP followed by ASCT (control Arm A), R-CHOP + ibrutinib/R-DHAP followed by ASCT and followed by ibrutinib maintenance^a (experimental Arm A+I),^b and R-CHOP + ibrutinib/R-DHAP followed by ibrutinib maintenance^a (experimental Arm I) as future standard based on the comparison of FFS assessed by central medical EU MCL Network case evaluation of investigator assessment Secondary - The secondary efficacy objective was to compare the efficacy of the three treatment groups in terms of secondary efficacy endpoints - Another secondary objective was to determine the safety and tolerability of ibrutinib during the entire treatment period and to compare the safety profile of the three treatment groups in terms of secondary toxicity endpoints
Statistical analysis	Analyses of the primary and secondary endpoints presented within this submission were conducted on the FAS, comprised of patients from the ITT analysis set who consented at the time of the CCO. As the one-sided tests pre-specified within the protocol (version 1.1. 18 December 2015) were powered to detect superiority of the Arm A versus Arm I (or the superiority of A+I versus A or A+I versus I but not the superiority of Arm I versus Arm A), supplementary analyses with two-sided statistical tests were pre-specified in the supplementary SAP in line with the convention for regulatory decision-making purposes. These tests were pre-specified prior to receipt of patient level data. As the two-sided tests were powered to detect superiority of either Arm A or Arm I, these tests were used to analyse the efficacy data presented in this submission in line with the analyses described in the supplementary SAP, and are described in more detail below.

	Analysis of primary endpoint • Derivation of FFS used 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 counted for FFS evaluation • Two-sided unstratified log-rank tests for statistical significance at the 5% level (with a 2-sided 1.67% significant level for each treatment comparison) were conducted. Results were provided in the form of Arm I versus Arm A as compared with Arm A versus Arm I • An unstratified Cox's regression model with study treatment (treatment groups) as the sole explanatory variable were performed to provide HR with two-sided 95% CIs Assumptions: • Noninformative censoring was assumed for all types of censoring • Identical baseline hazards between treatment groups Analysis of secondary endpoints As the analyses for the secondary endpoints were pre-specified as descriptive in the protocol (multiplicity control was not pre-specified for secondary endpoints), all analyses of secondary endpoint were descriptive rather than inferential in nature. • The analysis of the PFS endpoint was conducted using the same approach as for the FFS endpoint including use of the prespecified statistical methodology of tSPRT for controlling the overall alpha for the planned sequential analyses within each pairwise comparison • OS was described by K-M plots with all groups presented in one plot. The OS distribution and median OS with its two-sided 95% CI was estimated using the K-M method. OS was analysed using the unstratified log-rank test for treatment comparison • ORR and CRR were estimated according to the crude proportion of confirmed responders (PR or CR) and summarised by treatment Arm. CRR, ORR, and PR to CR conversion rates were compared using RR with their associated two-sided 95% CIs Safety analyses All safety analyses were conducted on the safety analysis set based on actual treatment received, unless otherwise specified. Safety was analysed using the incidence and severity of AEs and laboratory test results. The baseline value for safety analyses was defined as the value collected at the time closest to and prior to the start of study treatment Subgroups For the primary efficacy endpoint (FFS), subgroup analyses were performed with respect to the following subgroups with sufficient sample size. ○ Sex (male/female) ○ MIPI risk group (low/medium/high) ○ Ki-67 index (<30%/≥30%) ○ Cytology (blastoid or pleomorphic/classic or small cell/not assessed) ○ p53 expression (≤50%/>50%) ○ Rituximab maintenance (yes/no) The subgroup analyses were performed using the multivariate Cox regression model that included treatment group and subgroup indicator as

	main effects and treatment-by-subgroup interaction in the model. Statistical tests were done on the treatment-by-subgroup interaction terms. HRs between each pair (A versus I, A+I versus A, and A+I versus I)^b of the three treatment groups within each subgroup level and their CI were calculated using non-stratified Cox regression model. Subgroup analysis results were presented graphically in a forest plot.
Sample size, power calculation	The following assumptions were used to estimate the sample size and the trial duration as per the pre-specified protocol, as such these assumptions relate to the ITT population rather than the FAS population. • Randomisation period of up to 5 years • Additional follow-up period of up to 5 years • Randomisation rate of 174 per year • Allocation ratio of 1:1:1 • Drop-out rate 5% of randomised patients • Three pairwise log-rank tests for FFS with local one-sided significance level 0.05/3; overall significance level one-sided 5% • FFS curve for control Arm A as estimated from the experimental Arm of MCL Younger trial of the European MCL Network (CCO 7 April 2013) • Power 95% to detect an FFS superiority of A versus I (HR 0.60, 5-year FFS: 64.8% versus 48.5%) • Power 90% to detect an FFS superiority of A+I versus A and of A+I versus I (HR 0.60, 5-year FFS: 77.1% versus 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 versus I and at 190 events for A+I versus A and A+I versus I Up to 870 patients from up to 250 international sites were planned to be enrolled.^c The maximal trial duration will 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. The sample size and trial duration calculations were done using the Planning and Evaluation of Sequential Trials Version 3 software to adjust for the sequential statistical design.
Data management, patient withdrawals	In general, the study consists of the following study phases: • Screening Phase: Period of up to 28 days (i.e., upon informed consent) prior to first treatment • Treatment Phase: The overall treatment phase is defined as the period between the date of the first dose of study drug and the date of the last dose of study drug (or date of ASCT when applicable) • Observation or Follow-up: From after the last dose of study drug (or date of ASCT when applicable) until death, loss to follow-up, withdrawal of consent or end of the study, whichever occurs first Unless specified otherwise, the baseline value is defined as the last non-missing value collected within 28 days before or on the administration of the first dose of study medication. For patients who have been randomised but not treated, the randomisation date will be used as the reference date for baseline value calculation. Safety assessments were presented chronologically by study day as described below. Unless specified otherwise, the date of first dose of study treatment (randomisation date for patients who have been randomised but not treated) was used as the reference date for study day calculation. Data censoring was applied for the outcome analysis as follows: • In patients with complete or partial response at the end of induction therapy and without progression or death, FFS was censored at the last adequate disease assessment date. Patients without any lymphoma

	disease evaluation during or at the end of induction were censored one day after randomisation - For PFS, patients alive without progression at latest follow-up will be censored at the latest lymphoma assessment date - In patients without documented death during observation time, OS was censored at the last contact date alive
Source: Adapted from table 8, CS³. ^a Rituximab maintenance was added as per national treatment guidelines. ^b Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib and is therefore not relevant to clinical decision making in the UK. ^c A total of 809 patients provided explicit consent for their data to be included in HTA submissions or were deceased and are included in the FAS. AE = adverse event; ASCT = autologous stem cell transplant; CCO = clinical cut off; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; CRR = complete response rate; FAS = full analysis set; FFS = failure-free survival; HR = hazard ratio; HTA = Health Technology Assessment; I = ibrutinib; ITT = intention-to-treat; K-M = Kaplan-Meier; MCL = Mantle cell lymphoma; MIPI = MCL International Prognostic Index; MUE = median unbiased estimate; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PR = partial response; RR = risk ratio; tSPRT = truncated sequential probability ratio test; SAP = statistical analysis plan	

3.2.4 Efficacy results

3.2.4.1 FFS

Table 3.7 provides a summary of the FFS data. There was a greater number of events 87 (32.3%) in Arm A compared to 61 (22.8%) in Arm I. There was one participant who had stable disease at the end of induction (0.4%) in Arm I compared with 5 (1.9%) in Arm A. There was a greater proportion of patients who experienced disease progression in Arm A versus Arm I, 60 (22.3%) and 49 (18.3%) respectively. There was also a greater number of deaths reported in Arm A 22 (8.2%) compared to Arm I, 11 (4.1%). Kaplan-Meier (K-M) estimates provided a HR of 0.639 (98.33% CI 0.428 to 0.953; p=0.0068).

Table 3.7: FFS (FAS)

FFS results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	61 (22.8%)	87 (32.3%)
Stable disease at the end of induction	1 (0.4%)	5 (1.9%)
Disease progression	49 (18.3%)	60 (22.3%)
Death	11 (4.1%)	22 (8.2%)
Number of events censored, n (%)	207 (77.2%)	182 (67.7%)
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	██████████	██████████
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	██████████	██████████
Range ^a	██████████	██████████
HR (2-sided 98.33% CI) ^b	0.639 (0.428, 0.953)	
p-value ^c	0.0068	
FFS rate (95% CI)		
6-month	██████████	██████████
12-month	██████████	██████████

FFS results	Arm I (N=268)	Arm A (N=269)
24-month	██████	██████
36-month	██████	██████
48-month	0.818 (0.765, 0.860)	0.703 (0.643, 0.755)
60-month	0.754 (0.688, 0.808)	0.646 (0.578, 0.707)
72-month	██████	██████
84-month	██████	██████
Based on Table 11, CS.³ Percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators ^a Censored observation ^b HR is from an unstratified Cox regression model and HR < 1 favours Arm I versus A, ^c2-sided p-value is from an unstratified log-rank test. CI = confidence interval; CS = company submission; FAS = full analysis set; FFS = failure-free survival; HR = hazard ratio; NE = not estimable		

3.2.4.2 OS

Table 3.8 provides a summary of data relating to OS. There were 60 events (22.3%) in Arm A compared to 33 (12.3%) in Arm I. K-M estimates provided a HR of 0.522 (98.33%CI 0.341 to 0.799; p=0.0023).

Table 3.8: OS (FAS)

Table 12: OS (FAS)

OS Results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	33 (12.3%)	60 (22.3%)
Number of events censored, n (%) ^a	235 (87.7%)	209 (77.7%)
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)	████████	████████
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% percentile (95% CI)	████████	████████
Range ^b	████████	████████
HR (2-sided 95% CI) ^c	0.522 (0.341, 0.799)	
p-value ^d	0.0023	
Survival rate (95% CI)		
6-month	████████	████████
12-month	████████	████████
24-month	████████	████████
36-month	████████	████████
48-month	0.896 (0.852, 0.928)	0.796 (0.741, 0.840)
60-month	0.856 (0.800, 0.897)	0.753 (0.690, 0.805)
72-month	████████	████████
84-month	████████	████████
Based on table 12, CS. ³		
^a In patients without documented death during observation time, OS was censored at the last contact date alive, percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators		
^b Censored observation		
^c HR is from an unstratified Cox regression model and HR <1 favours Arm I versus A		

^d 2-sided p-value is from an unstratified log-rank test

CI = confidence interval; CS = company submission; FAS = full analysis set; FFS = failure-free survival; HR = hazard ratio; NE = not estimable; OS = overall survival

3.2.4.3 PFS

There were a greater number of PFS events reported in Arm A (87, 32.3%) compared to 60 (22.4%) in Arm I (Table 3.9). Number of disease progression events were 63 (23.4%) in Arm A compared to 49 (18.3%) in Arm I. There were 24 (8.9%) deaths in Arm A compared to 11 (4.1%) in Arm I. K-M estimates provided a HR of 0.633 (95% CI 0.424 to 0.946; p=0.0060).

Table 3.9: PFS (FAS)

PFS Results	Arm I (N=268)	Arm A (N=269)
Number of events, n (%)	60 (22.4%)	87 (32.3%)
Disease progression	49 (18.3%)	63 (23.4%)
Death	11 (4.1%)	24 (8.9%)
Number of events censored, n (%)		
Median Kaplan–Meier estimate, months		
25% percentile (95% CI)		
Median (95% CI)	NE (NE, NE)	NE (77.44, NE)
75% percentile (95% CI)		
Range ^a		
HR (2-sided 98.33% CI) ^b	0.633 (0.424, 0.946)	
p-value ^c	0.0060	
PFS rate (95% CI)		
6-month		
12-month		
24-month		
36-month		
48-month	0.824 (0.772, 0.865)	0.710 (0.651, 0.761)
60-month	0.760 (0.696, 0.813)	0.655 (0.587, 0.714)
72-month		
84-month		
Based on Table 13, CS. ³		
Percentages are calculated with the number of subjects in the FAS in each treatment group as the denominators.		
^a Censored observation		
^b HR is from an unstratified Cox regression model and HR <1 favours Arm I versus A		
^c 2-sided p-value is from an unstratified log-rank test		
CI = confidence interval; CS = company submission; FAS = full analysis set; HR = hazard ratio; NE = not estimable; PFS = progression-free survival		

3.2.4.4 Response rates

Table 3.10 provides a summary of complete response rate (CRR) and overall response rate (ORR) at the end of induction. For ORR, response in Arm I was compared to in Arm A (relative risk [RR] =). For CRR, response in Arm I was compared to in Arm A (RR =). CR was

in Arm I compared to 96 (35.7%) in Arm A. PR was ██████████ in Arm I compared to 1 ██████████ in Arm A. Arm I demonstrated lower stable disease (SD) (██████████) progressed disease (PD) (██████████) and not estimable (NE) (██████████) compared with Arm A, SD (██████████), PD (██████████) and ██████████.

Table 3.10: Summary of CRR and ORR at the end of induction (FAS)

Response	Arm I (N=268)	Arm A (N=269)
ORR ^a (CR, PR), n (%)	██████████	██████████
RR (2-sided 95% CI) ^b	██████████	
p-value ^c	██████████	
CRR ^d , n(%)	██████████	██████████
RR (2-sided 95% CI) ^b	██████████	
p-value ^c	██████████	
Best overall response, n (%)		
CR	██████████	██████████
PR	██████████	██████████
SD	██████████	██████████
PD	██████████	██████████
NE	██████████	██████████
Based on table 14, CS. ³		
^a ORR is defined as the proportion of subjects with a best response of CR or PR.		
^b RR >1 favours I versus A.		
^c p-value is from the Fisher's exact test.		
^d CRR is defined as the proportion of subjects who achieve a best response of CR.		
CI = confidence interval; CR = complete response; CRR = complete response rate; CS = company submission; FAS = final analysis set; NE = not estimable; ORR = objective response rate; PR = partial response; PD = progressive disease; RR = relative risk; SD = stable disease		

Table 3.11 provides a summary of overall CRR and ORR. For ORR, response in Arm I was 258 (96.3%) compared to 248 (92.2%) in Arm A (RR = 1.044, 95% CI 1.001 to 1.089; p = 0.0297). For CRR, response in Arm I was 180 (67.2%) compared to 174 (64.7%) in Arm A (RR = 1.038, 95% CI 0.919 to 1.173; p = 0.5851). CR was 180 (67.2%) in Arm I compared to 174 (64.7%) in Arm A. PR was 78 (29.1%) in Arm I compared to 74 (27.5%) in Arm A. Arm I demonstrated lower SD (n=1, 0.4%) PD (n=3, 1.1%) and NE (n=6, 2.2%) compared with Arm A, SD (n=3, 1.1%), PD (n=11, 4.1%) and NE (N = 7, 2.6%).

Table 3.11: Summary of CRR and ORR (FAS)

Response	Arm I (N=268)	Arm A (N=269)
ORR ^a (CR, PR), n (%)	258 (96.3%)	248 (92.2%)
RR (2-sided 95% CI) ^b	1.044 (1.001, 1.089)	
p-value ^c	0.0627	
CRR ^d , n(%)	180 (67.2%)	174 (64.7%)
RR (2-sided 95% CI) ^b	1.038 (0.919, 1.173)	
p-value ^c	0.5851	
Best overall response, n (%)		

CR	180 (67.2%)	174 (64.7%)
PR	78 (29.1%)	74 (27.5%)
SD	1 (0.4%)	3 (1.1%)
PD	3 (1.1%)	11 (4.1%)
NE	6 (2.2%)	7 (2.6%)
Source: Table 15, CS. ³ ^a ORR is defined as the proportion of subjects with a best response of CR or PR. ^b Relative Risk >1 favours I versus A. ^c p-value is from the Fisher's exact test. ^d Complete response rate is defined as the proportion of subjects who achieve a best response of CR. CI = confidence interval; CR = complete response; CRR = complete response rate; CS = company submission; FAS = final analysis set; NE = not estimable; ORR = objective response rate; PR = partial response; PD = progressive disease; RR = relative risk; SD = stable disease		

Table 3.12 provides a summary of PR to CR conversion rates after the end of induction therapy. The conversion rate was 60 (43.5%) in Arm I compared to 76 (50.7%) in Arm A (RR = 0.858, 95%CI 0.67 to 1.099; p = 0.2389).

Table 3.12: Summary of PR to CR conversion rate post induction (FAS)

Response	Arm I (N=268)	Arm A (N=269)
PR at the end of induction, n	138	150
PR to CR conversion rate, n (%)	60 (43.5%)	76 (50.7%)
Relative risk (2-sided 95% CI) ^a	0.858 (0.670, 1.099)	
p-value ^b	0.2389	
Source: Table 16, CS. ³		
Percentages are calculated with the number of subjects in the full analysis set in each treatment group with PR at end of induction as the denominators.		
^a Relative Risk >1 favours I versus A.		
^b p-value is from the Fisher's exact test.		
CI = confidence interval; CR = complete response; CS = company submission; FAS = full analysis set; PR = partial response		

3.2.4.5 Subsequent treatments used in the relevant studies

Table 3.13 provides a summary subsequent treatments reported in the CS.

Table 3.13: Subsequent treatments reported in TRIANGLE

Subsequent treatment	Arm I (N=268)	Arm A (N=269)
<i>Subjects with one or more subsequent anticancer therapy</i>		
Antineoplastic agents		
Combinations of antineoplastic agents		
Combinations of antineoplastic agents		
Bendamustine; cytarabine; rituximab		
Cytarabine; dexamethasone; oxaliplatin; rituximab		
Bendamustine; rituximab		
Carmustine; cytarabine; etoposide; melphalan		
Cyclophosphamide; doxorubicin hydrochloride; prednisone; rituximab; vincristine sulphate		
Cyclophosphamide; rituximab		

Subsequent treatment	Arm I (N=268)	Arm A (N=269)
Bendamustine; bortezomib; rituximab		
Bendamustine; obinutuzumab		
Bortezomib; cyclophosphamide; doxorubicin; prednisone; rituximab		
Bortezomib; cyclophosphamide; rituximab		
Cisplatin; cytarabine; dexamethasone		
Cisplatin; cytarabine; etoposide; methylprednisolone; rituximab		
Cisplatin; dexamethasone; gemcitabine; rituximab		
Cyclophosphamide; doxorubicin hydrochloride; prednisone; vincristine sulphate		
Cyclophosphamide; doxorubicin; prednisone; rituximab; vincristine		
Cyclophosphamide; fludarabine		
Cyclophosphamide; prednisone; rituximab; vincristine sulphate		
Cytarabine; etoposide; melphalan; thiotepa		
Cytarabine; methotrexate		
Fludarabine; melphalan		
Gemcitabine; oxaliplatin		
Gemcitabine; oxaliplatin; rituximab		
Ibrutinib; rituximab		
Lenalidomide; rituximab		
Bruton's tyrosine kinase inhibitors		
Ibrutinib		
Acalabrutinib		
Nemtabrutinib		
Pirtobrutinib		
Tg 1701		
Zanubrutinib		
Antineoplastic cell and gene therapy		
CAR t-cells nos		
Brexucabtagene autoleucel		
Cd20 (clusters of differentiation 20) inhibitors		
Rituximab		
Dexamethasone; rituximab		
Obinutuzumab		
Other antineoplastic agents		
Venetoclax		
Nitrogen mustard analogues		
Cyclophosphamide		
Bendamustine		
Cyclophosphamide; dexamethasone		
Monoclonal antibodies and antibody drug conjugates		
Loncastuximab tesirine		
Purine analogues		

Subsequent treatment	Arm I (N=268)	Arm A (N=269)
Fludarabine phosphate		
Pyrimidine analogues		
Gemcitabine hydrochloride		
Cytarabine		
Anthracyclines and related substances		
Doxorubicin		
Pixantrone		
Ethylene imines		
Thiotepa		
Folic acid analogues		
Methotrexate		
Podophyllotoxin derivatives		
Etoposide		
Proteasome inhibitors		
Bortezomib		
Bortezomib; dexamethasone		
Vinca alkaloids and analogues		
Vincristine		
Immunosuppressants		
Other immunosuppressants		
Lenalidomide		
Uncoded		
Allogenic stem cells nos		
Zilovetamab vedotin		
Donor lymphocyte infusion		
Ibrutinib; lenalidomide; rituximab		
Investigational drug		
Uncoded		
Autologous stem cells nos		
Source: Table 17, CS. ³ CS = company submission; nos = not otherwise specified.		

EAG comment: Please see Section 4 for a discussion related to subsequent treatments, and the implications of any lack of generalisability on both effectiveness and cost.

3.2.4.6 *Health-related quality of life*

The EAG note that HRQoL was not measured in this study.

EAG comment: HRQoL was not reported in the CS, which does raise questions as to the effect of ibrutinib on HRQoL (see Sections 2.4 and 3.2.6).

3.2.5 Inverse probability of censoring weighting - adjusted analyses (statistical adjustment for rituximab maintenance)

In the company's evidence submission, the inverse probability of censoring weighting (IPCW) method was used to adjust for insufficient rituximab maintenance in the TRIANGLE trial (59.7% in Arm I and 62.5% in Arm A) in comparison to clinical practice. The IPCW adjustment approach was preformed where patients who did not receive rituximab maintenance were artificially censored at the time when they would have received rituximab maintenance therapy (which was assumed to be 30-days post-ASCT in Arm A and at the start of ibrutinib maintenance therapy in Arm I).³ In terms of the IPCW analysis approach, the company stated:³ *"To adjust for potential bias due to informative censoring, patients that received rituximab maintenance in Arm A and Arm I in TRIANGLE were assigned weights over time, such that these accounted not only for themselves but also participants with similar characteristics in the same study arm (both those at baseline and those measured throughout the trial [time-varying covariates]) who were censored and did not receive rituximab maintenance".* The company further stated:³ *"the covariates adjusted for within the IPCW analyses were based on clinical expert feedback, the use of variables in comparative efficacy for patients with previously untreated MCL who were eligible for transplant in the literature, and the availability of variables in the dataset."*

The company stated that the IPCW-adjustment used the assumption (on the basis of clinical experts' opinion consulted at a November 2025 Advisory Board) that 85% of patients would receive rituximab maintenance therapy.³ The list of covariates included in the IPCW-adjusted analyses are provided in Table 3.14 below.

Table 3.14: Covariates considered within the IPCW-adjusted analysis

Covariates collected at baseline	Covariates collected continuously throughout the trial
Cytology	LDH
Ki-67	WBC
P-53	ECOG PS
Bone marrow involvement	Serum Beta-2-microglobulin
B-symptoms	Complete responder (yes/no)
	Treatment failure (yes/no)
Based on Table 18 of CS. ³ Stabilised time-dependent weights were estimated for each Arm separately, derived from the probability of receiving rituximab maintenance. The probability of receiving rituximab maintenance within each time period was estimated using two logistic regression models. CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IPCW = inverse probability of censoring; LDH = lactate dehydrogenase; WBC = white blood count	

3.2.5.1 Results of IPCW-adjusted primary analyses

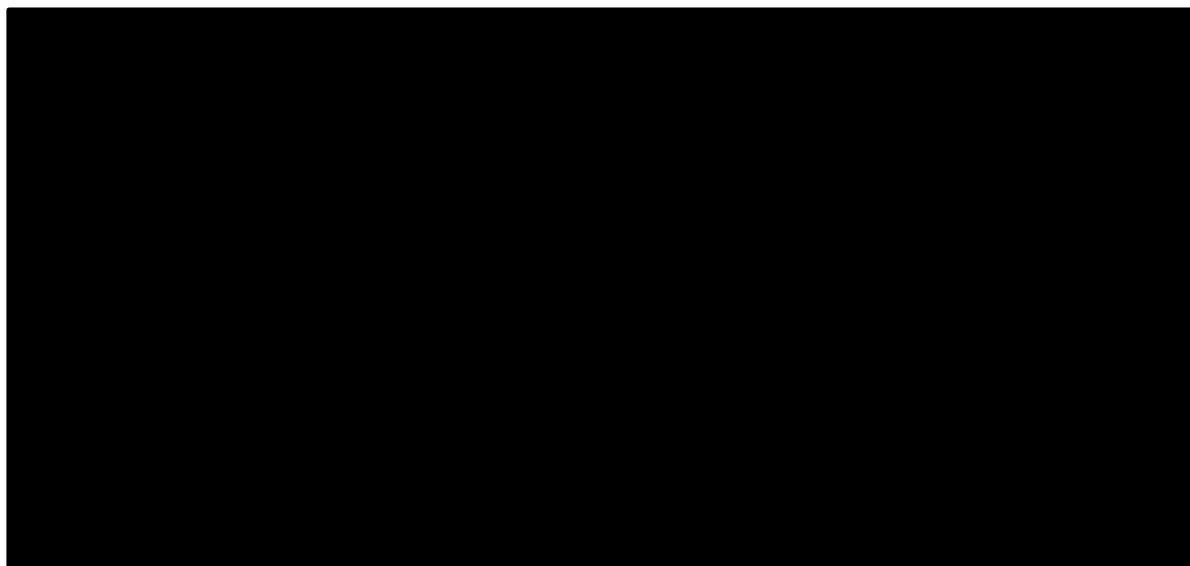
The results of the IPCW-adjusted analyses showed that the HRs for the FFS and OS were consistent with those derived in the unadjusted analyses. Table 3.15 below shows the comparison of results from the IPCW-adjusted and unadjusted analysis for the TRIANGLE trial. The associated K-M curves for the IPCW-adjusted analysis are presented in Figure 3.3 and Figure 3.4 below.

Table 3.15: Comparison of results from the IPCW-adjusted and unadjusted analysis (TRIANGLE; FAS)

Endpoint	IPCW-adjusted analysis	Unadjusted analysis
FFS, HR (95% CI)		
OS, HR (95% CI)		
Based on Table 19 of CS. ³		

Endpoint	IPCW-adjusted analysis	Unadjusted analysis
^a 98.33% CI. CI = confidence interval; CS = company submission; HR = hazard ratio; FAS = full analysis set; FFS = failure-free survival; IPCW = inverse probability of censoring weighting; OS = overall survival		

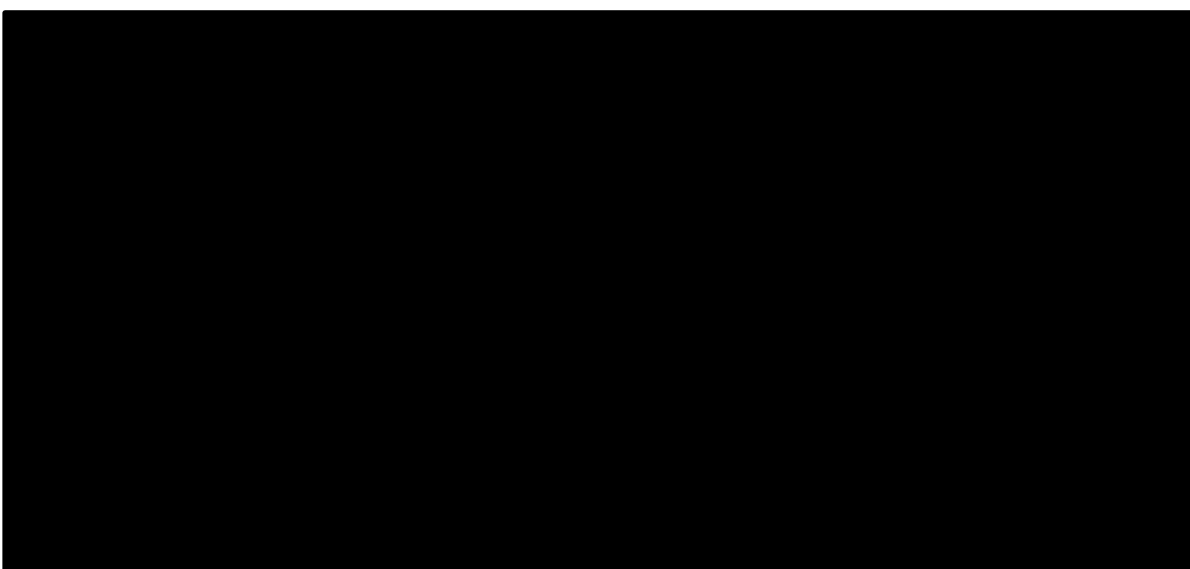
Figure 3.3: K-M plot for FFS (IPCW-adjusted analyses)



Based on Figure 10 of CS.³

ASCT = autologous stem cell transplant; CI = confidence interval; CS = company submission; FFS = failure-free survival; HR = hazard ratio; IPCW = inverse probability of censoring weighting; K-M = Kaplan-Meier; NA = not available

Figure 3.4: K-M plot for OS (IPCW-adjusted analyses)



Based on Figure 11 of CS³

ASCT = autologous stem cell transplant; CI = confidence interval; CS = company submission; HR = hazard ratio; IPCW = inverse probability of censoring weighting; K-M = Kaplan-Meier; NA = not available; OS = overall survival

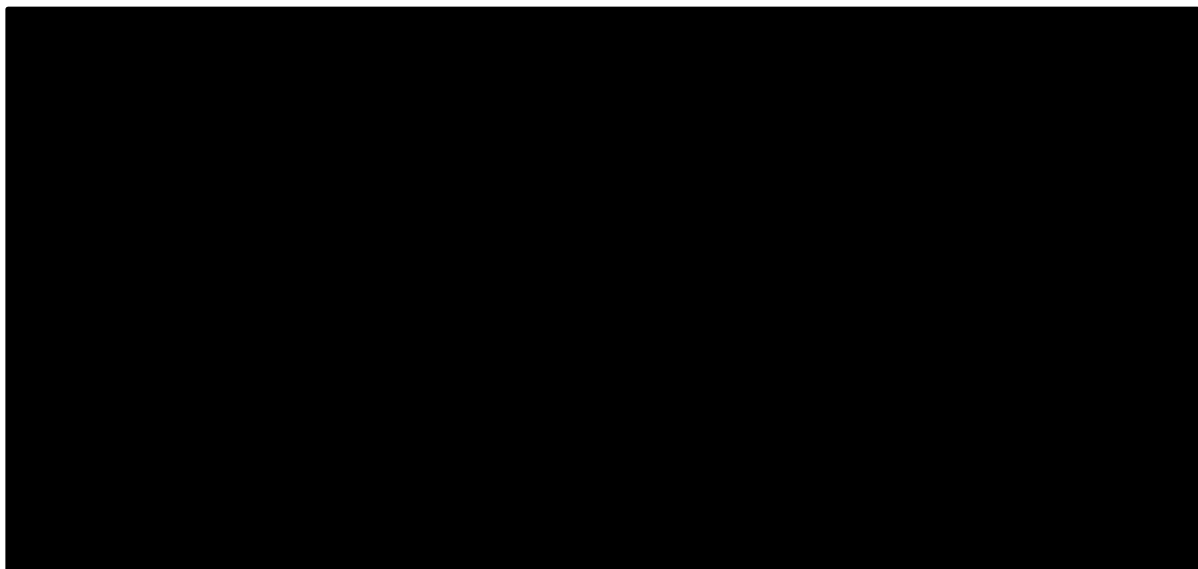
3.2.5.2 Results of IPCW-adjusted EAG requested sensitivity analyses

The EAG noted that for the IPCW-adjusted analysis in the CS, it is assumed that 85% of patients would receive rituximab maintenance therapy, which is stated to have been based on clinical expert opinion.³ However, the Advisory Board Report from November 2025, which the company refers to shows that the question posed to the clinical experts was whether or not the 85% was appropriate, as opposed to what the figure ought to be.¹⁶ Also, it appears from the responses from one of the experts that there might have been a misunderstanding of why the percentage was not 100%: one stated that it was based on the outcome of the LyMA trial, but this trial compared rituximab maintenance with no maintenance. Another stated that early progression might be the reason for less than 100%.¹⁷ Also, the ESMO and BSH guidelines both recommend rituximab maintenance. Therefore, the EAG asked the company to conduct a sensitivity analysis where 100% rituximab use is assumed. In responding to the EAG request, the company performed a sensitivity analysis where 100% rituximab use is assumed during the clarification stage. The company conducted the IPCW-adjusted sensitivity analyses where 100% of patients in both Arm I and Arm A of the TRIANGLE trial were simulated to receive rituximab maintenance. The results of the IPCW adjusted sensitivity analyses with the assumption of 100% rituximab use showed that the HRs of FFS and OS were generally consistent with those observed in the unadjusted analyses (see Table 3.16 and Figures 3.5 and Figure 3.6 below).

Table 3.16: Results from the IPCW-adjusted 100% rituximab use and unadjusted analysis (TRIANGLE; FAS)

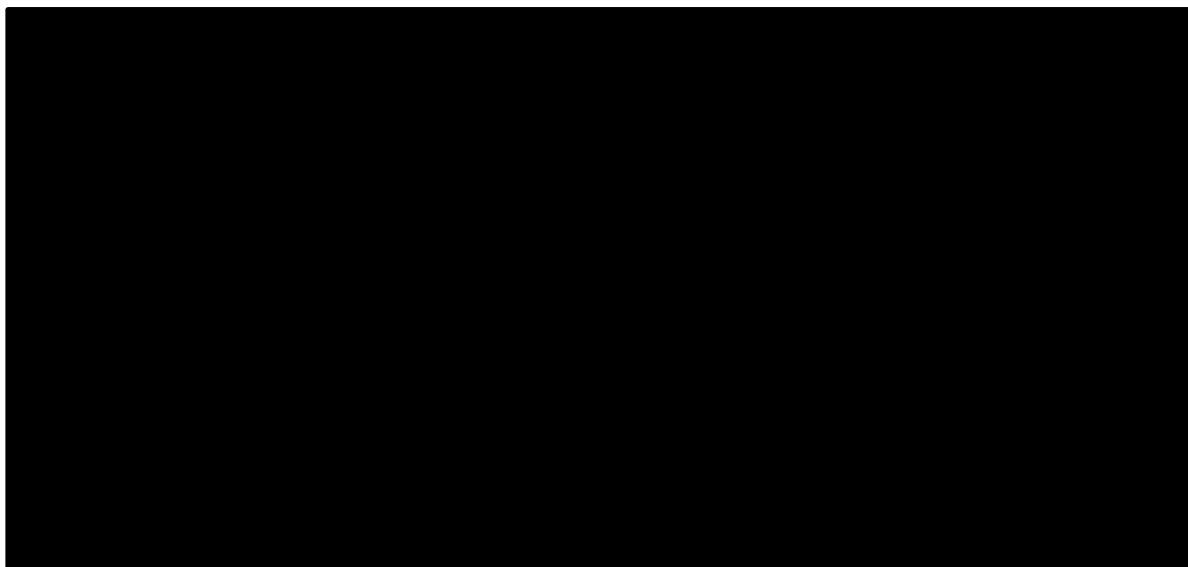
Endpoint	IPCW-adjusted analysis (100%)	Unadjusted analysis
FFS, HR (95% CI)		
OS, HR (95% CI)		
Based on Table 3 of company's clarification response. ⁸ CI = confidence interval; HR = hazard ratio; FAS = full analysis set; FFS = failure-free survival; IPCW = inverse probability of censoring weighting; OS = overall survival		

Figure 3.5: K-M plot for FFS (IPCW-adjusted analyses)



Based on Figure 1 of company's clarification response

ASCT = autologous stem cell transplant; CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; IPCW = inverse probability of censoring weighting; K-M = Kaplan-Meier; NA = not available

Figure 3.6: K-M plot for OS (IPCW-adjusted analyses)

Based on Figure 2 of company's clarification response

ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; IPCW = inverse probability of censoring weighting; K-M = Kaplan-Meier; NA = not available; OS = overall survival

3.2.5.3 Results of EAG requested two stage estimation analyses

The EAG considered that the need for adjustment for insufficient rituximab maintenance is analogous to treatment switching to a treatment that is not used in clinical practice for which IPCW is also used, although other methods are available and recommended in NICE Technical Support Document (TSD) 16.¹⁸ Therefore, the EAG asked the company to justify the use of IPCW as opposed to any other method of adjustment. The EAG also asked the company to consider using alternative statistical approaches (e.g. two-stage estimation [TSE] approach), given the analogy of the movement to maintenance in TRIANGLE with that to progression, which is often the basis for choosing this method. In responding to the EAG request, the company made the following statement:⁸

“NICE DSU Technical Support Document (TSD) 16 recommends rank-preserving structural failure time model (RPSFTM), inverse probability of censoring weighting (IPCW) and two stage estimation (TSE) as appropriate methods to address bias arising from treatment switching or deviations from the intended treatment pathway, with method selection driven by the nature of treatment switching and the plausibility of the underlying assumptions.

RPSFTM methods are best suited to simple, direct treatment switching patterns, typically involving switching from a control arm to a single active treatment. This is not the case in TRIANGLE, where adjustment for the lower proportion of patients receiving rituximab maintenance is required in both treatment arms, rendering this approach unsuitable.

TSE methods were considered appropriate in principle, assuming a clinically meaningful secondary baseline, and were therefore explored. The results of these analyses are presented in response to Question A6b), below. In TRIANGLE, the start of ibrutinib maintenance in Arm I and the start of ASCT in arm A were used as secondary baselines. However, implementation of TSE requires several additional modelling choices, including selection of parametric survival models for each treatment arm in stage 1 estimation of the acceleration factor, decisions regarding re-censoring versus no re-

censoring when deriving counterfactual survival, and identification and adjustment for time varying confounding at the secondary baseline, which introduce additional complexity and potential sensitivity.

IPCW was therefore selected as the primary method of adjustment, as it provides a more direct adjustment approach by censoring at the potential start time of receiving rituximab maintenance treatment and re weighting the remaining patients with similar characteristics (both baseline and time-varying), thereby preserving the randomised cohorts. Relevant baseline and time varying covariates were available in TRIANGLE and a sufficient number of patients continued rituximab maintenance in TRIANGLE to support stable and reliable weight estimation.”

In responding to the EAG’s request, the company used the TSE approach to perform statistical adjustment for the analyses of the TRIANGLE trial during the clarification stage. The company stated that TSE analyses were performed by assuming the same parametric distribution for both treatment Arms, as well as by using the same set of prognostic factors as the IPCW analyses presented in the CS.⁸ The company stated that TSE was implemented using the start of ibrutinib maintenance in Arm I and the start of ASCT in Arm A as the secondary baseline. In stage 1, parametric accelerated failure time (AFT) models were fitted from the secondary baseline, adjusting for prognostic factors, to estimate the acceleration factor associated with receiving rituximab maintenance versus not receiving rituximab maintenance. In stage 2, observed post-secondary baseline survival times for patients who did not receive rituximab maintenance were replaced with counterfactual survival times derived from the stage 1 model, and added to the observed time to secondary baseline. The adjusted treatment effect was then estimated by fitting a Cox proportional hazards (PH) model using these counterfactual outcomes with randomised treatment as a covariate. The results of TSE analyses showed that these results of HRs for FFS and OS were generally consistent with those results of the IPCW analyses presented in the CS. The TSE-adjusted analyses results are presented in Table 3.17 below.

Table 3.17: TSE-adjusted analyses results (TRIANGLE; FAS)

Endpoint	85% R-maintenance setting adjustment methods	HR (95% CI), p-value
FFS	IPCW	
	TSE Exponential	
	TSE Weibull	
	TSE Gamma	
	TSE Log-logistic	
	TSE Log-normal	
OS	IPCW	
	TSE Exponential	
	TSE Weibull	
	TSE Gamma	
	TSE Log-logistic	
	TSE Log-normal	
Based on Table 4 of company’s clarification response. ⁸ CI = confidence interval; FAS = full analysis set; FFS = failure-free survival; HR = hazard ratio; IPCW = inverse probability of censoring weighting; OS = overall survival; TSE = two stage estimation		

In conclusion, the EAG considered the IPCW approach used by the company for statistical adjustment for insufficient rituximab maintenance in the TRIANGLE trial to be appropriate and adequately

justified. In responding to the EAG's request, the company also used the TSE approach to perform statistical adjustment for the analyses of the TRIANGLE trial during the clarification stage. The results of IPCW analyses, assuming 100% rituximab maintenance and the TSE analyses showed that these results of HRs for PFS and OS were generally consistent with those results of the IPCW analyses assuming 85% presented in the CS. Generally, both the IPCW sensitivity analyses with the assumption of 100% rituximab use and the TSE analyses demonstrated that the results of IPCW primary analyses presented in the CS were reasonably robust, and that the HRs for FFS and OS might plausibly lie in a range between [REDACTED] and [REDACTED], respectively. It is likely that there is little variation in the HRs because the percentage use of rituximab in the trial was similar between the Arms. The IPCW method and 85% use causes only the HR of FFS to change (small decrease), and most of the other methods/assumptions (including IPCW with 100% use and TSE except exponential for FFS) cause the HR to increase. However, the direction of the effect is made more difficult to predict because, although subgroup analyses showed a clear increase in the HR for FFS with rituximab maintenance, the effect of rituximab is probably biased by the choice to use it being made after induction/consolidation. Therefore, although there is little variation in HRs, there is some uncertainty as to the best method for adjustment, which makes this a Key Issue.

3.2.6 Subgroup analysis

The company stated that:³ *“Subgroup analyses demonstrated that FFS results in the FAS were consistent across almost all subgroups. Most analyses demonstrated that the ibrutinib regimen (Arm I) was associated with at least numerical improvements in FFS vs. the ASCT regimen (Arm A), with the exception of patients in Arm I with a blastoid or pleomorphic MCL who did not show a difference in treatment effect in comparison to patients in Arm A. Given that the study was not powered to detect differences in subgroups and owing to the small patients numbers associated with these subgroups however, these results should be interpreted with caution (29 in Arm I and 27 Arm A, respectively).”*

EAG comment: The EAG agrees that there are no obvious differences between subgroups, although the sample size of some groups was small. It is worth noting that there was a substantial difference in the HR for FFS between with and without rituximab maintenance i.e. 0.810 (95% CI 0.489 – 1.342) and 0.469 (0.305 – 0.723). This might suggest that increased use of rituximab maintenance would reduce advantage to ibrutinib over ASCT. However, the choice of maintenance was made after randomisation, specifically after induction/consolidation and is therefore the effect is probably biased. Therefore, the effect of adjustment for rituximab maintenance (see Section 3.2.5) is made more difficult to predict.

3.2.7 Adverse events

3.2.7.1 Treatment duration and dosage

Treatment duration was considerably greater for Arm I than Arm A (median of 28.45 months for patients in Arm I versus 5.16 months for patients in Arm A).³ The company provided further details of treatment duration and dosage in Section 2.12.1 of the CS.

3.2.7.2 Summary of treatment-emergent adverse events

The number of treatment emergent adverse events (TEAEs) during the induction phase was 259 (97.7%) in Arm I and 262 (97.8%) in Arm A. There were 228 (86%) grade ≥ 3 in Arm I compared to 220 (82.1%) in Arm A. There were 119 (44.9%) serious TEAEs in Arm I compared to 110 (41.0%) in Arm A. There was 1 (0.4%) TEAE leading to death in Arm I, compared to 3 (1.1%) in Arm A.

Table 3.18: Summary of TEAEs during the induction phase (SAS)

TEAEs, n (%)	Arm I N=265	Arm A N=268
Any TEAE	259 (97.7%)	262 (97.8%)
Grade ≥ 3	228 (86.0%)	220 (82.1%)
Ibrutinib-related ^a	148 (55.8%)	-
Any serious TEAE	119 (44.9%)	110 (41.0%)
Grade ≥ 3	90 (34.0%)	89 (33.2%)
Ibrutinib-related ^a	22 (8.3%)	-
TEAEs leading to death ^b	1 (0.4%)	3 (1.1%)
Within 30 days of last dose of study treatment	1 (0.4%)	0
TEAE leading to ibrutinib discontinuation ^c	13 (4.9%)	-
TEAE leading to ibrutinib dose reduction ^c	10 (3.8%)	-
Source: Table 21, CS. ³ ^a An AE is categorised as related if assessed by the investigator as related or not related to Ibrutinib. The causal relationship of an AE to study treatment was only collected for ibrutinib. ^b AEs leading to death are based on AE outcome of fatal. This includes patients with fatal TEAEs and date of death >30 days after EOT. ^c Data are not reported for Arm A. AE = adverse event; CS = company submission; EOT = end of treatment; SAS = safety analysis set; TEAE = treatment-emergent adverse event		

Table 3.19 provides a summary of TEAEs for the overall study period. There were 263 (99.2%) TEAEs in Arm I compared to 267 (99.6%) in Arm A. There were a greater number of serious TEAEs in Arm I (171, 64.5%) compared to Arm A (123, 45.9%). There was a greater number of serious TEAEs grade ≥ 3 in Arm I (146, 55.1%) compared to Arm A (105, 39.2%). There were 6 (2.3%) TEAEs leading to death in Arm I compared to 11 (4.1%) in Arm A.

Table 3.19: Summary of TEAEs (SAS) – overall study period

TEAEs, n (%)	Arm I N=265	Arm A N=268
Any TEAE	263 (99.2%)	267 (99.6%)
Grade ≥ 3	247 (93.2%)	250 (93.3%)
Ibrutinib-related ^a	212 (80.0%)	-
Any serious TEAE	171 (64.5%)	123 (45.9%)
Grade ≥ 3	146 (55.1%)	105 (39.2%)
Ibrutinib-related ^a	50 (18.9%)	-
TEAE leading to death ^b	6 (2.3%)	11 (4.1%)
Within 30 days of last dose of study treatment	4 (1.5%)	5 (1.9%)
TEAE leading to ibrutinib discontinuation ^c	61 (23.0%)	-
TEAE leading to ibrutinib dose reduction ^c	43 (16.2%)	-
COVID-19 TEAE	52 (19.6%)	5 (1.9%)
COVID-19 serious TEAE	23 (8.7%)	4 (1.5%)
COVID-19 TEAE leading to death	4 (1.5%)	2 (0.7%)

TEAEs, n (%)	Arm I N=265	Arm A N=268
Source: Table 22, CS. ³		
^a An AE is categorised as related if assessed by the investigator as related or not related to ibrutinib. The causal relationship of an AE to study treatment was only collected for ibrutinib.		
^b AEs 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.		
^c Data are not reported for Arm A.		
AE = adverse event; CS = company submission; EOT = end of treatment; SAS = safety analysis set; TEAE = treatment-emergent adverse event		

3.2.7.3 Most common TEAEs

Table 3.20 provides a summary of common TEAEs. There were fewer blood and lymphatic symptom disorders in Arm I (199, 75.1%) compared to Arm A (221, 82.5%). There was a greater number of infections and infestations in Arm I (186, 70.2%) compared to Arm A (137, 51.1%). There were fewer general disorders and administration site conditions in Arm I (144, 54.3%) compared to Arm A (175, 65.3%). There was a similar number of investigations across the two groups 153 (57.7%) versus 155 (57.8%) in Arm I and Arm A, respectively. There was a greater number of nervous system disorders in Arm I (135, 50.9%) compared to Arm A (104, 38.8%). There was a greater number of skin and subcutaneous tissue disorders in Arm I (91, 34.3%) compared to Arm A (51, 19.0%). There was a greater number of respiratory, thoracic, and mediastinal disorders in Arm I (83, 31.3%) compared to Arm A (63, 23.5%). There was a greater number of metabolism and nutrition disorders in Arm A compared to Arm I. There was a greater number of musculoskeletal and connective tissue disorders, vascular disorders, renal and urinary disorders, cardiac disorders, injury, poisoning, and procedural complications and ear and labyrinth disorders in Arm I compared to Arm A.

Table 3.20: Summary of most common (≥10.0%) TEAEs (SAS)

TEAE, n (%)	Arm I N=265	Arm A N=268
	All grade	All grade
Blood and lymphatic system disorders	199 (75.1%)	221 (82.5%)
Anaemia	119 (44.9%)	155 (57.8%)
Neutropenia	112 (42.3%)	110 (41.0%)
Thrombocytopenia	105 (39.6%)	121 (45.1%)
Febrile neutropenia	37 (14.0%)	71 (26.5%)
Leukopenia	33 (12.5%)	37 (13.8%)
Infections and infestations	186 (70.2%)	137 (51.1%)
Pneumonia	27 (10.2%)	14 (5.2%)
COVID-19	37 (14.0%)	3 (1.1%)
Gastrointestinal disorders	169 (63.8%)	190 (70.9%)
Nausea	84 (31.7%)	105 (39.2%)
Diarrhoea	75 (28.3%)	78 (29.1%)
Vomiting	49 (18.5%)	47 (17.5%)
Constipation	44 (16.6%)	49 (18.3%)
Stomatitis	24 (9.1%)	42 (15.7%)

TEAE, n (%)	Arm I N=265	Arm A N=268
	All grade	All grade
General disorders and administration site conditions	144 (54.3%)	175 (65.3%)
Pyrexia	57 (21.5%)	89 (33.2%)
Mucosal inflammation	22 (8.3%)	74 (27.6%)
Fatigue	46 (17.4%)	31 (11.6%)
Investigations	153 (57.7%)	155 (57.8%)
Platelet count decreased	87 (32.8%)	91 (34.0%)
Neutrophil count decreased	68 (25.7%)	65 (24.3%)
White blood cell count decreased	24 (9.1%)	38 (14.2%)
Blood creatinine increased	42 (15.8%)	32 (11.9%)
Nervous system disorders	135 (50.9%)	104 (38.8%)
Headache	29 (10.9%)	28 (10.4%)
Peripheral sensory neuropathy	28 (10.6%)	14 (5.2%)
Paraesthesia	28 (10.6%)	14 (5.2%)
Skin and subcutaneous tissue disorders	91 (34.3%)	51 (19.0%)
Rash	36 (13.6%)	15 (5.6%)
Respiratory, thoracic, and mediastinal disorders	83 (31.3%)	63 (23.5%)
Cough	33 (12.5%)	12 (4.5%)
Metabolism and nutrition disorders	89 (33.6%)	96 (35.8%)
Hypokalaemia	37 (14.0%)	43 (16.0%)
Musculoskeletal and connective tissue disorders	85 (32.1%)	57 (21.3%)
Vascular disorders	65 (24.5%)	60 (22.4%)
Hypertension	33 (12.5%)	21 (7.8%)
Renal and urinary disorders	68 (25.7%)	56 (20.9%)
Acute kidney injury	29 (10.9%)	31 (11.6%)
Cardiac disorders	54 (20.4%)	22 (8.2%)
Injury, poisoning, and procedural complications	55 (20.8%)	32 (11.9%)
Ear and labyrinth disorders	39 (14.7%)	27 (10.1%)
Source: Table 23, CS. ³		
CS = company submission; SAS = safety analysis set; TEAEs = treatment-emergent adverse events		

3.2.7.4 Most common TEAEs related to ibrutinib

A summary of the most frequently reported TEAEs related to ibrutinib, defined as occurring in $\geq 5.0\%$ of patients, is provided in Table 3.21. Overall, 80.0% of patients in Arm I experienced an ibrutinib-related AE. No fatal AEs related to ibrutinib were observed in Arm I.³

Table 3.21: Summary of most common ($\geq 5.0\%$) TEAEs related to ibrutinib (SAS)

TEAE, n (%)	Arm I N=265
	All grade
Blood and lymphatic system disorders	103 (38.9%)
Anaemia	40 (15.1%)
Neutropenia	61 (23.0%)
Thrombocytopenia	29 (10.9%)
Infections and infestations	65 (24.5%)
Pneumonia	13 (4.9%)
Gastrointestinal disorders	35 (13.2%)
Nausea	14 (5.3%)
Diarrhoea	24 (9.1%)
General disorders and administration site conditions	37 (14.0%)
Investigations	66 (24.9%)
Platelet count decreased	20 (7.5%)
Neutrophil count decreased	30 (11.3%)
White blood cell count decreased	57 (21.5%)
Nervous system disorders	36 (13.6%)
Skin and subcutaneous tissue disorders	49 (18.5%)
Rash	19 (7.2%)
Respiratory, thoracic, and mediastinal disorders	25 (9.4%)
Metabolism and nutrition disorders	14 (5.3%)
Musculoskeletal and connective tissue disorders	42 (15.8%)
Muscle spasms	17 (6.4%)
Vascular disorders	24 (9.1%)
Hypertension	14 (5.3%)
Cardiac disorders	27 (10.2%)
Atrial fibrillation	19 (7.2%)
Source: Table 24, CS. ³	
CS = company submission; SAS = safety analysis set; TEAE = treatment-emergent adverse event	

3.2.7.5 Serious adverse events

Table 3.22 provides a summary of treatment-emergent serious adverse events (TESAEs). There were similar numbers of blood and lymphatic system disorders across the two groups (30, 12.5% Arm I versus 30, 11.2% Arm A). There was a greater number of grade ≥ 3 infections and infestations (72, 27.2% in Arm I versus 36, 13.4% in Arm A) and grade 3/4 (56, 21.1% in Arm I versus 27, 10.1% in Arm A). There were similar numbers of grade 5 in Arm I (4, 1.5%) versus Arm A (6, 2.2%). There were similar results for both groups for grade ≥ 3 and grade 3/4 gastrointestinal disorders however a greater number of grade 5 in Arm A (4, 1.5%) versus Arm I (0, 0.0%). There was a greater number of general disorders and administration site conditions in Arm I versus Arm A for grade ≥ 3 (18, 6.8% versus 13, 4.9%) however a similar number of grade 3/4 across the two groups and a 1 grade 5 in Arm A and 0 in

Arm I. There was a similar number of investigations across the groups. There was a greater number of nervous system disorders in Arm I versus Arm A for grade ≥ 3 (14, 5.3% versus 7, 2.6%) and grade 3/4 (11, 4.2% versus 5, 1.9%). There was a smaller number of respiratory, thoracic, and mediastinal disorders in Arm I versus Arm A for grade ≥ 3 (3, 1.1% versus 7, 2.6%) and grade 3/4 (2, 0.8% versus 5, 1.9%). There were 2 (0.7%) grade 5 events in Arm A compared to 0 in Arm I. There were similar results across both groups for metabolism and nutrition disorders. There were more events of grade 3/4 Vascular disorders in Arm I versus Arm A (4, 1.5% versus 1, 0.4%) whilst all other results were the same across groups. There was a greater number of grade ≥ 3 renal and urinary disorders in Arm I versus Arm A (25, 9.4% versus 20, 7.5%) and grade 3/4 (13, 4.9% versus 7, 2.6%). There was 1 grade 5 event in Arm A versus 0 in Arm I. There was a greater number of cardiac disorders in Arm I versus Arm A (grade ≥ 3 ; 19, 7.2% versus 4, 1.5%. grade 3/4; 11, 4.2% versus 3, 1.1%, grade 5; 1, 0.4% versus 0, 0.0%). There was also a greater number of injury, poisoning, and procedural complications and neoplasms benign, malignant and unspecified (including cysts and polyps) in Arm I versus Arm A.

Table 3.22: Summary of TESAEs (SAS)

TESAE, n (%)	Arm I N=265			Arm A N=268		
	Grade ≥ 3	Grade 3/4	Grade 5	Grade ≥ 3	Grade 3/4	Grade 5
Blood and lymphatic system disorders	33 (12.5%)	33 (12.5%)	0	30 (11.2%)	30 (11.2%)	0
Thrombocytopenia	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	6 (2.2%)	0
Febrile neutropenia	28 (10.6%)	28 (10.6%)	0	19 (7.1%)	19 (7.1%)	0
Infections and infestations	72 (27.2%)	56 (21.1%)	4 (1.5%)	36 (13.4%)	27 (10.1%)	6 (2.2%)
Pneumonia	11 (4.2%)	9 (3.4%)	0	8 (3.0%)	7 (2.6%)	1 (0.4%)
COVID-19	12 (4.5%)	9 (3.4%)	2 (0.8%)	3 (1.1%)	2 (0.7%)	1 (0.4%)
Sepsis	2 (0.8%)	2 (0.8%)	0	6 (2.2%)	3 (1.1%)	3 (1.1%)
COVID-19 pneumonia	10 (3.8%)	7 (2.6%)	2 (0.8%)	1 (0.4%)	0	1 (0.4%)
Device related infection	0	0	0	1 (0.4%)	1 (0.4%)	0
Herpes zoster	1 (0.4%)	1 (0.4%)	0	0	0	0
Gastrointestinal disorders	21 (7.9%)	17 (6.4%)	0	23 (8.6%)	16 (6.0%)	4 (1.5%)
Diarrhoea	2 (0.8%)	2 (0.8%)	0	3 (1.1%)	2 (0.7%)	0
Vomiting	9 (3.4%)	7 (2.6%)	0	4 (1.5%)	3 (1.1%)	0
General disorders and administration site conditions	18 (6.8%)	8 (3.0%)	0	13 (4.9%)	7 (2.6%)	1 (0.4%)
Pyrexia	8 (3.0%)	2 (0.8%)	0	8 (3.0%)	4 (1.5%)	0
Investigations	11 (4.2%)	5 (1.9%)	0	11 (4.1%)	7 (2.6%)	0
Platelet count decreased	0	0	0	6 (2.2%)	6 (2.2%)	0

TESAE, n (%)	Arm I N=265			Arm A N=268		
	Grade ≥3	Grade 3/4	Grade 5	Grade ≥3	Grade 3/4	Grade 5
Blood creatinine increased	5 (1.9%)	0	0	4 (1.5%)	0	0
Nervous system disorders	14 (5.3%)	11 (4.2%)	0	7 (2.6%)	5 (1.9%)	0
Respiratory, thoracic, and mediastinal disorders	3 (1.1%)	2 (0.8%)	0	7 (2.6%)	5 (1.9%)	2 (0.7%)
Metabolism and nutrition disorders	11 (4.2%)	11 (4.2%)	0	11 (4.1%)	11 (4.1%)	0
Vascular disorders	5 (1.9%)	4 (1.5%)	0	5 (1.9%)	1 (0.4%)	0
Renal and urinary disorders	25 (9.4%)	13 (4.9%)	0	20 (7.5%)	7 (2.6%)	1 (0.4%)
Acute kidney injury	18 (6.8%)	10 (3.8%)	0	14 (5.2%)	4 (1.5%)	1 (0.4%)
Renal failure	5 (1.9%)	2 (0.8%)	0	4 (1.5%)	2 (0.7%)	0
Cardiac disorders	19 (7.2%)	11 (4.2%)	1 (0.4%)	4 (1.5%)	3 (1.1%)	0
Atrial fibrillation	12 (4.5%)	8 (3.0%)	0	1 (0.4%)	1 (0.4%)	0
Injury, poisoning, and procedural complications	7 (2.6%)	6 (2.3%)	0	4 (1.5%)	3 (1.1%)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (1.9%)	4 (1.5%)	1 (0.4%)	1 (0.4%)	0	1 (0.4%)
Source: Table 25, CS. ³ CS = company submission; SAS = safety analysis set; TEAE = treatment-emergent adverse event						

3.2.7.6 Adverse events of special interest – haemorrhage

There was a similar number of haemorrhage events across the two groups (see Table 3.23).

Table 3.23: Incidence of treatment-emergent major haemorrhagic events (SAS)

AESI, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Subjects with any treatment-emergent major haemorrhage events	10 (3.8%)	8 (3.0%)	0	9 (3.4%)	8 (3.0%)	1 (0.4%)
Gastrointestinal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Catheter site haemorrhage	2 (0.8%)	2 (0.8%)	0	0	0	0
Epistaxis	3 (1.1%)	3 (1.1%)	0	3 (1.1%)	3 (1.1%)	0
Gastric haemorrhage	0	0	0	1 (0.4%)	0	1 (0.4%)

AE SI, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Anal haemorrhage	1 (0.4%)	0	0	0	0	0
Blood loss anaemia	0	0	0	1 (0.4%)	1 (0.4%)	0
Haematoma	3 (1.1%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Haemorrhage intracranial	1 (0.4%)	1 (0.4%)	0	0	0	0
Intestinal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Rectal haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Subarachnoid haemorrhage	0	0	0	1 (0.4%)	1 (0.4%)	0
Source: Table 26, CS. ³						
AE SI = adverse event of special interest; CS = company submission; SAS = safety analysis set						

3.2.7.7 Other significant AEs

Table 3.24 provides a summary of other significant AEs. There was a greater number of atrial fibrillations in Arm I versus Arm A for all grades (26, 9.8% versus 6, 2.2%) and grade 3/4 (10, 3.8% versus 5, 1.9%). There was a greater number of all grades, other cardiac arrhythmia (excluding atrial fibrillation) in Arm I versus Arm A (34, 12.8% versus 24, 9%). However, the same number of grade 3/4 and 1 grade 5 in Arm A and 0 in Arm I. There was a greater number of hypertension events (all grades) in Arm I versus Arm A (36, 13.6% versus 24, 9.0%), numbers of events for the other grades were equivalent. There was a greater number of interstitial lung disease (all grades) in Arm I versus Arm A (12, 4.5% versus 1, 0.4%), the other grades were equivalent. There were fewer cytopenic AEs in Arm I versus Arm A (all grades; 224, 84.5% versus 233, 86.9%. grade 3/4; 209, 78.9% versus 225, 84.0%). There was a [REDACTED] number of tumour lysis syndrome events in Arm I versus Arm A (all grades; [REDACTED]% versus [REDACTED]%. grade 3/4; [REDACTED]% versus [REDACTED]%). There was a greater number of infections in Arm I versus Arm A (all grades; 186, 70.2% versus 137, 51.1%, grade 3/4; 72, 27.2% versus 56, 20.9%) although similar number of grade 5 (Arm I: 4, 1.5% versus Arm A: 6, 2.2%).

Table 3.24: Incidence of other significant AEs (SAS)

Significant AE, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Cardiac arrhythmias						
Atrial fibrillation	26 (9.8%)	10 (3.8%)	0	6 (2.2%)	5 (1.9%)	0
Other cardiac arrhythmia (excluding atrial fibrillation)	34 (12.8%)	7 (2.6%)	0	24 (9.0%)	7 (2.6%)	1 (0.4%)
Cardiac failure	5 (1.9%)	0	0	3 (1.1%)	1 (0.4%)	0
Hypertension	36 (13.6%)	14 (5.3%)	0	24 (9.0%)	12 (4.5%)	0
Interstitial lung disease	12 (4.5%)	2 (0.8%)	0	1 (0.4%)	1 (0.4%)	0
Ischemic stroke	2 (0.8%)	0	0	2 (0.7%)	0	0
Cytopenic AEs	224 (84.5%)	209 (78.9%)	0	233 (86.9%)	225 (84.0%)	0
Tumour lysis syndrome	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Significant AE, n (%)	Arm I N=265			Arm A N=268		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Hepatotoxicity including hepatic failure	5 (1.9%)	0	0	2 (0.7%)	0	0
Infections	186 (70.2%)	72 (27.2%)	4 (1.5%)	137 (51.1%)	56 (20.9%)	6 (2.2%)
Source: Table 27, CS. ³ AE = adverse event; CS = company submission; SAS = safety analysis set						

3.2.7.8 Deaths

There was a total of 93 deaths, with 60 (22.4%) in Arm A compared 33 (12.5%) in Arm I to 30 (11.2%) deaths in Arm A and 14 (5.3%) in Arm I were attributed to PD. There were 4 (1.5%) COVID-19 related deaths in Arm I and 2 (0.7%) in Arm A.

Table 3.25: Number of deaths (SAS)

	Arm I (n=265)	Arm A (n=268)
Deaths n (%)	33 (12.5%)	60 (22.4%)
Deaths attributed to PD n (%)	14 (5.3%)	30 (11.2%)
COVID-19 related deaths n (%)	4 (1.5%)	2 (0.7%)
Based on CS, Table 224 and Section 2.12.8. ³ CS = company submission; PD = progressed disease		

EAG comment: The company concluded that increased exposure with similar AE rates indicates greater tolerability of ibrutinib than ASCT:³ “*Safety data from TRIANGLE demonstrate that the ibrutinib regimen is associated with an improved tolerability profile; patients can be exposed to the ibrutinib regimen for five times as long before experiencing a similar toxicity profile to the ASCT regimen, thus alleviating the substantial HRQoL burden associated with existing treatment.*” Indeed, treatment duration was considerably greater for Arm I than Arm A (median of 28.45 months for patients in Arm I versus 5.16 months for patients in Arm A). However, the EAG note that the CSR shows that treatment duration in Arm A+I was almost identical to Arm I, at a median of 29.21 months. Therefore, although it is plausible that, as well as increased survival, HRQoL is improved, but it is unclear what the role of ASCT toxicity is in this. Also, although AEs were equivalent across a number of types, the EAG note there were some AEs where numbers were greater in Arm I compared to Arm A. These include serious TEAEs, grade ≥ 3 TEAEs, COVID-19 TEAEs, infections and infestations, nervous system disorders, skin and subcutaneous disorders and cardiac disorders. The EAG note a higher incidence of infection and infestations might be because of a drop in white blood cells (neutropenia),¹⁹ although rates of neutropenia were almost identical between Arms. The company state that the higher rate of COVID-19 in Arm I was explained by the fact that: “*a high proportion of patients had already completed the approximate 5 months of study treatment in Arm A before March 2020, while study treatment was still ongoing for patients in Arm I, who received study treatment with up to 2 years ibrutinib maintenance, with or without rituximab maintenance.*” However, the EAG understands that COVID-19 and infection events generally were counted over the whole study follow-up, which was a median of ■■■ months and ■■■ months for Arm I and Arm A, respectively. Therefore, patients in Arm A would have continue to have been exposed to the risk of infection with no obvious reason why the amount of exposure would differ between Arms other than due to differences in survival.

Given the observation of worse AE profile for Arm I despite the argument that ASCT is best avoided because of its toxicity, following a meeting with the EAG clinical expert, in an email the EAG asked the EAG clinical expert: “You mentioned that ibrutinib can be quite toxic (my interpretation of what you said):

- *How do you think that ibrutinib and ASCT compare in terms of toxicity or adverse event profile?*
- *What do you think are the implications for this toxicity/those adverse events for quality of life?”*

The EAG clinical expert replied: “Ibrutinib –

Cardiac toxicities around 10% at 3 years – arrhythmias and vascular e.g. hypertension

Infections – risk continues throughout time on Ibrutinib (so 30 months)

Other toxicities – easy bruising near universal, at one level trivial, but another level patients need to be aware of not knocking hands etc, how they do activities, wearing gloves...

Continue throughout 30 months and persist for a while after maintenance stops

ASCT –

Upfront toxicities (mortality 1-2%, in patient stay, 3-month recovery to full health) but then only the toxicities from Rituximab maintenance alone – smaller increase in infection risk, little else.

QOL difficult to compare:

ASCT high up-front burden on QOL, for which patients are counselled extensively, but may be better than Arm I 6 months post ASCT for some patients. Certainly at 12 months.

Overall QOL is generally good I would say, with fewer than 10% in each arm having a long-term toxicity of treatment.”

This seems to be consistent with what was observed in TRIANGLE i.e. the toxic effects of ASCT are potentially serious and include mortality, but short-term, whereas the those of ibrutinib are longer term and likely to reduce HRQoL. In conclusion, lack of measurement of HRQoL, increased rate of some AEs and the doubtful interpretation of increased treatment duration means that there is uncertainty as to the effect of ibrutinib on HRQoL, which is highlighted as a Key Issue.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

There was no indirect treatment comparison (ITC). **EAG comment:** Not applicable.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

There was no ITC.

EAG comment: The EAG consider that an ITC was unnecessary given that the TRIANGLE trial provide an adequate source of comparative evidence for the intervention and the only relevant comparator in the scope (see Section 2.3). This is notwithstanding the potential discrepancy between the proportion of patients who might receive rituximab maintenance in UK clinical practice and who received it in TRIANGLE (see Section 2.3), and the appropriate method of adjustment (see Section 3.2).

3.5 Additional work on clinical effectiveness undertaken by the EAG

None undertaken.

3.6 Conclusions of the clinical effectiveness Section

The CS, Appendices and response to clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on ibrutinib with R-CHOP for untreated MCL when an ASCT is suitable.^{3,8,14} Searches were conducted on 13 September 2024, and updated on 9 May 2025 and 30 October 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of bibliographic databases, conference proceedings and trials registers were searched. Although the EAG has recorded comments and observations in the sections above, overall, the EAG has no major concerns about the literature searches conducted.

The main source of clinical effectiveness evidence is the TRIANGLE trial, which is a randomised, open-label, three-Arm, parallel group, study conducted in multiple sites across Europe and Israel in patients ≥ 18 years of age and ≤ 65 years of age with untreated MCL, eligible for ASCT. Patients randomised to the following treatment Arms in a 1:1:1 ratio:

- Arm I: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)/rituximab, dexamethasone, high-dose cytarabine and cisplatin (R-DHAP or rituximab, dexamethasone, high-dose cytarabine and oxaliplatin [R-DHAOX]) with ibrutinib followed by 2-years of ibrutinib maintenance $\pm$ rituximab
- Arm A: R-CHOP/R-DHAP followed by HDT-ASCT $\pm$ rituximab maintenance
- Arm A+I: R-CHOP/R-DHAP with ibrutinib followed by HDT-ASCT and 2-years of ibrutinib maintenance $\pm$ rituximab

The company presented results for a comparison of two Arms only, I and A on the basis that they are the intervention and comparator in the DP, and that A+I is not licensed in the UK (see Sections 2.2 and 2.3 for a discussion of any related issues). The EAG consider that the trial was well designed, and the EAG considered that the population was generalisable to the population in the DP: although some RWE provided by the company showed that there was a higher proportion of male patients, subgroup analyses showed little effect of sex on the primary outcome, FFS. Although median FFS, OS and PFS were not reached for either Arm, there was a significant decrease in the rate of all three events in Arm I versus Arm A, at a median follow-up of [REDACTED] and [REDACTED] months, respectively.

Statistical adjustment for rituximab maintenance to estimate the effect of higher use in clinical practice was performed using the IPCW method, as recommended in NICE TSD 16 for treatment switching. The EAG considered the IPCW approach used by the company for statistical adjustment for insufficient rituximab maintenance in the TRIANGLE trial to be appropriate and adequately justified. In responding to the EAG's request, the company also used the TSE approach to perform statistical adjustment for the analyses of the TRIANGLE trial during the clarification stage. The results of IPCW analyses, assuming 100% rituximab maintenance and the TSE analyses showed that these results of HRs for PFS and OS were generally consistent with those results of the IPCW analyses assuming 85% presented in the CS. Therefore, both the IPCW sensitivity analyses with the assumption of 100% rituximab use and the TSE analyses demonstrated that the results of IPCW primary analyses presented in the CS were robust, and that the HRs for FFS and OS might plausibly lie in a range between [REDACTED] and [REDACTED] respectively.

One of the main advantages of ibrutinib according to the company is that ASCT can be avoided without any loss of efficacy, and this does seem to be demonstrated in TRIANGLE. Unfortunately, no HRQoL data were collected in TRIANGLE, although the company argues that the avoidance of ASCT by use of ibrutinib is likely to enhance HRQoL given the toxicity associated with ASCT. The company suggest that increased exposure with similar AE rates indicates greater tolerability of ibrutinib than ASCT: *“Safety data from TRIANGLE demonstrate that the ibrutinib regimen is associated with an improved tolerability profile; patients can be exposed to the ibrutinib regimen for five times as long before experiencing a similar toxicity profile to the ASCT regimen, thus alleviating the substantial HRQoL burden associated with existing treatment.”* Indeed, treatment duration was considerably greater for Arm I than Arm A (median of 28.45 months for patients in Arm I versus 5.16 months for patients in Arm A). However, the EAG note that the CSR shows that treatment duration in Arm A+I was almost identical to Arm I, at a median of 29.21 months. Therefore, although it is plausible that, as well as increased survival, HRQoL is improved, but there is little evidence to support this.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

4.1.1 *Searches performed for cost effectiveness Section*

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness (CE), resource use identification and HRQoL presented in the CS and Appendices.^{3, 14} The evidence based checklist for the PRESS from Canada's Drug Agency (formerly the CADTH) was used to inform this critique.¹³ The EAG has presented only the major limitations of each search strategy in the report.

Appendices E, F and G of the CS provide details of SLRs conducted to identify relevant studies on CE, cost/health care resource use of ibrutinib and HRQoL with R-CHOP for untreated MCL when an ASCT is suitable.¹⁴ The CE and resource use searches were conducted in December 2023 and the HRQoL searches were conducted in December 2023. Both sets of searches were updated in October 2025.

EAG comments:

- A single set of searches was undertaken to identify relevant studies on the economic evidence and health care resource use of ibrutinib with R-CHOP for untreated MCL when an ASCT is suitable. An additional set of searches was conducted to identify relevant HRQoL data. The CS, and Appendices E, F and G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{3, 8, 14}
- These databases were searched for the economic evidence and evidence about healthcare resource use: Embase, MEDLINE and MEDLINE In-Process (7 December 2023); EconLit (23 November 2023). The searches were updated in May 2025 and October 2025. The INAHTA database was searched in the 2025 updates but not the original search. The start date of the searches was not specified, but no date limit was applied except for limiting conference abstracts to those published since 2020. Searches for the HRQoL SLR were conducted in MEDLINE (including In-Process) and Embase (searched on 7 December 2023) and PsycINFO (searched in November 2023, exact date not given). Update searches were performed in MEDLINE and Embase on 8 May 2025 and 28-29 October 2025. Searches of additional resources such as NHS EED and the Cochrane Library may have identified further relevant studies. The start date of the searches was not given, and no date limits were applied except for limiting conference abstracts to those published from 2020 to date.
- For all economic and HRQoL searches, six key conference proceedings were manually searched for the last 4 years (in four cases), or the last 2 years (in two cases).
- For the economic searches, 14 HTA sources were searched. The date of the original search is not known, and updates were performed in May and November 2025, with the date ranges detailed in the CS appendices.¹⁴ Searching HTA sources for information on HRQoL may have identified further relevant references.
- The economic evidence and healthcare resource use searches contained a population facet for MCL. This was then combined with a study design filter containing terms for costs and economic evaluations. This study design filter used was not referenced, however it did contain an extensive combination of subject heading terms and free text terms, and the EAG considered them appropriate.
- The HRQoL searches contained the same population facet for MCL as the economic searches. This was then combined with a study design filter containing terms for HRQoL. The exact version of

the CADTH (now the CDA-AMC) filter is not referenced, so the EAG is not clear if it is the latest version.

- The CE and the HRQoL searches both included a line to identify studies on first-line therapy, and the EAG note that this line was not present in the clinical effectiveness searches.
- The EAG notes the use of a publication date limit in the updates and would prefer the use of a limit to find material added to the database since a specified date, as anything that falls outside the publication date limit, but added to the database since the original search or previous update could have been missed.
- HemaSphere proceedings are not included in the economic or HRQoL searches, although they were searched for evidence on clinical effectiveness.
- There was some inconsistency in the choice of search terms, as the same terms were not used across all the conference proceedings.
- The EAG is unclear of the rationale for using terms including 'woman' and 'man' in line 34 of the Embase search and line 35 of the MEDLINE search as part of the search designed to remove case reports and reviews, and is concerned that this may have removed relevant studies.
- In the economic and HRQoL searches, some of the figures for the number of records found given in the search strategies in appendices to the original CS¹⁴ do not match the figures in the PRISMA flowcharts sent as part of the company's response to the clarification letter.⁸ The EAG believe that the PRISMA figure may reflect the application of a date limit, but there are instances where the figure in the flowchart is greater than the figure in the strategy, so this is unclear.
- Three trials registries, ClinicalTrials.gov; EUCTR; and the newer European Medicines Agency (EMA) registry were searched but the dates of the searches are not in the report.
- The EAG does not agree with the comment (p.129) about PsycINFO not including content relating to oncology.¹⁴ Searching cancer.mp. or exp Neoplasms/ finds 92000+ references. The EAG notes that the original search found zero results, but thinks that is because there were only 199 results about MCL specifically, rather than because there was no cancer content at all. Keyword fields could also have been included. The EAG feels that updates should have been run in PsycINFO to make sure no new references were missed.
- In the MEDLINE search, line 1 should read Lymphoma, Mantle-Cell/, and not Lymphoma mantle cell/, which returns zero results. The EAG assumes this is a typographical error.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company are presented in CS appendices E and F (Tables 29 and 43).

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective.

4.1.3 Findings of the CE review

The PRISMA flow diagram for the economic SLR can be found in CS Appendix Figures 2 and 4.

A total of four effectiveness studies, reporting on two unique CE studies were included (CS, Appendix Table 30). The first analysis was published as a journal article and was critically appraised by NICE (TA370) and the SMC in 2015. The second analysis was critically appraised by CDA-AMC and was conducted from the Canadian healthcare perspective and assessed the CE of acalabrutinib in combination with BR versus BR alone for the treatment of adult patients with previously untreated MCL who were ineligible for ASCT.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.1: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Consistent with NICE reference case
Perspective on costs	NHS and PSS	Consistent with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Consistent with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Consistent with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	Consistent with NICE reference case
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Consistent with NICE reference case
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Consistent with NICE reference case
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Consistent with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Consistent with NICE reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Consistent with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Consistent with NICE reference case
CS = company submission; EAG = External Assessment Group; EQ-5D = European Quality of Life-5 Dimensions; HTA = Health Technology Assessment; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALYs = quality-adjusted life years; UK = United Kingdom		

4.2.2 Model structure

A semi-Markov model with four distinct health states (failure-free on first-line treatment [FF 1L], progression-free on second-line treatment [PF 2L], PD, and dead) was developed in Microsoft Excel® (Figure 4.1). This approach was chosen to explicitly model three lines of active treatment informed by TRIANGLE (FF 1L) and RAY-3001 (PF 2L and PD).

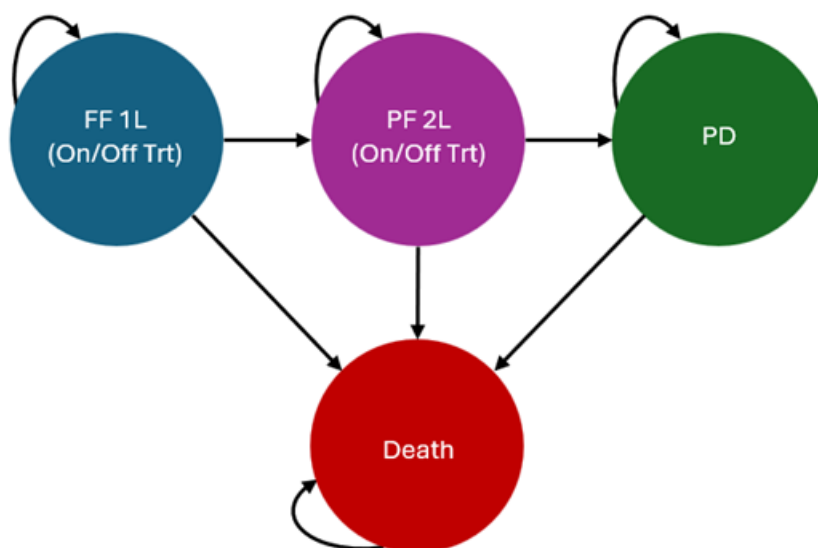
All patients entered the model in the FF 1L state, in which they were treated with either the ibrutinib regimen or the ASCT regimen (failure-free was defined as not having experienced SD at the end of induction, PD or death from any cause). From the FF 1L state, patients could either remain in this state or fail first-line treatment and transition to second-line treatment in the PF 2L state (alive and pre-progression on second-line treatment) or death state. Patients in the FF 1L and PF 2L states could be on and off treatment as in both states patients could receive treatments with fixed durations. Patients in the PF 2L state remained in this state until PD or death. Patients entering the PD state received third-line treatment and remained in this state until death. Death could occur at any time in the economic model and is an absorbing health state. The model used a 21-days cycle length with a half-cycle correction and a lifetime time horizon of 43 years.

Key modelling assumptions:

- FF 1L state
 - All patients in the FF 1L state were assumed to either stay in this state, experience pre-failure mortality, or move to second-line treatment (i.e. patients could not transition directly to the PD state).
 - Ibrutinib and ASCT regimens are fixed-duration treatments, hence patients may be on or off active treatment while they are in FF 1L state.
 - Transitions from the FF 1L state were informed by FFS data, i.e. time from randomisation to SD at the end of induction immunochemotherapy, PD and death, whichever came first.
 - FFS data were split into pre-failure mortality and time to treatment failure (TTF), i.e. time from randomisation to SD at the end of induction immunochemotherapy, or PD, whichever came first. Pre-failure mortality data was used to inform FF 1L to death transitions, whereas TTF was used to inform FF 1L to PF 2L (i.e. start of second-line treatment) transitions.
 - The per cycle pre-failure mortality probability was assumed to be dependent of first-line treatment received (██████ for the ibrutinib regimen and ██████ for the ASCT regimen).
 - For TTF, patients who experienced a pre-failure mortality event were censored, patients alive without failure at the latest contact were censored at the latest tumour assessment date and patients without any lymphoma restaging during or at the end of induction were censored at the date of randomisation.
 - The impact of ASCT was implicitly modelled as part of first-line treatment in the comparator Arm.
- PF 2L state
 - All patients entering the PF 2L state were assumed to receive second-line treatment.
 - Duration of second-line treatments could be fixed or until PD, hence patients may either remain on active treatment or until the end of treatment whilst in this state.
 - Following first-line treatment informed by the patient population from TRIANGLE, the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001 was assumed to inform the second-line treatment population in the economic model.
 - Transitions from the PF 2L state were informed by PFS data from the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001 (TRIANGLE focussed on first-line setting and post-failure data was considered too immature).
 - PFS data were split into pre-failure mortality and time to progression (TTP). Pre-failure mortality was used to inform PF 2L to death transitions, whereas TTP was used to inform PF 2L to PD transitions.
 - The per cycle pre-progression mortality probability (██████) was assumed to be independent of first-line treatment received.

- Second-line treatment types and distributions, and consequently treatment effectiveness were assumed to be dependent of first-line treatment. Differential second-line treatment effectiveness was modelled for transitions from the PF 2L to PD state by applying weighted average HRs to the reference ibrutinib TTP curve from RAY-3001 to form treatment-specific TTP curves for the ibrutinib and ASCT regimens.
- PD state
 - All patients entering the PD state were assumed to receive third-line treatment. Patients in the PD state were assumed to remain on their third-line treatment until death.
 - Transitions from the PD state were informed by post-progression survival (PPS) data from the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001.
 - Transitions from the PD state to death were assumed to be independent of previous lines of treatment received.
- Treatment effectiveness
 - Both induction regimen were assumed to be equally effective (R-CHOP with R-DHAP or R-DHAox versus the NORDIC chemotherapy regimen, i.e. R-Maxi-CHOP alternating with R-cytarabine).
 - No explicit assumptions related to waning of the ibrutinib regimen treatment effect were modelled.
- Resources and costs
 - First-line induction medical resource use was not included in the health economic model.
 - A relative dose intensity of 100% for all medications besides ibrutinib was assumed.
 - No drug wastage (besides vial wastage) was assumed.

Figure 4.1: Model structure



Based on Figure 12 of the CS

CS = company submission; FF 1L = failure-free on first-line treatment; PF 2L = progression-free on second-line treatment; PD = progressed disease

EAG comments: The main concerns of the EAG relate to: a) the modelling of ASCT, b) the suitability of TTF as a proxy for initiation of second-line treatment, c) the assumption that second-line treatment is initiation immediately following failure on first-line treatment, and d) the assumption that all non-death failures in first-line treatment receive second-line treatment.

- a) The EAG questions the company's approach of implicitly modelling ASCT as part of first-line treatment in the comparator Arm. More specifically, the EAG is concerned about the lack of explicitly modelling long-term ASCT benefits while including its short-term risks. Long-term benefits of ASCT (in terms of survival, as supported by the BSH guideline)⁵ are not explicitly captured in the company's current modelling approach, as the use of TRIANGLE data in the company's economic model was limited to the first-line treatment setting and ASCT was not explicitly incorporated in the model structure. On the other hand, as noted by the company in its response to clarification, the short-term mortality risk associated with ASCT was explicitly modelled by assuming differential pre-failure mortality rates (informed by TRIANGLE) for the ibrutinib and ASCT regimens. However, the EAG considers this approach clinically implausible, as it assumes a constant differential pre-failure mortality probability that is also applied to long-term failure-free patients (more detailed discussion in Section 4.2.6 comment d). In response to clarification, the company argued that the long-term impact of ASCT was implicitly captured through selection of survival curves aligned with expert elicitation. The EAG does not consider this a substitute for explicit modelling of long-term ASCT consequences. Alternatively, it would like to see an updated economic model including ASCT represented in health or tunnel states, or at least a scenario analysis including more explicit adjustments to the current economic model to reflect the long-term benefits of ASCT.
- b) The EAG questions the suitability of TTF as a proxy for initiation of second-line treatment, more specifically that patients without response to treatment at the end of induction immunochemotherapy would move on to second-line therapy. In response to clarification, the company argued that this assumption was validated by UK clinical experts at an Advisory Board and is in line with the BSH treatment guidelines for MCL stating that "*stable disease following induction immunochemotherapy is an indication of treatment failure given that only patients achieving at least a PR can proceed to the next phase of first-line treatment*". A scenario analysis using TTP (i.e. excluding SD at the end of induction immunochemotherapy as a failure event) as opposed to TTF increased the incremental net health benefit (iNHB), indicating that the company's base-case approach is likely conservative.
- c) The EAG questions whether immediate initiation of second-line therapy following failure on first-line treatment is reflective of UK clinical practice. The company considered this a reasonable assumption as the input from UK-based consultant haematologists did not include any watch and wait strategies and only a minor proportion of patients was expected to be treated with best supportive care (BSC) (i.e. 1.1%). The EAG agrees with the company's justification.
- d) The EAG questions the assumption that all non-death failures in first-line treatment receive second-line treatment, i.e. patients cannot transition from FF 1L to PD directly. The company explained that all three alive health states in the economic model (i.e. FF 1L, PF 2L and PD) represent a line of treatment received in MCL, and as a consequence patients could not receive a third-line treatment (PD) before having received a second-line treatment (PF 2L). They further acknowledged that there may be a minority of patients in UK clinical practice that would be too frail to receive an active second-line treatment upon failure on first-line and experience PD shortly thereafter. These patients are reflected in the company's economic model by those receiving second-line BSC. The EAGs clinical expert agrees that all patients failing on first-line treatment would be recommended a second-line treatment in UK clinical practice, and the EAG therefore agrees that the company's assumption is reasonable.

4.2.3 Population

Consistent with the NICE scope, the population considered in the CS (CS, Table 1) was adults with untreated MCL who are eligible for ASCT.

Baseline characteristics (CS, Table 28) for the health economic model were based on the TRIANGLE FAS population (pooled across Arm I and Arm A). Specifically, age and sex are included to determine general population mortality and utility inputs. Mean body weight and body surface area (BSA) are included in to calculate drug acquisition costs for intravenous (IV) treatments.

EAG comments: The main concerns of the EAG relate to: a) representativeness of TRIANGLE for UK clinical practice; b) use of the baseline median (instead of mean) age; c) omission of subgroup analyses specified in the final scope.

- a) In response to clarification question B3, the company argued based on clinical expert opinion that *“patient characteristics included within the model can be considered reflective of UK clinical practice”* and acknowledged *“that the paucity of real-world data investigating MCL patients in the UK is a challenging but inherent limitation of evaluating rare diseases and consider that in the absence of real-world data, clinical expert opinion represents the best available evidence to evaluate the generalisability of the TRIANGLE trial to UK clinical practice”*. In conclusion, as summarised in Section 3.6, the EAG consider that TRIANGLE is generalisable to UK clinical practice.
- b) The median rather than the mean age was used to inform the baseline patient characteristics in the health economic model. In response to clarification question B3, the company argued that *“the mean can be disproportionately influenced by extreme values within the data set. As such, the median was used within the model to minimise any potential influence of outliers on the model inputs”*. Based on clarification response Table 9, it appears that using the median, rather than the mean age only has a minor impact on the estimated CE.
- c) The final scope stipulates *“If evidence allows, subgroups based on baseline clinical disease characteristics, cytology of mantle cell lymphoma, p53 expression and receipt of rituximab maintenance may be considered”*. Moreover, subgroup analyses are provided considering clinical effectiveness (CS Figure 9). However, no subgroup analyses were provided in CS Section 3.12. In CS Table 1, it is stated *“subgroups are not considered in the cost-effectiveness analysis (see Section 3) given that they are not anticipated to be important for decision-making in UK clinical practice”*. In response to clarification question B4, the company argued that *“current treatment guidelines for patients with untreated MCL eligible for ASCT do not recommend any subgroups based on baseline disease characteristics to guide treatment selection”* ... *“furthermore, sample sizes for all subgroups based on baseline clinical disease characteristics, cytology of MCL and p53 expression are extremely limited. As such, cost-effectiveness analyses within these subgroups in the economic model would yield results that are insufficiently robust and uncertain, as well as being not relevant to UK clinical practice, and therefore have not been provided”*. Unfortunately, the company did not provide the subgroup analyses requested by the EAG in clarification question B4. According to the EAG, the importance of subgroups for decision-making should be decided upon by the committee.

4.2.4 Intervention and comparators

Consistent with the scope, the comparator in the CS was defined as the ASCT regimen, consisting of six alternating cycles of R-CHOP and R-DHAP or R-DHAox followed by ASCT (CS Figure 13 and

CS Table 31). Based on feedback from the company's clinical experts indicating predominant use of the NORDIC induction regimen in UK clinical practice, the comparator was modelled as a weighted mixture of two induction regimens: alternating R-CHOP with R-DHAP or R-DHAOx (20% of patients) and the NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine; 80% of patients). The company assumed these induction regimens to be equally effective (i.e. only affecting costs).

According to the final scope, the intervention was defined as “ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, with or without ASCT, followed by ibrutinib monotherapy”. In the CS, however, the ibrutinib regimen was defined as six alternating cycles of R-CHOP and R-DHAP or R-DHAOx without ASCT, with ibrutinib (560 mg once daily [QD]) administered on days 1-19 of R-CHOP cycles and as fixed-duration maintenance for 2 years (CS Figure 13 and CS Table 30). The third regimen evaluated in the pivotal trial (TRIANGLE), in which ibrutinib was combined with ASCT, was not included in the economic analyses.

EAG comments: The main concerns of the EAG relate to: a) omission of a treatment strategy including both ibrutinib and ASCT; b) the induction regimens selected for the ASCT strategy; c) the induction regimens selected for the ibrutinib strategy and d) the duration of rituximab maintenance therapy.

- a) The pivotal trial for this submission is TRIANGLE (e.g. for informing first-line treatment effectiveness). This trial considered treatment strategy (A+I), that consisted of both ibrutinib and ASCT. In the CS it is stated “*Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib*”. This is inconsistent with the final scope stating “*Ibrutinib with R-CHOP, alternating with R-DHAP or R-DHAOx without ibrutinib, with or without ASCT, followed by ibrutinib monotherapy*”. Therefore, a treatment strategy explicitly permitted by the scope (A+I) was excluded: this is discussed in detail in Section 2.2. Note also that the EAG clinical expert indicated that it would be useful to have ASCT as an option after first-line failure on ibrutinib, which was not permitted as subsequent treatment (see Section 4.2.9.4).
- b) In response to clarification question B1, the company indicated that the induction regimens selected for the ASCT strategy were based on clinical expert input during the November 2025 Advisory Board: “*All clinical experts agreed that the NORDIC regimen is predominantly used in UK clinical practice, and ultimately concluded that 80% of patients treated with the ASCT regimen receive the NORDIC induction chemotherapy regimen. They considered that the remaining 20% of patients receive a mixture of other immunochemotherapy regimens, including alternating R-CHOP and R-DHAP (or R-DHAOx)*”. The EAG clinical expert indicated that indeed both regimens are used in UK clinical practice but was unsure about the 80%/20% distribution. The EAG clinical expert was not aware of any data indicated supporting this distribution. Scenario analyses conducted by the company (clarification response Table 6) indicated that increasing the proportion of patients receiving alternating R-CHOP and R-DHAP (or R-DHAOx) for the ASCT regimen would reduce the costs of the ASCT regimen and thus increase the incremental costs for the ibrutinib regimen. Similarly, regarding the assumed 85%/15% split between R-DHAOx and R-DHAP, the company stated that “*During the November 2025 advisory board, clinical experts stated that within the alternating R-CHOP and R-DHAP (or R-DHAOx) induction regimen, R-DHAOx would be preferentially used over R-DHAP due to its more tolerable safety profile and more user-friendly method of administration given that it can be administered in an outpatient setting. Following discussion, the clinical experts reached consensus that 85% of rituximab-eligible patients would likely receive R-CHOP alternating with R-DHAOx and 15% of rituximab-eligible patients would receive R-CHOP alternating with R-DHAP in UK clinical practice*”. The EAG clinical expert was not aware of any data indicated supporting this 85%/15% split between R-DHAOx and R-DHAP.

- c) The company assumed that the NORDIC chemotherapy regimen was not used in combination with ibrutinib. In response to clarification question B1, the company indicated that this was in line the UK MA for ibrutinib and that *“use of the NORDIC regimen with the ibrutinib regimen would be off-license and is therefore not relevant for UK decision making”*. Consistently, the EAG clinical expert agreed that the NORDIC regimen would not be used in combination with ibrutinib as it is more toxic. Hence, it is likely that ibrutinib will be used as per the TRIANGLE trial protocol.
- d) According to the CS, rituximab maintenance therapy might be 2 or 3 years: *“Following ASCT, the BSH recommends three years of treatment with rituximab maintenance therapy, based on the LyMA trial; however, rituximab maintenance treatment is only reimbursed by NICE for two years following ASCT. As such, most regional NHS trusts recommend and prescribe rituximab maintenance for two years. Feedback from UK clinical experts at the November 2025 advisory board indicated that there are discrepancies in prescribing practice across the UK, with some NHS trusts reimbursing up to three years of rituximab maintenance. Additionally, clinical experts noted that some patients may self-fund the third year of rituximab maintenance treatment”*. In response to clarification question B2, the company stated that *“The UK clinical experts consulted at the November advisory board subsequently unanimously validated that a 90:10 split between two versus three years of rituximab maintenance is representative of usage in UK clinical practice”*. The company provided scenario analyses (clarification response Table 7) to explore the impact of the abovementioned uncertainty (either 2 or 3 years of rituximab maintenance therapy). These analyses indicated that the impact on the incremental costs was minor (approximately [REDACTED] difference), assuming 2 years of rituximab maintenance therapy (90% in the CS base-case) would be more favourable for the ibrutinib strategy.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the National Health Service (NHS) and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is three weeks with a lifetime time horizon (43 years), and a half-cycle correction is applied.

EAG comment: The approach is in concordance with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for intervention and comparators are the TRIANGLE and RAY-3001 trials. TRIANGLE, a phase III randomised, open-label, three-Arm, parallel group, study in patients ≥ 18 years of age and ≤ 65 years of age with untreated MCL, was used to inform first-line treatment efficacy and mortality (i.e. FF 1L state) in the economic model. RAY-3001, a phase III randomised, open-label, multicentre, trial evaluating the efficacy of ibrutinib among patients with relapsed/refractory MCL who had received at least one rituximab-containing chemotherapy regimen, was used to inform efficacy and mortality in later lines of treatment (i.e. PF 2L and PD states).

The company conducted standard parametric survival analyses for transition probabilities requiring extrapolation of trial data, guided by the NICE Decision Support Unit (DSU) TSD 14. Selection of the most appropriate distributions in the company's base-case was based on the following considerations:

- Assessment of the proportionality of hazards between treatment Arms using log-cumulative hazards plots and Schoenfeld residual plots.
- Visual fit of the predicted extrapolation to the shape of the observed K-M data.
- Statistic fit of the extrapolated data to the observed data using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) statistics.

- Clinical plausibility and external validation of long-term predications based on clinical expert interviews.

4.2.6.1 Transitions from the FF 1L state

4.2.6.1.1 FF 1L to death

Pre-failure mortality data, i.e. death from any cause following randomisation prior to failure on first-line treatment, from the ibrutinib and ASCT Arms of TRIANGLE were used to inform transitions from the FF 1L to death state. As the number of pre-failure deaths in TRIANGLE was limited (4.1% for ibrutinib and 8.2% for ASCT), pre-failure annual mortality rates were calculated and converted to per-cycle mortality probabilities of [REDACTED] and [REDACTED] for the ibrutinib and ASCT regimens, respectively.

4.2.6.1.2 FF 1L to PF 2L

TTF data, i.e. time from randomisation to SD at the end of induction immunochemotherapy, or PD), from the ibrutinib (Arm I) and ASCT (Arm A) arms of TRIANGLE were used to inform transitions from the FF 1L to PF 2L state (i.e. start second-line treatment). Patients experiencing a pre-failure mortality event were censored in TTF. Patients alive without failure at the latest contact were censored at the latest tumour assessment date, whereas patients without any lymphoma restaging during or at the end of induction were censored at the date of randomisation.

Standard parametric survival analyses were conducted to extrapolate the observed TTF data. Based on visual assessment of the log-cumulative hazards (CS Figure 15) and assessment of the Schoenfeld residual plot and statistics (CS Figure 16), the company assumed hazards to be non-proportional. The company considered the majority of curves to provide a similar visual (CS Figures 17 and 18) and statistical fit (CS Table 34) to the observed data and therefore, also considering the relatively immature TRIANGLE TTF data, used clinical plausibility as their primary consideration for selecting their base-case curve. The exponential and Gamma curves were selected in the company's base-case for the ibrutinib and ASCT regimens respectively as these most closely aligned with UK clinical expert estimates (CS Table 36).

4.2.6.2 Transitions from the PF 2L state

4.2.6.2.1 PF 2L to death

Pre-progression mortality data from the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001 were used to inform transitions from the PF 2L to death state for both the ibrutinib and ASCT regimen. A similar approach as for FF 1L to death was applied, resulting in a per cycle mortality probability of [REDACTED].

4.2.6.2.2 PF 2L to PD

TTP data from the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001 were used to inform transitions from the PF 2L to PD state for both the ibrutinib and ASCT regimen. TTP was derived from PFS data, censored for pre-progression mortality, to avoid double-counting.

Standard parametric survival analyses were conducted to extrapolate the observed TTP data. The company considered that all curves provided a similar visual fit to the first 24 months of K-M data, with poorer visual fit to the tail end due to lower patient numbers at risk (CS Figure 21). Statistical fit to the observed data was also deemed reasonably comparable between curves, with the exponential providing

the best statistical fit based on both AIC and BIC (CS Table 42). As for the FF 1L to PF 2L transitions, clinical plausibility was the company's primary consideration for selecting the base-case TTP curve, resulting in the log-logistic curve to be used in the company's base-case as it most closely aligned with expert estimates (CS Table 44).

From the Advisory Board, small differences in the types and distributions of second-line treatments were expected between patients following first-line treatment with the ibrutinib or ASCT regimen. Types and distributions of second-line treatments for the ibrutinib and ASCT regimens were informed by feedback from UK clinical experts (Table 4.3). To account for differential efficacy of these second-line treatments, the company derived a PFS HR of 1.26 (from the MANTLE-FIRST study) to inform the relative treatment effectiveness of ibrutinib versus R-BAC, BR and BSC. For ibrutinib versus zanubrutinib, a HR of 1.00 was applied as these were assumed to have equal efficacy based on UK clinical expert input (Table 4.2). Combined with the anticipated second-line treatment distributions, weighted average HRs of 1.103 and 1.012 for the ibrutinib and ASCT regimens respectively were calculated and applied to the reference ibrutinib TTP curve from RAY-3001 to form treatment-specific TTP curves for the ibrutinib and ASCT regimens.

Table 4.2: Distribution of subsequent treatment use in second-line

First-line treatment	Second-line treatment					
	Ibrutinib	Zanubrutinib	R-BAC	BR	BSC	Weighted average HR
Ibrutinib	-	57.6%	31.3%	10.0%	1.1%	1.103
ASCT	10.0%	84.8%	2.4%	2.0%	0.8%	1.012
HR versus second-line ibrutinib	N/A	1.00	1.26	1.26	1.26	N/A
Based on CS Table 39, Table 40 and Table 41. ³ ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; CS = company submission; HR = hazard ratio; N/A = not applicable; R-BAC = rituximab, bendamustine and cytarabine						

4.2.6.3 Transitions from the PD state

4.2.6.3.1 PD to death

PPS data from the ibrutinib Arm of the subgroup that received one prior line of treatment in RAY-3001 were used to inform transitions from the PD to death state for both the ibrutinib and ASCT regimen.

Standard parametric survival analyses were conducted to extrapolate the observed PPS data. As the PPS data from RAY-3001 were considered mature, the company selected its most appropriate parametric model mainly based on statistical and visual fit to the observed data. The company considered the exponential and Gompertz curves to have the best statistical fit to the observed data (CS Table 45), while visual fit to the first 12 months of K-M data of all curves was considered good (CS Figure 24). Based on external validation, the company ruled out the Gompertz as its 20-year PPS estimate was deemed implausible. Based on these consideration, the company selected the exponential to inform PPS in its base-case.

An overview of all modelled transition probabilities is reported in Table 4.3 below.

Table 4.3: Overview of the modelled transition probabilities

Transition probability	Approach	Ibrutinib regimen	ASCT regimen	Source
FF 1L to death	Constant probability of pre-progression death, capped by general population mortality	Per cycle probability of death: █████	Per cycle probability of death: █████	Pre-failure mortality from TRIANGLE
FF 1L to PF 2L	Standard parametric survival curves fitted to observed TTF curves.	Exponential	Gamma	TTF from TRIANGLE
PF 2L to death	Constant probability of pre-progression death, capped by general population mortality	Per cycle probability of death: █████		Pre-progression mortality from RAY-3001
PF 2L to PD	Standard parametric survival curves fitted to observed ibrutinib TTP curve, to which differential weighted HRs were applied	Log-logistic + weighted HR of 1.103	Log-logistic + weighted HR of 1.012	TTP from RAY-3001
PD to death	Standard parametric survival curves fitted to observed PPS curves	Exponential		PPS from RAY-3001

Source: CS.³
ASCT = autologous stem cell transplant; CS = company submission; FF 1L = failure-free on first-line treatment; HR = hazard ratio; PD = progressed disease; PF 2L = progression-free on second-line treatment; TTF = time-to-treatment failure; TTP = time-to-progression

No explicit assumptions regarding waning of the relative treatment effect were discussed in the CS.

EAG comment: The main concerns of the EAG relate to: a) modelling differential pre-failure mortality rates, b) the use of annual mortality rates to inform transitions to death from FF 1L and PF 2L, c) the use of RAY-3001 to inform transition probabilities beyond first-line treatment in the economic model, d) the likely overestimation of the ibrutinib second-line treatment effect and underestimation of the ASCT second-line treatment effect, e) the use of HRs from MANTLE-FIRST to inform second-line relative treatment effectiveness, f) assumption of third-line treatment effectiveness being equal for the

ibrutinib regimen and ASCT regimen, g) treatment waning, and h) external validation of extrapolated TTF and TTP curves.

- a) The company modelled different transition probabilities for FF 1L to death for the ibrutinib and ASCT regimens, implying differences in pre-failure mortality. In response to clarification, the company justified that the high toxicity and mortality risk associated with ASCT translated to increased pre-failure mortality in the ASCT regimen. The EAG requested a scenario analysis including separate modelling of ASCT-related mortality, but the company did not provide this arguing that this would further reduce the sample size informing this transition. The EAG is concerned that long-term pre-failure mortality in the company's base-case is currently overestimated and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case.
- b) The EAG questions the company's approach of using an annual mortality rate approach over parametric survival modelling to inform transitions to the death state from the FF 1L and PF 2L states. In response to clarification, the company stated that the number of pre-failure mortality events was limited and parametric extrapolations would therefore be associated with considerable uncertainty. Although the EAG agrees with this statement, it considers the assumed constant hazard of an annual mortality rate clinically implausible as the ASCT-related mortality risk is likely to be higher in the first months after treatment and is expected to decrease thereafter. Despite the potential of poor fit to the observed data and implausible extrapolations when the number of observed events is limited, parametric survival modelling allows capturing the time-varying hazards associated with ASCT-related mortality risk. The EAG would therefore like to see this explored in a scenario analysis.
- c) The EAG questions the suitability of RAY-3001 to inform transitions beyond first-line treatment in the company's economic model. Patients in RAY-3001 are not an appropriate reflection of patients entering second-line treatment in the economic model after being treated with the ibrutinib regimen, as all patients in RAY-3001 were ibrutinib-naïve at study entry. Likewise, patients in RAY-3001 are not reflective of patients entering second-line treatment in the economic model after being treated with the ASCT regimen, as prior ASCT treatment in RAY-3001 was limited to [REDACTED]. Consequently, the observed second-line treatment effects in RAY-3001 are unlikely to reflect the outcomes of patients who have previously been exposed to ibrutinib or ASCT.
- d) The EAG is concerned about the likely overestimation of the ibrutinib second-line treatment effect and underestimation of the ASCT second-line treatment effect. The company assumed that second-line BTKi treatment (either ibrutinib or zanubrutinib) is equally effective in BTKi-experienced patients (i.e. received ibrutinib regimen at first-line) and BTKi-naïve patients (i.e. received ASCT regimen at first-line). The EAG and EAG clinical expert anticipate that effectiveness would likely be lower in retreated patients. Based on that, and the fact that [REDACTED]% of the patients received prior ASCT, the second-line treatment effect for the ibrutinib regimen is likely overestimated. In contrast, the relatively [REDACTED] of patients receiving prior ASCT likely resulted in an underestimation of the second-line treatment effect for the ASCT regimen. TTP estimates provided by the EAG's clinical expert suggest a substantial second-line treatment efficacy benefit for the ASCT regimen compared to the ibrutinib regimen (Table 4.4), which seems currently not reflected in the company's base-case analysis and supports the EAG's concern about the likely over- and underestimation of second-line treatment efficacy for the ibrutinib and ASCT regimens, respectively. Although the bias introduced by this issue likely favours the ibrutinib regimen, the magnitude is unclear to the EAG. Scenario analyses should be explored in which differential second-line treatment effectiveness is not only reflected by the distributions of patients receiving different second-line treatments, but also by decreased BTKi efficacy in treatment-experienced

versus treatment-naïve patients. Similarly increased treatment effectiveness should be reflected for patients treated with ASCT.

Table 4.4: EAG's clinical expert estimated TTP in UK clinical practice

Treatment	TTP						
	1 years (%)	2 years (%)	3 years (%)	4 years (%)	5 years (%)	10 years (%)	20 years (%)
Ibrutinib	40	20	15	10	<10	<5	<5
ASCT	80	70	60	55	50	30-40	20-30
ASCT = autologous stem cell transplant; EAG = External Assessment Group; TTP = time-to-progression; UK = United Kingdom							

- e) The EAG has several concerns regarding the company's approach to modelling second-line relative treatment effectiveness. First, although MANTLE-FIRST reports separate relative treatment effects for ibrutinib versus R-BAC and versus BR, the company applies a single HR for both comparators in its economic model. Second, the company assumed BSC efficacy to be equal to the efficacy of rituximab-based chemotherapy. In response to clarification, the company acknowledged that BSC is likely less effective than rituximab-based chemotherapy in clinical practice, but clarified that this simplifying assumptions was based on a lack of empirical evidence to inform the relative efficacy of ibrutinib versus BSC. Finally, the MANTLE-FIRST study indicates ibrutinib treatment-effect modification by TTP, which is currently not reflected by the company in its model: the ibrutinib PFS benefit seems more pronounced among early progressors (<24 months), and no apparent PFS advantage over R-BAC was shown among late progressors. The EAG would like to see an updated economic model and scenario analysis informing the relative treatment effect of ibrutinib versus R-BAC and BR based on different HRs, as indicated by the results of MANTLE-FIRST, as well as for ibrutinib versus BSC. Additionally, it would be informative to explore second-line treatment efficacy analyses accounting for early and late progressors. Meanwhile, the EAG explored a scenario analysis assuming equal efficacy between ibrutinib, zanubrutinib and R-BAC (i.e. HR of 1.00), and applying a HR of 0.56 (i.e. the inverse of 1.77 reported in MANTLE-FIRST) to inform the relative treatment effect of ibrutinib versus BR and BSC.
- f) The company assumed equal third-line treatment effectiveness between the ibrutinib regimen and ASCT regimen (i.e. transition from PD to death). It is unclear to the EAG whether this assumption is appropriate, as it was not supported by evidence and deviated from the company's approach of modelling second-line treatment effectiveness. Hence, the EAG believes it would have been informative if the company explored scenarios assuming differential third-line treatment effectiveness and/or evidence to support the current assumptions related to third-line treatment.
- g) Waning of the ibrutinib treatment effect over time was not discussed nor explored in the CS. The log-cumulative hazards plot in CS Figure 15 shows converging TTF hazards of the ibrutinib and ASCT regimens in the observed TRIANGLE data, which may be an indication of ibrutinib treatment effect waning. The EAG therefore considers this informative to be further explored in scenario analyses in which treatment waning in the FF 1L health state is assumed to start gradually at different time points.
- h) The EAG questions the company's approach to external validation of extrapolated outcomes. Long-term estimates from reconstructed FFS and OS curves were compared with clinical expert input to validate the extrapolated TTF and TTP curves, respectively. However, these reconstructed curves depend on several modelling assumptions. The reconstructed FFS curve included mortality, which was modelled using a pre-failure annual mortality rate, while the reconstructed OS curve combined multiple transitions, including pre-failure mortality on first-line treatment, failure on first-line

treatment, pre-progression mortality on second-line treatment, and transitions from PD to death. The EAG considers these reconstructed curves unsuitable proxy's for selecting and validating parametric survival curves (i.e. TTF and TTP), as these are conditional on other modelling assumptions that the EAG considers questionable (e.g. assuming a constant pre-failure annual mortality rate). The CS stated that clinical plausibility was the primary consideration when selecting the base case extrapolations for both TTF and TTP, which suggests that the company's base-case parametric survival curves may be suboptimal. To resolve this issue, external validation of extrapolated outcomes should be reassessed by seeking long-term clinical expert estimates based on the actually modelled outcomes. The EAG considers that mortality in the reconstructed FFS was likely overestimated for the ASCT regimen due to the inclusion of a constant pre-failure mortality rate that was critiqued by the EAG in Section 4.2.6 of this report. The EAG therefore explored a scenario analysis including the log-normal distribution (best statistical fit, more optimistic long-term estimates) for TTF for the ASCT regimen. For TTP, CS Figure 21 suggested that the company's base-case log-logistic distribution produced relatively optimistic long-term estimates, and the EAG therefore explored the exponential distribution (best statistical fit, moderate long-term estimates) in a scenario analysis.

4.2.7 Adverse events

First-line adverse events (AEs) of grade ≥ 3 occurring in over 5% of patients, within 30 days after end of treatment, in either treatment Arm of TRIANGLE were included, see Table 4.5. This resulted in a disutility of 0.0138 and 0.0181 for the ibrutinib and ASCT regimen respectively (CS Table 51). Moreover, the cost of AE management was £1,471.41 and £2,486.62 for the ibrutinib and ASCT regimen respectively (CS Table 74).

Table 4.5: AE incidence, costs and disutility

AE	Incidence for ibrutinib regimen	Incidence for ASCT regimen	Assumed AE duration (days)	One-off cost per AE	One-off disutility per AE
Neutropenia	39.2%	38.8%	15	£734.61	-0.160
Anaemia	21.5%	34.3%	23	£710.90	-0.090
Thrombocytopenia	34.7%	42.5%	23	£734.61	-0.110
Febrile neutropenia	14.0%	26.5%	15	£734.61	-0.160
Leukopenia	9.4%	11.2%	15	£602.04	-0.160
Platelet count decreased	29.4%	33.2%	23	£750.35	-0.110
Neutrophil count decreased	24.2%	23.1%	15	£734.61	-0.160
White blood cell count decreased	6.4%	13.4%	15	£602.04	-0.160
Lymphocyte count decreased	4.5%	5.6%	15	£602.04	-0.160
Pneumonia	5.3%	4.1%	18	£709.43	-0.195
Stomatitis	1.5%	7.8%	21	£520.26	-0.151
Nausea	4.2%	7.8%	11	£601.59	-0.061
Diarrhoea	5.3%	6.0%	21	£601.59	-0.103

Mucosal inflammation	1.9%	13.1%	21	£520.26	-0.151
Hypokalaemia	6.4%	4.5%	15	£622.04	-0.160
Source: Based on CS Tables 48, 50, 72. ³					
AE = adverse event; ASCT = autologous stem cell transplant; CS = company submission					

EAG comment: The main concerns of the EAG relate to: a) inclusion of abnormal blood values as AEs and the risk of double counting with other AEs and b) only AEs associated with first-line treatment (within 30-days of end of treatment) are explicitly modelled.

- a) The CS base-case includes several AEs related to abnormal blood values, including leukopenia, decreased platelet count, decreased neutrophil count, decreased white blood cell count and decreased lymphocyte count. Assumptions were required to inform the impact of these events on HRQoL (CS Table 50) and costs (CS Table 72). The EAG notes that these events are typically reported as laboratory abnormalities in clinical trials and might often be asymptomatic. It is therefore unclear whether they have an autonomous impact on HRQoL or costs, or whether their impact overlaps with that of other modelled toxicities, potentially resulting in double counting. In response to clarification question B11 the company stated that “*Grade 3 AEs are classified as severe or medically significant but not immediately life-threatening, indicated for hospitalisation or prolongation of hospitalisation, disabling and/or limiting self-care activities of daily living such as bathing, dressing, feeding and toilet use. Grade 4 AEs are defined as life-threatening or where urgent intervention is required, and Grade 5 AEs are events related to death. Therefore, by definition it is anticipated that Grade ≥ 3 AEs would impact patients HRQoL*”. However, the company acknowledge that some of the blood value abnormalities included in the economic model may be less likely to impart an autonomous impact on HRQoL in UK clinical practice. Hence, to minimise the risk of double counting, the company “*updated the Company base case to remove both the disutilities and costs associated with AEs that may be frequently reported as laboratory abnormalities and may be asymptomatic. Specifically, leukopenia, neutrophil count decrease, white blood cell decrease and lymphocyte count decrease have been removed from the economic model. Platelet count decrease has not been removed from the updated base case given feedback from a clinical expert that patients with severely low platelet count may require more involved care, such as prophylactic platelet transfusions, and thus low platelet count would have a significant autonomous impact on patient HRQoL and impart a financial burden on the NHS*”, see clarification response Table 5. Moreover, clarification response Table 12 indicated that the disutilities and costs associated with blood value abnormalities only have a minor impact on the estimated CE. The EAG believes the company’s (updated) approach is reasonable.
- b) The CS model includes first-, second-, and third-line treatments; however, only AEs associated with first-line treatment (within 30-days of end of treatment) are explicitly modelled. Given that the model might predict differential incidences in second- and third-line treatments between strategies, it is unclear whether excluding AEs in later lines may bias results. In response to clarification question B12, the company argued that the impact of AEs at later lines would be minimal and not impact decision-making. The EAG believes that it is reasonable to assume that excluding the impact of second-, and third-line treatments has a minimal impact on incremental outcomes.

4.2.8 Health-related quality of life

HRQoL was not routinely collected in the TRIANGLE trial. Hence, the company informed the health state utilities using evidence from the SHINE trial (FF 1L health state) and pooled evidence from the RAY-3001 and SPARK trials (PF 2L and PD health states), see CS Table 53.

SHINE is a multicentre, randomised, double-blind, Phase III study comparing ibrutinib in combination with bendamustine plus rituximab (BR) and rituximab maintenance, to placebo + BR and rituximab maintenance in patients aged ≥ 65 years with previously untreated stage II, III, or IV MCL who were ineligible for ASCT. SPARK is a single Arm, open-label, multicentre, Phase II trial investigating the impact of ibrutinib in patients with relapsed/refractory MCL who had received prior rituximab-containing chemotherapy and who had progressed after bortezomib therapy.

4.2.8.1 HRQoL data identified in the literature review

The SLR identified 12 studies (CS Appendix F, Table 44); seven unique studies reporting on MCL patients and five unique studies including mixed populations. The seven studies reporting on MCL patients (nine publications) are summarised in a PRISMA flow diagram (CS Appendix F, Figure 4). Two studies reported European Quality of Life-5 Dimensions (EQ-5D) utilities in i) previously untreated MCL (TA 370/SHINE trial) and ii) CD20+ B-cell non-Hodgkin's lymphoma patients (CS Appendix F, Table 45). The latter was not specific to patients with MCL and hence not considered relevant by the company.

4.2.8.2 Health state utility values for the FF 1L health state (treatment independent)

The company perceived SHINE with its patient population (CS Table 49) as the most relevant source of FF 1L health state utilities. Additionally, access to its IPD enables HRQoL analyses. In SHINE, EuroQol Five Dimensions Five Levels (EQ-5D-5L) data were collected every 12 weeks for the first 12 months, then every 16 weeks. The company used utility data (cross-walked to the EuroQol Three Dimensions Three Levels [EQ-3D-3L]) from progression-free patients (i.e. PFS as proxy for FFS) receiving ibrutinib in combination with immunochemotherapy at first-line (data cut-off: June 2021; median follow-up: 84.7 months). Including a total of [REDACTED] patients ([REDACTED] observations; data were restricted to week 361, including up to [REDACTED] repeated measurements per individual).

To account for the differences between the SHINE and TRIANGLE patient populations, a mixed-model repeated measures (MMRM) analysis with autoregressive correlation structure, accounting for within-patient correlation, was used including the following covariates (identified via UK clinical experts):

- sex
- presence of AEs during EQ-5D measurement (none, Grade 1 or 2, Grade ≥ 3)
- latest available ECOG PS (0, 1, ≥ 2)
- baseline disease stage (II, III, IV)
- presence of B-symptoms (yes/no)
- creatinine clearance below 30 ml/min (yes/no)
- bone marrow involvement (yes/no)

The baseline characteristics of Arm I of the TRIANGLE trial were applied to these coefficients to estimate the utility value for the treatment-independent FF 1L health state of [REDACTED] (CS Table 53).

4.2.8.3 Health state utility values for the PF 2L and PD health states (treatment-independent)

According to the CS clinical experts, following first-line treatment, patients with MCL commonly receive BTKis in UK clinical practice, hence, utility values from patients with MCL receiving BTKis at second-line were used to inform these health states. As such, the health state utility values (HSUVs) for PF 2L and PD for the two BTKis recommended by NICE in the second-line setting (ibrutinib [TA502] and zanubrutinib [TA1081]) were identified by the company as most appropriate. Specifically,

pooled EQ-5D-5L data (■■■■ pre-progression and ■■■■ post-progression observations) from the RAY-3001 (■■■■) and SPARK (■■■■) trials were used). In TA502 (TA502 CS Table 63), a mixed-model analysis was carried out (accounting for potential autocorrelation) to determine the mean HRQoL pre (PF 2L utility: 0.780) and post progression (PD utility 0.680) for patients in the ibrutinib Arm of the two trials.

4.2.8.4 Disutility values

To account for the HRQoL impact resulting from the toxicity of first-line treatments, a one-off disutility was applied to patients in each Arm in the first model cycle (Table 4.5). The company stated that AE disutility data were not available from TRIANGLE, thus informed AE disutilities and duration by published literature CS Table 50).

The company assumed a utility decrement associated with IV administration for treatments requiring IV administration. Specifically, a decrement of 0.04 was applied per infusion visit, assuming one administration per day in case of multiple components of a treatment regimen are administered. No disutility was modelled for the administration of oral or subcutaneous treatments (CS Table 52).

EAG comment: The main concerns of the EAG relate to: a) internal consistency of health-state utilities across lines of therapy; b) regression model for FF 1L health state utilities; c) regression model for PF 2L and PD health state utilities and d) clarity on HRQoL data collected in the TRIANGLE trial.

- a) The EAG considers internal consistency of health-state utilities across lines of therapy to be a potential key driver of incremental QALYs and therefore decision uncertainty. HRQoL in the economic model was informed by EQ-5D data from the SHINE trial for the FF 1L health state, and pooled EQ-5D data from the RAY-3001 and SPARK trials for the PF 2L and PD health states. In response to clarification question B14, the company argued that the utility values used within the model are considered to represent the best available data and considered them to be clinically plausible and not just a modelling artefact. The EAG believes the selected sources to inform the HSUVs is reasonable.
- b) The company used EQ-5D-5L data from the SHINE trial (progression-free patients in the ibrutinib Arm), mapped to EQ-5D-3L and analysed using a MMRM approach to inform FF 1L health state utilities. In response to clarification question B15, the company provided additional details regarding the EQ-5D-3L data. The company restricted the data to progression-free observations. The company did not provide a MMRM model including SHINE trial data from both progression-free and progressed observations, including PD as a covariate. This might have allowed using both FF 1L and PF 2L health state utilities from one evidence source.
- c) The company used EQ-5D-5L data from the ibrutinib Arms of the RAY-3001 and SPARK trials were pooled and analysed using a mixed model to estimate PF 2L and PD health state utilities. In response to clarification question B16, the company apologised that owing to the time that has passed since the original analysis was performed, it was not possible to replicate the approach to pooling EQ-5D-5L data from the ibrutinib Arms of the RAY-3001 and SPARK trials, as per TA502. Therefore, in response to the EAG's query, a new utility analyses using more recent data cuts was performed. Although these updated values differed slightly from those presented previously in TA502, these did not substantially impact the estimated incremental QALYs and thus CE. Additionally, the scenario analysis provided in clarification response Table 14 demonstrated that removal of the decrement between the PF 2L and PD health states included in the economic model has a minimal impact on CE results. The company concluded in response to clarification question B16, that the pooled EQ-5D utilities across trials as used in the base-case setting are appropriate. The EAG believes this is reasonable

- d) According to the CS, HRQoL was not routinely collected in the TRIANGLE trial. In response to clarification question B14, the company confirmed that HRQoL data were not collected within TRIANGLE.

4.2.9 Resource use and costs

The cost categories included in the model were drug acquisition costs, and medical costs associated with treatment administration, subsequent treatment, resource use for routine care and monitoring, management of AEs and ASCT complications, treatment failure and terminal care.

Cost inputs were informed by sources aligned with the costing perspective of the NHS in England, for instance, the NHS Reference Costs 2024/25,²⁰ British National Formulary (BNF)²¹ and the drugs and pharmaceutical electronic market information tool (eMIT).²²

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, the SLR identified thirteen studies reporting resource use and cost information on adult patients with untreated MCL. Out of these, the company stated that one study addressed transplant-eligible patients with MCL but not in an UK setting. None of the identified studies were used in the health economic model.

4.2.9.2 Treatment costs

First-line treatment consisted of induction, consolidation, and maintenance. Consolidation was applicable to ASCT but not ibrutinib. Dosing regimens and relative dose intensities (RDI) were based on the TRIANGLE protocol²³ and licensed dosing regimens for each treatment.²⁴ An overview is presented in Table 4.6.

Induction regimens differed by treatment Arm, and shares were informed by clinical expert opinion.¹⁶ For ibrutinib, patients received R-CHOP either alternating with R-DHAox or R-DHAP. For ASCT, a further differentiation was made, where the majority of patients received the NORDIC regimen (R-Maxi-CHOP alternating with R-cytarabine) and the remaining ones received either received R-CHOP alternating with R-DHAox or R-DHAP. The ASCT procedure itself was split into stem-cell apheresis, HDT, and transplant. An ASCT one-off cost estimate of £42,040.84 sourced from NICE NG52 guidance.²⁵ Induction (and consolidation) lasted up until to cycle six (18 weeks) for the ibrutinib Arm and cycle seven (21 weeks) for the ASCT Arm.

Maintenance consisted of either only rituximab (ASCT) or rituximab given with ibrutinib for the intervention. Although rituximab maintenance is reimbursed by the NHS up to 2 years,²⁶ the company assumed in line with clinical expert feedback that 10% of patients receive it for 3 years and 90% for 2 years.¹⁶

Drug unit costs^{21, 22} for each first-line treatment can be found in CS Table 56, where a Patient Access Scheme (PAS) discount of ■% was applied to ibrutinib. Whereas the CS stated that “[d]rug wastage was not considered in the cost-effectiveness analysis”,³ the health economic model included vial wastage.

Table 4.6: First-line treatment costs (excluding administration costs)

Component	Patients receiving	RDI	Treatment duration	Acquisition cost (per administration)

	ASCT Regimen	Ibrutinib regimen			
R-CHOP alternating with R-DHAP or R-DHAOx					
	20% of patients	100% of patients			
R-CHOP	100%	100%	100%	Cycles 1, 3, 5	£1,320.96
Ibrutinib	N/A	100%	95.2%	Cycles 1, 3, 5	£[REDACTED]
R-DHAP	15%	15%	100%	Cycles 2, 4, 6	£1,819.77
R-DHAOx	85%	85%	100%	Cycles 2, 4, 6	£1,926.80
NORDIC chemotherapy regimen (R-Maxi-CHOP alternating with R-cytarabine)					
	80% of patients	0% of patients			
Maxi-CHOP	100%	N/A	100%	Cycles 1, 3, 5	£1,745.51
R-cytarabine	100%	N/A	100%	Cycles 2, 4, 6	£1,788.19
ASCT					
Stem-cell apheresis	87%	N/A	N/A	Cycle 4	£6,386.86
HDT	87%	N/A	N/A	Cycle 6	£2,150.32
ASCT	87%	N/A	N/A	Cycle 7	£42,040.84
Maintenance					
Rituximab 375 mg/m ²	[REDACTED]	[REDACTED]	100%	Once every 2 months for 2–3 years after transplant ^c	£1,257.35
Ibrutinib 560 mg	N/A	[REDACTED]	92.9%	Daily for 2 years after transplant	[REDACTED]

Source: Based on CS Tables 55, 57.³

^a Pegfilgrastim was assumed to be given once at Day 6.

^b Assumed to be included in ASCT unit price.

^c 90% of patients receiving rituximab maintenance were assumed to receive treatment for 2 years; 10% of patients were assumed to receive treatment for 3 years.

ASCT = autologous stem cell transplantation; BEAM = carmustine, cytarabine, etoposide and melphalan; CS = company submission; G-CSF = granulocyte colony-stimulating factor; h = hour; HDT = high-dose chemotherapy; IV = intravenous; N/A = not applicable; Q12h = every 12 hours; R- = rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAOx = rituximab, dexamethasone, high-dose cytarabine and oxaliplatin; R-DHAP = rituximab, dexamethasone, high-dose cytarabine and cisplatin; RDI = relative dose intensity; THAM = total body irradiation, cytarabine and melphalan; WBC = white blood cell count

4.2.9.3 Administration costs

Intravenous, subcutaneous and oral administration was costed using the NHS Reference Costs 2024/25,²⁰ whereby no costs were assumed for oral administration (CS Table 59).

First-line treatment components, i.e. R-DHAP and R-Cytarabine, were assumed to be administered in an inpatient setting in UK clinical practice lasting for two days.^{27,28} For these, no additional administration costs were applied to avoid double counting. HDT inpatient administration costs were not applied as the company assumed that these were already included in ASCT one-off costs.

4.2.9.4 Subsequent treatment costs

Subsequent treatments and their distributions were informed by clinical expert opinion¹⁶ (Table 4.7). The CS states that patients receive second-line and third-line treatment conditional on the prior line treatment received. In its analysis, the company chose to condition third-line on first-line treatment. For third-line, the bendamustine and rituximab regimen was used as a proxy for further rituximab-based regimen options also available in UK clinical practice.

Subsequent treatments were administered to alive and progression-free (second-line) or progressed (third-line) patients. Dosing regimens depended on whether the treatment was pursued up to progression or was of fixed duration and hence capped by the maximum treatment duration³ (Table 64). A 100% RDI was assumed by the company for subsequent treatments.

Drug acquisition costs can be found in CS Table 65, and administration costs as detailed in Section 4.2.9.3 applied.

Table 4.7: Distribution of subsequent treatment use in second-line and third-line treatment

Treatment Arm	Subsequent treatment	First-line treatment	
		Ibrutinib	ASCT
Second-line treatment	Ibrutinib	-	10%
	Zanubrutinib	58%	85%
	R-BAC	31%	2%
	BR	10%	2%
	BSC	1%	1%
Third-line treatment	R-BAC	42%	67%
	BR	33%	16%
	BSC	25%	16%

Source: Based on CS Tables 62, 63.³

Comment: Rounded to integer.

ASCT = autologous stem-cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; CS = company submission; R-BAC = rituximab, bendamustine and cytarabine

4.2.9.5 Health state costs

Health state-dependent resource use was identified via the ESMO treatment guidelines²⁹ and validated by clinical expert opinion.¹¹ By design, it was identical for the ibrutinib and ASCT treatment Arm, except for the FF 1L ASCT consolidation phase (CS Tables 67, 70). In the FF 1L health state, the CS differentiated between on/off active treatment, where the former captured resource use during consolidation and maintenance. Resource use occurrent during induction was disregarded, as it was assumed to be identical across Arms. For PF 2L and PD, resource use was assumed identical irrespective of second-line and third-line treatment received.

Annual resource use estimates per health stated were converted to cycles and costed with the National Schedule of NHS Costs Year 2024/25³⁰ or Personal Social Services Research Unit (PSSRU) 2024,³¹ see CS Table 68.

Table 4.8: Health state costs

			Cost per model cycle (£) Mean (SE)	Source
Health state				
FF 1L	On active treatment	Induction	-	Assumption
		Consolidation: ibrutinib	-	Assumption
		Consolidation: ASCT	£52.99 (5.30)	Clinical expert opinion, National Schedule of NHS Costs Year 2024/25, ³⁰ PSSRU 2024 ³¹
		Maintenance	£6.78 (0.68)	
	Off active treatment	£107.66 (10.77)		
PF 2L		£107.66 (10.77)		
PD		£107.66 (10.77)		

Source: Based on CS Tables 69, 71.³

ASCT = autologous stem-cell transplantation; CS = company submission; FF 1L = failure-free on first-line treatment; NHS = National Health Service; PF 2L = progression free on second-line treatment; PD = progressed disease; PSSRU = Personal Social Services Research Unit; SE = standard error

4.2.9.6 AE costs

AEs of grade ≥ 3 AEs occurring in over 5% of patients in either treatment Arm of TRIANGLE were included in the FF 1L health state and costed via the NHS Reference Costs 2024/25 (Section 4.2.7, Table 4.5). Several AE categories were assumed to be similar and thus assigned the same unit cost.

Moreover, the company referenced literature stating that 5% of patients undergoing ASCT require intensive care unit (ICU) admission^{32, 33} lasting for 5 days.³⁴ Hence, it assigned a daily one-off unit cost of £2,405.64 sourced from NHS Reference Costs 2024/25²⁰ to affected ASCT patients in the FF 1L health state.

4.2.9.7 Further event costs

Failure on first-line treatment or progression on second-line treatment induced resource use such as full-blood count, imaging or sometimes biopsy according to clinical experts (CS Table 75). These events were valued with NHS Reference Costs 2024/25.²⁰

Terminal care costs of (£13,409³¹) were applied as a one-off to patients that died in each cycle.

EAG comment: The main concerns of the EAG relate to: a) RDI assumption of 100% for all treatments but ibrutinib, b) ASCT unit costs, c) assumption on ICU events for ASCT patients, d) inconsistent drug wastage approach, e) subsequent treatment (distributions) for ibrutinib patients, f) reported resource use across treatment lines.

- a) The company only had RDI information for ibrutinib, collected within TRIANGLE during induction and maintenance (Table 4.6). For all other treatment (lines), including when ibrutinib was used as a second-line treatment option, the company made the simplifying assumption of a 100% RDI. It stated that this was reasonable particularly for ASCT, as standard protocols and guidelines would specify fixed mg/m² doses without recommending routine pre-emptive reductions. Although requested by the EAG, the company was unable to provide further evidence on RDI. The company presented a scenario analysis where the RDI for all treatments was standardised to 100%⁸ (Table

- 15), resulting in an increase in incremental costs from [REDACTED] to [REDACTED]. In TA502,³⁵ the company used in absence of RDI information the RDI from ibrutinib for all treatments. The EAG decided to apply such a coherent approach, standardising the RDI for all treatments to 100% in its base-case.
- b) The ASCT procedure itself was split into stem-cell apheresis (£6,386.86), HDT (£2,150.32), and transplant (£42,040.84). The latter was sourced from NICE NG52 guidance on non-Hodgkin's lymphoma issued in 2016,²⁵ not NHS Reference Costs. The company reasoned that the source itself, as well as its use in two prior Technology Appraisals (TAs) on non-Hodgkin's lymphoma^{27, 36} made it appropriate for the current CS decision problem. However, the company was unable to clarify which treatment components were actually addressed in this estimate. It assumed that the tariff title provided in NG52 "refers only to the transplant procedure itself", also because a similar differentiation has been made in the priorly cited NICE TAs.^{27,36} The EAG is concerned about the lack of insight into the sourced ASCT treatment composition and its cost, respectively. Furthermore, the publication is 10 years old, ignoring potential changes in cost structures in UK healthcare. Contrary, the NHS Reference Cost is a commonly used, regularly updated cost catalogue with clearly defined items to derive unit costs. It has also been used in other TAs³⁷ to derive ASCT costs. Considering that the company made a reasonable argument for the inclusion and clear differentiation of stem-cell apheresis, HDT and ASCT, the EAG preferred to use the most recent unit cost estimate of £21,247 from NHS Reference Costs 2024/2025 (ASCT unit cost from NHS Reference Costs 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions)²⁰ for ASCT in its EAG base-case, as presented in a scenario upon clarification (clarification response Table 17).
- c) The company costed ICU events for 5% of ASCT patients, based on literature and clinical expert feedback indicating a range of 5-11%.^{16,32,33} However, it stated during clarification that this assumption could not be validated with TRIANGLE as the trial did not capture the frequency of ICU events. According to the company, literature reported that ICU admissions would be mainly due to sepsis.^{32, 33} The EAG clinical expert agreed with the company's estimate, expecting likewise 5-10% having 5-day ICU admissions. The company further detailed that it does not expect double counting with healthcare resource utilisation (HCRU) associated with grade ≥ 3 AEs occurring in over 5% of patients in either TRIANGLE treatment Arm, as AEs were costed as non-elective short stays. These costs (ranging from £520.26 to £750.35) were considerably lower than HCRU associated with ICU events (£2,405.64/day). The EAG excluded ICU event costs in a scenario.
- d) Considering drug wastage, the CS health economic model base-case captures vial wastage such that intravenously administered vials may not be shared, but failed to incorporate per-pack costing for oral drugs, i.e., ibrutinib, prednisone and zanubrutinib. In response to clarification question B24 b), an exploratory scenario was presented which assumed that upon progression from first-line to second-line, half a pack of ibrutinib would be wasted, likewise for second-line to progression (third-line or death) for ASCT patients receiving ibrutinib. Due to low costs, prednisone was not adjusted. Zanubrutinib was not addressed. The scenario had a minor effect on incremental costs. The EAG noted that the log of model adaptations provided during clarification showed that oral wastage existed in the model but was removed,³⁸ with row 87 stating: "Removed oral wastage, including the relevant dropdown/row on the Drug and Admin Costs sheet and corresponding AND functions in the cost per dose calculations on the two Costs sheets (leaving IV wastage only)." The EAG criticises the thereby introduced, inconsistent approach on drug wastage which is not in line with NICE guidance and likely favours ibrutinib. It is concerned that the current scenario analysis fails to capture oral drug wastage apparent in UK clinical practice. Lacking options, it applied the available vial wastage setting together with the above-mentioned scenario on ibrutinib oral wastage presented by the company in response to clarification question B24 in the EAG base-case. However, in future

company analyses, the EAG would appreciate the inclusion of per-pack costing for oral drugs in line with NICE guidance.

- e) Subsequent treatments (second-line and third-line) were informed by expert opinion and showed high variability in treatment options and distributions considered applicable for UK clinical practice.^{8,16} Particularly, the company's clinical experts' expectations on second-line prescription of zanubrutinib to ibrutinib patients varied from 20% to 80%⁸ (clarification question B20). Moreover, the EAG clinical expert considered the subsequent treatment distributions for patients receiving 1L ibrutinib to be highly uncertain (in writing¹⁵ and orally during a meeting on 11 March 2026). Firstly, she questioned whether zanubrutinib would realistically be used as a 2L option in UK clinical practice following prior ibrutinib, given its positioning in treatment pathways and the uncertain appropriateness of switching to another BTK inhibitor after efficacy loss. Secondly, ASCT was also considered a potential (off-label) 2L option for patients who do not complete the full ibrutinib 1L treatment regimen. The EAG clinical expert did agree however on expected 2L and most shares for 3L treatment distributions for ASCT. The EAG is concerned about the uncertainty surrounding subsequent treatments and considers it a key issue. In a scenario analysis, the EAG informs subsequent treatment distributions by the EAG clinical expert's estimates (shared during a meeting on March 11th, 2026).

Table 4.9: Distribution of subsequent treatment use in 2/3L informed by EAG clinical expert used in a scenario analysis.

Treatment Arm	Subsequent treatment	First-line treatment	
		Ibrutinib	ASCT
Second-line treatment	Ibrutinib	-	10.0%
	Zanubrutinib	-	84.8%
	R-BAC	59.5%	2.4%
	BR	39.5%	2.0%
	BSC	1.1%	0.8%
Third-line treatment	R-BAC	-	50.0%
	BR	-	25.0%
	BSC	100%	25.0%

ASCT = autologous stem-cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; R-BAC = rituximab = bendamustine and cytarabine

- f) Annual resource use was assessed for ibrutinib and ASCT regimens for the FF 1L state, further specified by on active treatment (consolidation or maintenance) or off active treatment, as well as in the PF 2L and PD states. Following the EAG's request (clarification question B22), the company removed discrepancies apparent in annual resource use frequencies between the CS and clinical expert advice.¹¹

For PF 2L and PD, the company assumed resource use to be identical irrespective of second-line and third-line treatment received. This simplifying assumption is expected to have minor impact on cost-effectiveness conclusions according to the EAG.

Next to that, the EAG clinical expert expressed doubts that the annual resource use reported in the CS accorded with UK clinical practice in writing¹⁵ as well as orally during a meeting on 11 March 2026. However, the EAG does not expect these divergences in expected resource use to detrimentally affect conclusions on CE, as the EAG clinical expert did not highlight differences

between ibrutinib and ASCT treatment Arms. She did however flag the potential for double counting of resource use during ASCT consolidation (as this is provided in an inpatient setting, and ASCT costs were incorporated separately (addressed in Section 4.2.9 b) which again would, if so, only minorly decrease ASCT costs.

4.2.10 Disease severity

According to the CS: “this technology is not expected to meet the criteria for a severity modifier for this appraisal”.

EAG comment: The approach is in concordance with the NICE reference case.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

All reported results are based on the original CS, prior to EAG clarification phase. The company provided ICERs and iNHBs considering a WTP threshold of £30,000.

Both the CS deterministic and probabilistic base-case results indicated that ibrutinib with the PAS discount of █% is the dominant treatment alternative when compared to ASCT. █ (CS Tables 79, 81). In deterministic analyses, ibrutinib incurred incremental QALYs of █ and costs of █ versus ASCT (Table 5.1).

Table 5.1: Company's deterministic base-case CE results (with PAS)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000*	NHB at £30,000
Ibrutinib regimen	█	█	-	-	-	-	-
ASCT regimen	£205,721.59	█	█	█	Dominance	█	█

Source: CS Table 80.³
 * Calculated by EAG using the CS health economic model.
 ASCT = autologous stem cell transplantation; CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; PAS = Patient Access Scheme; QALY = quality-adjusted life year

The CS base-case probabilistic results indicated an incremental QALY gain of █ with ibrutinib compared to ASCT and reduced incremental costs of █ (Table 5.2).

Table 5.2: Company's probabilistic base-case CE results (with PAS)

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)	NHB at £20,000*	NHB at £30,000
Ibrutinib regimen	█	█	-	-	-	-	-
ASCT regimen	£207,013.07	█	█	█	Dominance	█	█

Source: CS Table 78.
 * Calculated by EAG using the CS health economic model.
 ASCT = autologous stem cell transplantation; CE = cost effectiveness; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; PAS = Patient Access Scheme; QALY = quality-adjusted life year

5.2 Company's sensitivity and scenario analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses (CS Section 3.11). The PSA encompassed 500 simulations, informed by a convergence plot for the ICER. The CE plane showed that in all simulations, positive incremental QALY gains were reached but incremental costs ranged in both

positive and negative quadrants. Ibrutinib indicated a [REDACTED]% ([REDACTED]%) probability of being cost-effective versus ASCT considering the £20,000 (£30,000) WTP threshold per QALY gained.

The CS stated that the DSA varied all parameters *ceteris paribus*, using $\pm 10\%$ for parameters when no 95% CI information or published ranges were available. The DSA identified the weighted average HR applied to derive second-line disease progression transition probability, the ibrutinib maintenance phase RDI and the AMR for the ASCT regimen in the FF 1L health state as the most impactful parameters. However, none changed the overall conclusion on CE.

The presented scenario analyses addressed uncertainties with regard to clinical effectiveness (Scenario 1-5, 8), utilities (Scenario 6, 7) and changes in the time horizon (Scenario 9). The following Scenarios had the largest impact on the probabilistic NHB at £30,000, although none changed the conclusions on CE:

- Second-line TTP extrapolation: exponential (Scenario 4), decreased NHB by [REDACTED]% to [REDACTED]
- Time horizon of 20 years (Scenario 9), decreased NHB by [REDACTED]% to [REDACTED]
- ASCT disutility scenario (Scenario 7), increased NHB by [REDACTED]% to [REDACTED]

EAG comments: The main concerns of the EAG relate to: a) input parameters not included in uncertainty analyses in health economic model, b) range applied to parameters with missing standard errors, c) most costs accruing in second-line.

- a) Upon EAG request (clarification response B26⁸), the company detailed the parameters not included in uncertainty analyses. Among others, RDIs except the one of ibrutinib were not varied, which the company justified with its categorical assumption of setting it to 100%. The EAG is concerned that ruling out variation for these RDIs could underestimate uncertainty. Although not listed by the company, the EAG further noticed that subsequent treatment distributions (although depicting considerable variation in estimates informed by clinical experts, see clarification response B20⁸) were neither reported in the “Parameter” sheet (which details inclusion in DSA/PSA) nor varied (presumably). Consequently, the EAG is not reassured that there are no additional input parameters missing in the DSA/PSA nor mentioned during clarification by the company but lacks a comprehensive overview, as the company did not adapt the model to make the “Parameter” sheet the sole source of model inputs (see Section 5.3, EAG comment a).
- b) According to the CS, parameters missing information on credibility intervals were assigned $\pm 10\%$ (lower/upper limit) of the deterministic value. From these, standard errors were calculated. As this assumption was made for most inputs, the EAG requested the company during clarification to perform a SLR to inform input parameters, CIs and their standard errors. However, it was not provided. The model settings facilitated a change to $\pm 30\%$ of the deterministic value, which the EAG would prefer to be used for standard errors (calculating CIs based on standard errors) in case of missing variation information in future analyses.
- c) The EAG noticed that [REDACTED] accrue during second-line (CS Table 82), despite the treatment under appraisal being modelled as first-line and its direct costs and gains being solely captured in the FF-1L health state. This further exacerbates issues identified in second-line by the EAG, where treatment distributions are informed by clinical expert opinion depicting high variation in estimates, and the EAG clinical expert expressing opposition to those following ibrutinib first-line in writing¹⁵ and orally (see EAG comments Section 4.2.4, a), Section 4.2.9, e)). The EAG set subsequent ASCT treatment distributions equal to subsequent treatment distributions for ibrutinib in a scenario, quantifying the major impact of assumptions surrounding these on CE. In summary, the EAG is concerned about the large, disproportional impact of second-line costs in light of the CS DP addressing a first-line treatment,

aforementioned uncertainties and those detailed in earlier Sections, and would like to see these addressed in future analyses.

5.3 Model validation and face validity check

5.3.1 Face validity assessment

The CS Section 3.14.1. states that the model structure, inputs and assumptions were reviewed by external health economic and UK MCL clinical experts. Survival data extrapolation was aligned with NICE TSD 14.³⁹

5.3.2 Technical verification

Technical verification of the health economic model was performed by health economists not involved in its development. They validated its logical consistency, calculations, inputs and their assigned distributions, VBA macros as well as assessed the face validity of model outcomes and the extreme value sensitivity analysis. No information on used validation checklists and findings was provided in this Section.

5.3.3 Comparisons with other technology appraisals

CS Section 3.14.1. states that the current CS used “similar” model inputs and approaches as in TA502³⁵ and TA891.⁴⁰

5.3.4 Comparison with external data used to develop the economic model

The internal validity of the model’s survival predictions for first-line FFS were compared to the observed K-M data in TRIANGLE (CS Figure 29). FFS and OS model outcomes were validated against clinical expert estimates.

5.3.5 Comparison with external data not used to develop the economic model

The company states that predicted OS estimates for ASCT were aligned with estimates for patients with untreated MCL in literature.⁴¹⁻⁴³ The CS further mentions “long-term studies” which were used for model outcome validation, yet no reference was provided for these. No further UK sources used were specified in this Section.

EAG comments: The main concerns of the EAG relate to: a) model transparency, b) validity assessments, c) limited cross-validation of CS, d) face validity of health economic model inputs, structure and outcomes as well as external validation.

- a) The CS health economic model’s “Parameter” sheet was not the original source of input values. This leaves room for error and decreases transparency, hindering comprehensive checking of model inputs and assumptions (such as uncertainty settings). Although requested by the EAG, the company did not update the health economic model accordingly but rather introduced additional guidance and labelling, stating that “With the exception of survival parameters, all model inputs are fed into and varied in the ‘Parameters’ sheet in the model”. However, for instance subsequent treatment distributions were not listed in the “Parameter” sheet. The EAG is concerned that more such errors might have occurred, and felt constrained in its ability to perform comprehensive model checking. Furthermore, several model mechanisms such as tunnel states and inclusion of efficacy inputs into the PSA seem to be implemented in VBAs. Taken together with the speed of VBAs

(used for PSA, DSA, scenarios), with e.g. 1,000 simulations for the PSA despite updating still taking one hour, the EAG sees serious transparency issues with regard to the health economic model setup, considering it a Key Issue. For its EAG analyses, it used 1,000 simulations. In future analyses, it would like to see that the company adheres to NICE guidance on parameter inclusion for uncertainty analyses,¹ supplemented with updated information on which parameters were included in uncertainty analyses, and if so, how they were included, with a strong preference to move VBA calculations insofar possible to the base Excel model environment.

- b) During clarification, the EAG requested more information on the performed validity assessments, findings as well as the provision of the TECH-VER checklist.² The company elaborated on validity assessments, provided a document used for technical verification and a log of model adaptations. Whereas the former addressed some of the items captured in the TECH-VER checklist, it is less exhaustive and does not provide information on changes performed on the found errors. Unfortunately, the company was unable to provide the TECH-VER checklist. The log of model adaptations could not easily be matched with the technical verification document but nevertheless proved insightful. Its transparency could have been strengthened by more detailed descriptions of changes and time logs.
- c) The EAG was concerned about the minimal cross-validation reported in CS Section 3. During clarification, the company reiterated that its economic SLR did not identify any prior NICE TAs in patients with previously untreated MCL eligible for ASCT and hence referred again to the two other ibrutinib appraisals^{35,40} which showed comparable model structures and features. The company mentioned one economic evaluation of VR-CAP versus R-CHOP in patients with untreated MCL who are ineligible for HSCT⁴⁴ reported in CS Appendix E.1.3, which was discarded because of differences between ASCT-eligible and ASCT-ineligible patient populations.¹⁶ The company further referred to justifications provided throughout the CS, during clarification, the validation performed by clinical experts, and the sensitivity and scenario analyses, concluding that no additional comparisons would be presented in response to clarification question B30. The EAG is concerned about the lack of cross-validation with other TAs (excluding in-house ibrutinib ones) or studies for (or beyond) the CS patient population and would have preferred if the company broadened the scope accordingly, to facilitate some comparison. However, it acknowledges the limited options the company had to respond to this issue.
- d) The EAG asked the company to elaborate on face validity assessments and external validations. The company responded that the November 2025 Advisory Board meeting¹⁶ was instrumental to assess the inclusion of external data sources to inform survival, the use of a (semi) Markov model versus a partitioned survival model and to capture the MCL disease course. During this meeting, model transition probabilities, utilities, subsequent treatment efficacies and distributions, and costs and resource use were also validated. For some, e.g. expected FFS, OS and subsequent treatment distributions, the experts had to provide estimates individually beforehand. Additionally, during clarification the company provided external validation with both evidence used and not used to develop the health economic model. Concerning evidence used to develop the economic model, the company reiterated on the appropriateness of TRIANGLE and RAY-3001, the use of clinical feedback for both model in- and outputs, the alignment of FFS and OS extrapolations of predicted landmark estimates with UK clinical expert estimates. Unfortunately, the company did not explore whether the model can reproduce the observed TTF/FFS curve from TRIANGLE when the transitions are recombined, as requested by the EAG. Concerning evidence not used to develop the economic model, the EAG made specific reference to the Haematological Malignancy Research Network (HMRN), an ongoing population-based UK cohort of patients with haematological cancers and related disorders.⁴⁵ The company did not perform an external validation with this population, flagging the mismatch in patient populations with HMRN capturing all MCL

patients, thus likely more frail and older ones with less use of ASCT, and the considerable difference in 5-year OS. However, the company referenced an HMRN analysis⁴⁶ on 22 patients with untreated MCL who received ASCT, showing 1-year and 3-year OS of 95.5% and 85.5%, respectively (CS health economic model: 1-year and 3-year OS of 97.2% and 88.5%).

6. Evidence Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the Key Issues related to the CE categorised according to the sources of uncertainty as defined by Grimm 2020:⁴⁷

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the Key Issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the Key Issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the EAG base-case.

6.1.1.1 Fixing errors

None identified

6.1.1.2 6.1.1.2 Fixing violations

1. Use NHS Reference Costs 2024/25 for ASCT (Section 4.2.9)
The EAG preferred to use the most recent unit cost estimate of £21,247 from NHS Reference Costs 2024/2025 (ASCT unit cost from NHS reference unit cost 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions)

6.1.1.3 Matters of judgement

2. Assume equal pre-failure mortality between ibrutinib and ASCT regimens (Section 4.2.6)

The EAG is concerned that, for ASCT, long-term pre-failure mortality in the company's base-case is currently overestimated and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case.

3. Set RDI of all drug treatments (including ibrutinib) to 100% (Section 4.2.9)

The company only had RDI information for ibrutinib, collected within TRIANGLE during induction and maintenance. For all other treatment (lines), including when ibrutinib was used as a second-line treatment option, the company made the simplifying assumption of a 100% RDI. The EAG decided to follow a coherent approach, standardising the RDI for all treatments to 100% in its base-case.

4. Drug wastage: use CS vial wastage and add scenario on ibrutinib wastage received during clarification (Section 4.2.9)

The CS health economic model base case captures vial wastage such that IV administered vials may not be shared, but failed to incorporate per-pack costing for oral drugs. During clarification, a scenario was presented which assumed that upon progression from first-line to second-line, half a pack of ibrutinib would be wasted, likewise for second-line to progression (third-line or death) for ASCT patients receiving ibrutinib.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

5. Second-line treatment efficacy: HR of 1.00 for ibrutinib versus R-BAC, HR of 1/1.77 for ibrutinib versus BR and ibrutinib versus BSC. (Section 4.2.6)
6. Use log-normal for extrapolation of TTF in ASCT regimen (Section 4.2.6)
7. Use exponential for extrapolation of TTP (Section 4.2.6)
8. Exclude ICU stays for ASCT (Section 4.2.9)
9. Use subsequent treatment distributions informed by EAG clinical expert (Section 4.2.9)
10. Use subsequent treatment distributions from ibrutinib for ASCT (Section 4.2.9)

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of Key Issues related to the CE (conditional on FEs highlighted in Section 5.1)

Key Issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER ^a	Resolved in EAG base-case ^b	Required additional evidence or analyses
Model structure: The modelling of ASCT	4.2.2	Methods	Explicitly incorporating ASCT in model structure	+	No	Yes
Treatment effectiveness and extrapolation: Pre-failure mortality	4.2.6	Methods	Explicitly modelling ASCT-related mortality	+	Partly (EAG adjustment 2)	No
Treatment effectiveness and extrapolation: Second-line treatment effectiveness	4.2.6	Bias & indirectness/unavailability of evidence	Including differential second-line treatment effectiveness depending on first-line treatment	+	No	Yes
Resource use and costs: subsequent treatment (distributions) for ibrutinib patients.	4.2.9	Unavailability of evidence	Scenarios with alternative inputs	Unclear	No	Yes
Model validation and face validity check: model transparency	5.3	Transparency and methods	Adhering to good modelling practices and (reporting on) technical model validation	Unclear	No	Yes

^a Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator.

^b Explored.

ASCT = autologous stem cell transplant; CE = cost effectiveness; EAG = Evidence Assessment Group; FE = fixing errors; FV = fixing violations; MJ = matters of judgement; ICER = incremental cost-effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. Table 6.3 provides probabilistic results of both the EAG and company base-cases. The exploratory scenario analyses are presented Tables 6.4 and 6.5. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the “EAG” sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic EAG base-case

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Deterministic CS base-case (updated as per clarification response)							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_1: Use NHS Reference Costs 2024/25 for ASCT							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_2: Assume equal pre-failure mortality between ibrutinib and ASCT regimens (set pre-failure mortality of ASCT equal to ibrutinib)							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_3: Set RDI of all drug treatments (incl. ibrutinib) to 100%							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_4: Drug wastage: add scenario on ibrutinib wastage received during clarification to current CS vial wastage							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
Deterministic EAG base-case (combining all of the above)							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
ASCT = autologous stem cell transplantation; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; NHS = National Health Service; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness-to-pay							

Table 6.3: Probabilistic EAG base-case

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Probabilistic CS base-case (updated as per clarification response)							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Probabilistic EAG base-case							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
ASCT = autologous stem cell transplantation; CS = company submission; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; Incr. = incremental; NHB = net health benefit; QALY = quality-adjusted life-year; WTP = willingness-to-pay							

Table 6.4: Deterministic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Deterministic EAG base-case							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_5: Second-line treatment efficacy: HR of 1.00 for ibrutinib versus R-BAC, HR of 1/1.77 for ibrutinib versus BR and ibrutinib versus BSC							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma"							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_7: Use exponential for extrapolation of TTP: set to "Exponential" from "Log-logistic"							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_8: Exclude ICU stays for ASCT							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_9: Use subsequent treatment distributions informed by EAG clinical expert							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_10: Use subsequent treatment distributions from ibrutinib for ASCT							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; CS = company submission; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; Incr. = incremental; NHB = net health benefit; NHS = National Health Service; QALY = quality-adjusted life-year; R-BAC = rituximab, bendamustine and cytarabine; RDI = relative dose intensity; TTF = time-to-failure; TTP = time-to-progression; WTP = willingness-to-pay							

Table 6.5: Probabilistic scenario analyses (conditional on EAG base-case)

Technologies	Total costs	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)	NHB (WTP = 20,000)	NHB (WTP = 30,000)
Probabilistic EAG base-case							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_5: Second-line treatment efficacy: HR of 1.00 for ibrutinib versus R-BAC, HR of 1/1.77 for ibrutinib versus BR and ibrutinib versus BSC							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma"							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_7: Use exponential for extrapolation of TTP: set to "Exponential" from "Log-logistic"							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_8: Exclude ICU stays for ASCT							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_9: Use subsequent treatment distributions informed by EAG clinical expert							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
EAG_10: Use subsequent treatment distributions from ibrutinib for ASCT							
Ibrutinib	██████	██████	-	-	-	-	-
ASCT	██████	██████	██████	██████	██████	██████	██████
ASCT = autologous stem cell transplantation; BR = bendamustine and rituximab; BSC = best supportive care; CS = company submission; EAG = External Assessment Group; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; ICU = intensive care unit; Incr. = incremental; NHB = net health benefit; NHS = National Health Service; QALY = quality-adjusted life-year; R-BAC = rituximab, bendamustine and cytarabine; RDI = relative dose intensity; TTF = time-to-failure; TTP = time-to-progression; WTP = willingness-to-pay							

6.3 EAG's preferred assumptions

The estimated EAG base-case ICER (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, was ██████ per QALY gained. The probabilistic EAG base-case analyses indicated CE probabilities of █████% and █████% for the ibrutinib regimen at WTP thresholds of £20,000 and £30,000 per QALY gained. The most influential adjustments were using NHS Reference Costs 2024/25 for ASCT and consistently setting the RDIs of all drug treatments to 100%. The ICER increased most in the scenario analysis with alternative assumptions regarding a) the extrapolation of TTF for ASCT (first-line), b) the extrapolation of TTP (second-line) as well as c) the subsequent treatment distributions.

6.4 Conclusions of the cost effectiveness Section

The CS, Appendices E, F and G, and response to clarification letter provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant studies on economic and QoL

aspects of ibrutinib with R-CHOP for untreated MCL when an ASCT is suitable.^{3, 8, 14} Searches were conducted in December 2023, with updates in May 2025 and October 2025. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases, conference proceedings and HTA resources were searched. The comments of the EAG are recorded above, but overall, the EAG has no major concerns about the literature searches conducted. The company's CE model complied with the NICE reference case. However, the EAG identified important areas of uncertainty relating to:

- 1) The modelling of ASCT.
- 2) The estimation of treatment effectiveness including first-line pre-failure mortality and second-line treatment effectiveness.
- 3) The estimation of subsequent treatment distributions and related costs.
- 4) The transparency and technical verification of the economic model.

Firstly, a key structural concern related to the modelling of ASCT. In the company's economic model, the effects of ASCT were implicitly captured through first-line transitions. As a result, long-term benefits of ASCT in terms of survival and HRQoL were not explicitly modelled, while the pre-failure mortality risk associated with ASCT appeared to be overestimated. The EAG considered this particularly important because ASCT is a defining feature of the comparator pathway and its effects are likely to extend beyond first-line treatment. The EAG therefore considered that the current modelling may underestimate the value of the ASCT-based strategy in terms of long-term effectiveness as well as potential HRQoL gains. Further analyses explicitly modelling ASCT, for example through ASCT-specific health or tunnel states, would help reduce this uncertainty. Related to this, the EAG identified substantial uncertainty in the estimation of treatment effectiveness and extrapolation. The company's base-case assumed differential pre-failure mortality between the ibrutinib and ASCT regimens, based on a small number of events in TRIANGLE and modelled this using an annual mortality rate approach rather than parametric survival modelling. The EAG considered this approach clinically implausible, particularly because ASCT-related mortality risk would be expected to be elevated in the short-term and lower thereafter, rather than being constant over time. In the absence of separate modelling of ASCT-related mortality, the EAG preferred to assume equal pre-failure mortality between regimens in its base-case.

Secondly, additional uncertainty arose because first-line transitions were informed by TRIANGLE, whereas transitions beyond first-line were informed by RAY-3001. The EAG questioned the suitability of RAY-3001 for this purpose because all patients in RAY-3001 were ibrutinib-naïve at study entry and prior ASCT use was limited. Therefore, the company's approach is likely to overestimate second-line effectiveness for patients treated with the ibrutinib regimen at first-line and underestimate second-line effectiveness for patients treated with the ASCT regimen at first-line. The EAG also questioned the company's approach to informing relative second-line treatment effectiveness from MANTLE-FIRST, because the HRs did not capture potential treatment-effect modification by TTP. Scenario analyses exploring alternative assumptions for second-line treatment effectiveness substantially increased the ICER, indicating that this is a major source of decision uncertainty.

Thirdly, the EAG identified important uncertainty in the estimation of treatment costs and healthcare resource use. In its base-case, the EAG updated the ASCT cost using the most recent NHS Reference Cost (2024/25), which had a substantial impact on costs for the ASCT regimen. For consistency, the EAG standardised the RDI of all drug treatments to 100%, because the company had only observed RDI data for ibrutinib and assumed 100% RDI for all remaining treatments. The EAG also noted uncertainty in the modelling of drug wastage and, more importantly, in the subsequent treatment

distributions used after first-line treatment. These subsequent treatment assumptions, informed by the company's clinical experts, drive a large proportion of total costs and differed from the views of the EAG's clinical expert. Scenario analyses demonstrated that alternative assumptions regarding subsequent treatment distributions materially affected the CE results.

Finally, the EAG expressed concerns regarding model transparency, technical verification and the characterisation of uncertainty. The submitted model did not use the parameter sheet as the primary source of model inputs, which reduced transparency and made systematic interrogation of the model more difficult. In addition, the model had relatively long run times for uncertainty analyses.

The probabilistic CS base-case (updated at clarification response) indicated that the ibrutinib regimen was both more effective (■■■■ QALY gain) and less costly (■■■■ savings) and thus dominated the ASCT regimen. The EAG base-case incorporated the following changes relative to the company base-case: use of NHS Reference Costs 2024/25 for ASCT, equal pre-failure mortality between the ibrutinib and ASCT regimens, standardisation of RDI for all drug treatments to 100%, and use of the company's vial wastage assumptions together with the simplistic clarification scenario for ibrutinib pack wastage. Based on these assumptions, the probabilistic EAG base-case ICER was ■■■■ per QALY gained. The probabilistic EAG base-case analyses indicated CE probabilities of ■■■■% and ■■■■% for the ibrutinib regimen at WTP thresholds of £20,000 and £30,000 per QALY gained, respectively. The most influential changes in the EAG base-case were the use of NHS Reference Costs 2024/25 for ASCT and the assumption of 100% RDI for all drug treatments. In the exploratory scenario analyses, the ICER increased most under alternative assumptions regarding the extrapolation of TTF for the ASCT regimen in first-line, the extrapolation of TTP in second-line, and the subsequent treatment distributions. These findings indicate that the model results are particularly sensitive to assumptions regarding treatment pathway structure, extrapolation of clinical effectiveness and subsequent treatment effectiveness and costs.

Overall, substantial uncertainty remains regarding the CE of the ibrutinib regimen compared with the ASCT regimen. The most important unresolved issues relate to the modelling of ASCT, the estimation of pre-failure mortality and second-line treatment effectiveness and the representation of subsequent treatment pathways in UK clinical practice. Further analyses explicitly incorporating ASCT-related long-term benefits, more appropriate evidence to inform treatment effects beyond first-line, and stronger evidence on subsequent treatment distributions would help reduce decision uncertainty.

7. References

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Single Technology Appraisal

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 15 April 2026** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **'confidential'** should be highlighted in turquoise and all information submitted as **'depersonalised data'** in pink.

Major Issues

Issue 1 Statements regarding the impact of prior BTKi exposure on differential BTKi efficacy lack empirical evidence

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 17, Section 1.5 ‘Scenario analyses in which differential second-line treatment effectiveness is not only reflected by the distributions of patients receiving different second-line treatments, but also by decreased BTKi efficacy in treatment-experienced versus treatment-naïve patients.’ Page 82, Section 4.2.6 ‘The company assumed that second line BTKi treatment (either ibrutinib or zanubrutinib) is equally effective in BTKi-experienced patients (i.e. received ibrutinib regimen at first-line) and BTKi naïve patients (i.e. received ASCT regiment at first-line). The EAG and EAG clinical expert anticipate that effectiveness would likely be lower in retreated patients.’	Please amend the text as follows: Page 17, Section 1.5 ‘Scenario analyses in which differential second-line treatment effectiveness is not only reflected by the distributions of patients receiving different second-line treatments, but also by potential decreased BTKi efficacy in treatment-experienced versus treatment-naïve patients. The EAG however acknowledge that there is no empirical evidence to support an assumption of differential BTKi efficacy in treatment-experienced versus treatment-naïve patients and therefore any scenario assessing this potential uncertainty would be purely arbitrary.’ Page 82, Section 4.2.6 ‘The company assumed that second line BTKi treatment (either ibrutinib or zanubrutinib) is equally effective in BTKi-	To avoid misleading statements and improve transparency, the EAG report should acknowledge the lack of empirical evidence to support assumptions of differential BTKi efficacy in treatment-experienced versus treatment-naïve patients in this setting. Given the 2-year fixed duration nature of the ibrutinib regimen, the vast majority of patients who progress following first-line treatment do so after they have finished their fixed-duration treatment. As such, for the vast majority of patients, progression to second-line treatment is not correlated with a loss of efficacy of ibrutinib. This is supported by data from the economic model; median FFS within the economic analysis is ■■■ years whereas only ■■■ of patients treated with the ibrutinib regimen have progressed to second-line treatment at 2 years. As such, there is no biological reason as to why patients who receive ibrutinib at 1L would	Not a factual inaccuracy

	experienced patients (i.e. received ibrutinib regimen at first-line) and BTKi naïve patients (i.e. received ASCT regimen at first-line). The EAG and EAG clinical expert anticipate that effectiveness would likely be lower in retreated patients. However, there is no empirical evidence in this setting to support this assumption and available evidence in a similar indication demonstrates that CLL/SLL patients remain sensitive to BTKis following fixed-duration treatment with ibrutinib.¹	experience reduced efficacy from a BTKi at 2L given that they have not previously 'failed' on a BTKi. To the best of the Company's knowledge, there is no empirical evidence to support differential treatment efficacy in this setting following a fixed-duration BTKi. On the contrary, empirical evidence exists which demonstrates that chronic lymphocytic leukaemia/small lymphocytic lymphoma patients remain sensitive to a BTKi following prior treatment with fixed-duration ibrutinib. As such, whilst not in MCL specifically, there is clear empirical evidence that patients remain sensitive to a BTKi following prior treatment with fixed-duration ibrutinib in lymphoma more broadly.¹ It is therefore factually inaccurate to imply that differential efficacy definitely exists in this setting and contradicts available empirical evidence. Statements relating to differential BTKi efficacy at 2L should therefore be amended to make clear that any predicted differences are based solely on opinion and are not supported by empirical evidence. It should additionally be made clear that any scenario analyses exploring such	

		differential efficacy would be purely arbitrary.	
Page 93, Section 4.2.9.7 ‘...given its positioning in treatment pathways and the uncertain appropriateness of switching to another BTK inhibitor after efficacy loss.’	Please amend the text as follows: ‘...given its positioning in treatment pathways ~~and the uncertain appropriateness of switching to another BTK inhibitor after efficacy loss.~~	There is no uncertainty in the economic model relating to patients losing efficacy with a BTKi at first-line switching to a BTKi and therefore this statement is factually inaccurate and should be removed. As noted in the response above, given ibrutinib is a fixed-duration regimen, progression following treatment with ibrutinib is rarely related to loss of efficacy of ibrutinib. This is supported by data from the economic model; median FFS within the economic analysis is ■■■ years whereas only ■■■ of patients treated with the ibrutinib regimen have progressed to second-line treatment at 2 years. As such, switching to another BTKi following loss of efficacy of ibrutinib at first-line is not anticipated to be a relevant issue for the vast majority of patients in UK clinical practice. Furthermore, as described in response to Clarification Question B7, it was assumed that any patients who experience early disease relapse on treatment with the ibrutinib regimen at first-line would be considered BTKi-	Not a factual inaccuracy

		resistant in clinical practice and therefore would not receive a BTKi at second-line. These patients are captured in the economic model via the proportion of patients in the second-line treatment distributions post-ibrutinib <u>not</u> receiving treatment with a BTKi at second-line. As such, there is no uncertainty in the economic model relating to patients losing efficacy with a BTKi at first-line switching to a BTKi and therefore this statement is factually inaccurate and should be removed.	

Issue 2 Incorrect statements regarding the impact of the Company's approach to long-term modelling of the ASCT regimen

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 14, Section 1.4 '.... the toxic effects of ASCT are potentially serious and include mortality, but short-term, whereas the those of ibrutinib are longer term and likely to reduce HRQoL.' Page 15, Section 1.5 'Long-term benefits of ASCT, in terms of both survival and HRQoL increase,	Please amend the text as follows: Page 14, Section 1.4 '.... the toxic effects of ASCT are potentially serious, with an associated substantial long-term impact on HRQoL and include mortality, ~~but short-term~~, whereas ~~the those of~~ ibrutinib is associated with reduced acute toxicity but also has some side effects that are	It is factually inaccurate to state that the Company's base case approach to modelling ASCT underestimates the relative long-term survival and HRQoL benefits of the ibrutinib regimen versus the ASCT regimen. These statements should therefore either be removed or amended as requested in the EAG report. <u>Survival</u>	Table 1.4 has been amended to address ambiguity. Comments related to sections 1.5, 1.6 4.2.2 and 6.4 did not highlight factual inaccuracies

are not (explicitly) captured in the economic model' Page 18, Section 1.6 'Further analyses explicitly incorporating ASCT-related long-term benefits, more appropriate evidence to inform treatment effects beyond first-line' Page 18, Section 1.6 'Long-term benefits of ASCT in terms of survival and health-related quality of life (HRQoL) were not explicitly modelled, while short-term mortality risks may have been overestimated. This modelling approach may underestimate the value of the ASCT-based treatment strategy.' Page 75, Section 4.2.2 'Long-term benefits of ASCT (in terms of survival, as supported by the BSH guideline) are not explicitly captured in the company's current modelling approach'	~~longer term and likely to may~~ reduce HRQoL.' Page 15, Section 1.5 'Long-term benefits and decrements of ASCT and ibrutinib, in terms of both survival and HRQoL increase, are not (explicitly) captured in the economic model; however, overall estimates of survival for both regimens are highly aligned with clinical estimates, demonstrating that the survival benefits are implicitly captured.' Page 18, Section 1.6 'Further analyses explicitly incorporating ASCT-related long-term benefits and decrements, more appropriate evidence to inform treatment effects beyond first-line. However, the EAG recognise that there is a paucity of data to inform these analyses and that they are therefore not feasible.' Page 18, Section 1.6	Johnson & Johnson would like to highlight that, unlike other indications, as ASCT is not curative in MCL, there is no robust evidence of a durable long-term ASCT benefit beyond the first-line setting in MCL.² After failure on first-line treatments, outcomes are driven mainly by subsequent therapies and disease biology. This is supported by the fact that UK and European guidance for refractory or relapsed MCL emphasise relapsed/refractory standards of care rather than historical ASCT receipt as key determinants of outcomes.^{2, 3} Therefore, there is no robust evidence of a durable long-term ASCT benefit beyond the first-line setting in MCL, with responses following treatment with the ASCT regimen likely attributable to subsequent treatment.⁴⁻⁶ As such, the Company's approach to implicitly modelling the long-term benefit of ASCT is appropriate. Furthermore, there is no empirical evidence to indicate that the base case modelling approach underestimates the long-term efficacy of the ASCT regimen. Long-term OS estimates from the base-case model were validated against UK clinical practice and external literature of	

Page 106, Section 6.4 ‘As a result, long-term benefits of ASCT in terms of survival and HRQoL were not explicitly modelled’ Page 106, Section 6.4 ‘The EAG therefore considered that the current modelling may underestimate the value of the ASCT-based strategy in terms of long-term effectiveness as well as potential HRQoL gains.’	‘Long-term benefits of ASCT and ibrutinib in terms of survival and health-related quality of life (HRQoL) were not explicitly modelled, while short-term mortality risks may have been overestimated. This modelling approach may underestimate the value associated with each treatment strategy; however, it is acknowledged that overall estimates of survival for both regimens are highly aligned with clinical estimates, suggesting that the survival benefits are implicitly captured. of the ASCT-based treatment strategy.’ Page 75, Section 4.2.2 ‘Long-term benefits of ASCT or ibrutinib (in terms of survival, as supported by the BSH guideline) are not explicitly captured in the company’s current modelling approach; however, overall estimates of survival for both regimens are highly aligned with clinical estimates, demonstrating	ASCT-treated patients. Model-predicted OS at 10, 15 and 20 years for the ibrutinib and ASCT regimens were clinically plausible and externally valid, with differences from clinical expert estimates of less than 2.5% at all landmark points. Additionally, predicted ASCT median OS (12.5 years) closely aligned with the Nordic MCL2 trial (12.7 years), and the model’s 7-year OS for ASCT (~70%) aligned with LyMA trial data (69.5%).⁷⁻⁹ Collectively, these data provide clear evidence that the Company’s modelling approach did not underestimate the long-term efficacy of the ASCT regimen. It should additionally be noted that the limitation regarding the lack of explicit capturing of the long-term efficacy of the ASCT regimen beyond the first line setting is consistent across model arms, given that no patients in RAY-3001 had received prior treatment with ibrutinib. As such, the Company would like to highlight that the use of data from the ibrutinib arm of RAY-3001 as the reference curve for later line transitions for both the ibrutinib and ASCT model arms likely represents a conservative approach to capturing the differential long-term efficacy of the ibrutinib regimen over the ASCT regimen. This is	

	that the survival benefits are implicitly captured.' Page 106, Section 6.4 'As a result, long-term benefits of ASCT or ibrutinib in terms of survival and HRQoL were not explicitly modelled; however, overall estimates of survival for both regimens are highly aligned with clinical estimates, demonstrating that the survival benefits are implicitly captured.' Page 106, Section 6.4 'The EAG therefore considered that the current modelling may underestimate the ~~value of the ASCT-based strategy in terms of~~ long-term effectiveness as well as potential HRQoL gains of ASCT and ibrutinib however, the EAG acknowledge that overall estimates of survival for both regimens are highly aligned with clinical estimates.'	supported by direct data from TRIANGLE; after a substantial median time on study of ~4.5 years, a nominally significant 36.7% reduction in the risk of disease progression or death in Arm I versus Arm A was observed.¹⁰ As disease progression is associated with worsening symptoms and therefore an increased clinical burden, as well as an increased risk of death, extending the time to progression is expected to translate to improvements in patient HRQoL and overall improvements in survival.¹¹ This is further supported by OS data from TRIANGLE whereby a nominally significant 48% reduction in the risk of death observed in patients receiving the ibrutinib regimens versus the ASCT regimen was reported.¹⁰ These results, combined with further efficacy results presented in Section 2.6 of the CS, clearly demonstrate that treatment with the ibrutinib regimen at first line is associated with extended survival and improved treatment efficacy in patients with untreated MCL, compared to the ASCT regimen at first line. These results would translate to long-term HRQoL and survival benefits in patients receiving first-line ibrutinib over the ASCT regimen. However, by	

		using a common reference arm to model later-line treatment efficacy for both the ASCT and the ibrutinib regimen, any continued survival benefits associated with the ibrutinib regimen are not captured in the model. As such, the approach utilised in the economic model is likely conservative. The EAG's statements regarding the impact of the Company's approach to the lack of explicit modelling of the ASCT regimen are therefore factually inaccurate and should either be removed entirely or amended as requested. Furthermore, it should be made clear that any potential limitations suggested by the EAG are applicable to both model arms; currently the EAG report only focuses on potential missing long-term benefits associated with the ASCT model arm which is misleading. <u>HRQoL</u> As described in detail in Section 1.3.5, ASCT is associated with substantial toxicity beyond the acute transplant period which translates to an extensive long-term HRQoL burden. Recovery to normal daily life, such as work, can take up to six months, leading to a long-lasting HRQoL impairment as patients must physically and psychologically	

		heal. A lymphoma patient described the experience as the “lowest point of [their] life,” noting that it took them “two to five months to feel [they] were recovering”.¹² Additionally, a 2024 long-term QoL study in the United States (US) on patients with MCL who received treatment with ASCT between 2000 and 2023 (n=106; median age at ASCT of 59 years, median follow-up from treatment with the ASCT regimen of 9.3 years) identified that 18% and 16% patients reported poorer physical and cognitive function, respectively, compared with the general population.¹³ This demonstrates that the ASCT regimen continues to detrimentally impact patients wellbeing, even ~9 years post-completion of the ASCT regimen. Conversely, there is no evidence that ibrutinib is associated with a negative long-term HRQoL impact. As such, contrary to the EAG’s statement, not explicitly modelling the long-term HRQoL impact of the ASCT or ibrutinib regimens is likely highly conservative. <u>Conclusion</u> Collectively, the above data provides clear empirical evidence that the Company’s base-case modelling approach does not underestimate long-	

		term ASCT outcomes. Whilst the Company acknowledges that some long-term effects of ASCT may not be fully captured, this represents an unavoidable limitation due to the paucity of available data in this setting, and represents a consistent limitation across both model arms which should be made clear in the report. Furthermore, given the lack of evidence for a durable long-term ASCT benefit beyond the first-line setting in MCL, and the substantial long-term HRQoL burden of ASCT, the Company's base case approach is, if anything, likely conservative. Consequently, claims that the long-term benefit of ASCT HRQoL is underreported in the Company's economic model are factually inaccurate.	
Page 14, Section 1.3, Table 1.4 'i.e. the toxic effects of ASCT are potentially serious and include mortality, but short-term,...' Page 67, Section 3.2 '...i.e. the toxic effects of ASCT are potentially serious and include mortality, but short-term,...'	Please amend as follows: Page 14, Section 1.3, Table 1.4 '...i.e. the toxic effects of ASCT are potentially serious and include mortality, ~~but short-term,...~~ Page 67, Section 3.2	As noted above, there is evidence that demonstrates the ASCT regimen continues to detrimentally impact some patients wellbeing, even ~9 years post-completion of the ASCT regimen.¹³ It is therefore not factually accurate to suggest that the detrimental impact of the ASCT regimen on patient HRQoL is short-term in all patients and therefore this statement should be removed.	Table 1.4 has been amended to address ambiguity.

	‘...i.e. the toxic effects of ASCT are potentially serious and include mortality, ~~but short-term,~~ ...’		
Page 15, Section 1.5, Table 1.5; Row: ‘What is the expected effect on the CE estimates?’ ‘Explicit inclusion of long-term ASCT benefits will likely decrease the iNMB.’ Page 102, Section 6.1.3, Table 6.1 The EAG indicate that the Company’s modelling of ASCT likely induces bias in favour of the intervention.	Page 15, Section 1.5, Table 1.5; Row: ‘What is the expected effect on the CE estimates?’ ‘The impact of Eexplicit inclusion of long-term ASCT benefits and decrements on will likely decrease the-iNMB is unknown’ Page 102, Section 6.1.3, Table 6.1 The expected impact on the ICER for the first key issue should be ‘Unclear’ rather than ‘+’.	As noted above, there is no evidence that the long-term impact of ASCT is underestimated in the current analysis, as clinical expert estimates and model-predicted estimates were closely aligned at all landmark estimates for both first-line regimens for the reconstructed FFS curves and reconstructed OS. Additionally, predicted OS estimates for the ASCT regimen were closely aligned to values reported in the literature for patients with untreated MCL, as shown in the comparison of landmark survival estimates with the MCL2 and LyMA trials above.⁷⁻⁹ As such, there is no empirical evidence to support that the current modelling approach underestimates the effectiveness of the ASCT regimen and therefore that changing the approach to the modelling of ASCT would either increase the ICER or decrease the iNMB. The expected impact on the ICER/iNMB should therefore be amended to reflect that the impact is uncertain and to maintain factual accuracy. Additionally, it should be made clear that explicit modelling of	Not a factual inaccuracy.

		ASCT would also capture the long-term decrements associated with ASCT on patient HRQoL, not just potential benefits.	
Page 82-83, Section 4.2.6.3.1 (text and Table 4.4) 'TTP estimates provided by the EAG's clinical expert suggest a substantial second-line treatment efficacy benefit for the ASCT regimen compared to the ibrutinib regimen (Table 4.4), which seems currently not reflected in the company's base-case analysis and supports the EAG's concern about the likely over- and underestimation of second-line treatment efficacy for the ibrutinib and ASCT regimens, respectively.'	This statement and the associated table (Table 4.4) should be removed.	Table 4.4 reports time to progression (TTP) in UK clinical practice for individuals receiving ibrutinib or ASCT. However, the table presents TTP values as percentages, whereas TTP is a time-to-event measure. Furthermore, it is unclear what these percentages are in relation to. The report also does not clarify what informed these estimates, for example, what subsequent treatments it was assumed that patients received following the ibrutinib or ASCT regimen. As such, the values presented appear both factually inaccurate and the underlying assumptions informing them is unclear. If these errors cannot be rectified, the table and accompanying text should be removed.	Not a factual inaccuracy.

Issue 3 Incorrect statements relating to the Company's approach to modelling pre-failure mortality

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 15/16, Section 1.5	Please amend the text as follows: Page 15/16, Section 1.5	The EAG report incorrectly states that the Company's approach to modelling pre-failure mortality	Not a factual inaccuracy.

‘..., whereas the short-term mortality risk associated with ASCT was overestimated’ ‘Additionally, the constant hazard assumption by using an annual mortality rate is clinically implausible as ASCT-related mortality risk is likely increased short-term and expected to decrease thereafter.’ Page 75, Section 4.2.2 ‘However, the EAG considers this approach clinically implausible, as it assumes a constant differential pre-failure mortality probability that is also applied to long-term failure-free patients (more detailed discussion in Section 4.2.6 comment d).’ Page 82, Section 4.2.6 ‘In response to clarification, the company justified that the high toxicity and mortality risk associated with ASCT translated to increased pre-failure mortality in the ASCT regimen.’	‘..., whereas the short-term mortality risk associated with ASCT ~~was~~ may be overestimated’ ‘Additionally, the constant hazard assumption by using an annual mortality rate ~~is~~ may be clinically implausible as ASCT-related mortality risk is likely increased short-term and expected to decrease thereafter. However, this approach was validated as preferential over the use of parametric extrapolation by an independent health economic expert consulted during the November 2025 advisory board.¹⁴’ Page 75, Section 4.2.2 ‘However, the EAG considers this approach clinically implausible, as it assumes a constant differential pre-failure mortality probability that is also applied to long-term failure-free patients. The EAG however acknowledge that this approach was validated as preferential over the use of parametric extrapolation by an independent health economic expert	overestimates ASCT-related mortality risk. The annual mortality rate (AMR) used to inform pre-failure mortality within the Company’s economic model was based on observed data from TRIANGLE, with a median follow up of 54.9 months.¹⁰ It was calculated as an annual rate averaged over the total number of person-years spent in the failure-free state which was subsequently converted into a per cycle probability for use in the economic model. It was therefore not anchored to the ASCT initiation period in TRIANGLE when pre-failure mortality on the ASCT regimen is elevated. The AMR is therefore based on appropriate direct data and does not overestimate the short-term mortality risk associated with ASCT. This is supported by feedback received from five UK clinical experts consulted at the November 2025 advisory board, who unanimously validated that the derived AMR for the ASCT regimen and its associated relative difference to the ibrutinib regimen was appropriate, with one expert	

‘In response to clarification, the company stated that the number of pre-failure mortality events was limited and parametric extrapolations would therefore be associated with considerable uncertainty. Although the EAG agrees with this statement, it considers the assumed constant hazard of an annual mortality rate clinically implausible as the ASCT-related mortality risk is likely to be higher in the first months after treatment and is expected to decrease thereafter. Despite the potential of poor fit to the observed data and implausible extrapolations when the number of observed events is limited, parametric survival modelling allows capturing the time-varying hazards associated with ASCT-related mortality risk. The EAG would therefore like to see this explored in a scenario analysis.’ Page 100, Section 6.1.1.3 ‘The EAG is concerned that, for ASCT, long-term pre-failure mortality in the company’s base-case is currently overestimated	consulted during the November 2025 advisory board (more detailed discussion in Section 4.2.6 comment d).¹⁴ Page 82, Section 4.2.6 ‘In response to clarification, the company justified that the high toxicity and mortality risk associated with ASCT translated to increased pre-failure mortality in the ASCT regimen; this was based on observed data from TRIANGLE over a follow-up period of 54.9 months.’ ‘In response to clarification, the company stated that the number of pre-failure mortality events was limited and parametric extrapolations would therefore be associated with considerable uncertainty. Although the EAG agrees with this statement, it considers the assumed constant hazard of an annual mortality rate may be clinically implausible as the ASCT-related mortality risk is likely to be higher in the first months after treatment and is expected to decrease thereafter.	noting that, if anything, the pre-failure mortality risk for the ASCT regimen was underestimated.¹⁴ Additionally, given that the number of pre-failure mortality events were limited across trial arms (22 of 269 patients – Arm A and 11 of 268 patients – Arm I), there would be insufficient evidence to inform the selection of an appropriate parametric curve. As such, any curve selected would be associated with greater uncertainty than an AMR derived from direct trial data. This was supported by feedback received from an independent health economic expert, who noted that given that the number of pre-failure mortality events were limited across trial arms an AMR-based modelling approach was more appropriate than parametric extrapolation to minimise uncertainty.¹⁴ Given these points, it is factually inaccurate to state that the Company’s base case approach over-estimates pre-failure mortality for the ASCT regimen as this directly contradicts feedback received from UK clinical experts.	

and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case.' Page 106, Section 6.4 'As a result, long-term benefits of ASCT in terms of survival and HRQoL were not explicitly modelled, while the pre-failure mortality risk associated with ASCT appeared to be overestimated.' Page 106, Section 6.4 'The EAG considered this approach clinically implausible, particularly because ASCT-related mortality risk would be expected to be elevated in the short-term and lower thereafter, rather than being constant over time.' Page 106, Section 6.4 'Therefore, the company's approach is likely to overestimate	However, use of an AMR and the value used by the company were validated as appropriate by UK clinical experts, with an independent health economist also noting that this approach is preferential over the use of parametric extrapolation.¹⁴ Despite the potential of poor fit to the observed data and implausible extrapolations when the number of observed events is limited, parametric survival modelling allows capturing the time-varying hazards associated with ASCT-related mortality risk. The EAG would therefore like to see this explored in a scenario analysis.' Page 100, Section 6.1.1.3 'The EAG is concerned that, for ASCT, long-term pre-failure mortality in the company's base-case may is currently be overestimated and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case.'	As a minimum, these sentences should be revised to 'may over-estimate' given that this is simply an opinion and is not supported by empirical evidence. Furthermore, to improve transparency, statements relating to pre-failure mortality should make clear that the Company's approach to modelling pre-failure mortality was based on direct data from TRIANGLE and considered both clinically plausible and more appropriate than parametric extrapolation by clinical and health economic experts.	

second-line effectiveness for patients treated with the ibrutinib regimen at first-line and underestimate second-line effectiveness for patients treated with the ASCT regimen at first-line.'	Page 106, Section 6.4 'As a result, long-term benefits of ASCT in terms of survival and HRQoL were not explicitly modelled, while the pre-failure mortality risk associated with ASCT ~~appeared to~~ may be overestimated. Page 106, Section 6.4 This statement should be removed Page 106, Section 6.4 'Therefore, the company's approach ~~is likely to~~ may overestimate second-line effectiveness for patients treated with the ibrutinib regimen at first-line and may underestimate second-line effectiveness for patients treated with the ASCT regimen at first-line.		
Page 82, Section 4.2.6 'The EAG requested a scenario analysis including separate modelling of ASCT-related	Please amend as follows: Page 82, Section 4.2.6 The EAG requested a scenario analysis including separate	The scenario analysis that sets pre-failure mortality equal between the ASCT regimen and the ibrutinib	Not a factual inaccuracy.

mortality, but the company did not provide this arguing that this would further reduce the sample size informing this transition. The EAG is concerned that long-term pre-failure mortality in the company's base-case is currently overestimated and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case.' Page 107, Section 6.4 'Further analyses explicitly incorporating ASCT-related long-term benefits, more appropriate evidence to inform treatment effects beyond first-line...'	modelling of ASCT-related mortality, but the company did not provide this arguing that this would further reduce the sample size informing this transition. The EAG is concerned that long-term pre-failure mortality in the company's base-case is may currently be overestimated and, in absence of an analysis modelling ASCT-related mortality separately, assumed equal pre-failure mortality between the ibrutinib and ASCT regimens in its base-case. Page 107, Section 6.4 'Further analyses explicitly incorporating ASCT-related long-term benefits, more appropriate evidence to inform treatment effects beyond first-line, although the EAG acknowledge the paucity of data in this setting to inform these analyses,...'	regimen lacks clinical plausibility and therefore should be removed. The inputs informing pre-failure mortality in the base case analysis are based on observed data from the TRIANGLE trial which provide direct evidence that the ASCT regimen is associated with an increased risk of pre-failure mortality versus the ibrutinib regimen, as validated by UK clinical experts.¹⁴ Specifically, in TRIANGLE, pre-failure annual mortality events occurred twice as frequently in patients receiving the ASCT regimen versus the ibrutinib regimen (8.18% [22/269] in Arm A versus 4.10% [11/268] of individuals in Arm I, respectively. These correspond to per-cycle probabilities of [REDACTED] (Arm I) and [REDACTED] (Arm A), which were integrated into the model. Of note, the AMRs informing the base case analysis were unanimously validated as appropriated by feedback received from 5 UK clinical experts.¹⁴ As the proposed scenario by the EAG assumes equal pre-failure mortality between regimens, the scenario	

		lacks clinical plausibility and contradicts direct evidence from TRIANGLE which represents the gold standard of evidence. The scenario should therefore be removed as it is not informative for UK decision-making.	
Page 82, Section 4.2.6 'In response to clarification, the company stated that the number of pre-failure mortality events was limited and parametric extrapolations would therefore be associated with considerable uncertainty'	Please amend as follows: 'In response to clarification, the company stated that the number of pre-failure mortality events was limited and parametric extrapolations would therefore be associated with considerable uncertainty. The Company noted that this approach was validated as more appropriate than parametric extrapolation by an independent health economic expert consulted during the November 2025 advisory board.'	To ensure factual accuracy within the EAG report, the EAG should capture the full justification provided by the company in response to clarification. In accordance with health economic expert opinion, given the limited number of mortality events, use of a constant AMR was the most appropriate approach to inform this transition probability. This is because when there are limited events as is the case for pre-failure mortality events in TRIANGLE, parametric extrapolations are highly sensitive to the chosen distribution and are therefore associated with considerable uncertainty when extrapolated over the model time horizon. The text should therefore be updated to explicitly note that	Not a factual inaccuracy.

		this approach was validated by a health economic expert.	

Issue 4 Inaccurate description of the Company's justification for the ASCT cost included in the economic model and the uncertainty surrounding this cost

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG's description of the Company's justification for the ASCT cost is not fully accurate. Page 92, Section 4.2.9.7 'Considering that the company made a reasonable argument for the inclusion and clear differentiation of stem-cell apheresis, HDT and ASCT, the EAG preferred to use the most recent unit cost estimate of £21,247 from NHS Reference Costs 2024/2025 (ASCT unit cost from NHS Reference Costs 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions)'	Page 92, Section 4.2.9.7 'Considering that the company made a reasonable argument for the inclusion and clear differentiation of stem-cell apheresis, HDT and ASCT, the EAG preferred to use the most recent unit cost estimate of £21,247 from NHS Reference Costs 2024/2025 (ASCT unit cost from NHS Reference Costs 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions). The EAG however recognise that the stated cost in the NHS Reference Costs was unanimously validated as too low and not appropriate for	To maintain factual accuracy of the justification provided by the Company, as discussed in response to the clarification question B19 and detailed in the advisory board report included within the reference pack of the ingoing submission, it should be made clear in the EAG report that the values suggested by the EAG were validated as too low and not appropriate for use by the Company's clinical experts during the November 2025 advisory board.¹⁴	Not a factual inaccuracy.

	use by the Company's clinical experts.'		
The use of an alternative cost for ASCT by the EAG is incorrectly described as 'fixing a violation'. Page 100, Section 6.1.1.2 'Fixing violations Use NHS Reference Costs 2024/25 for ASCT (Section 4.2.9) 'The EAG preferred to use the most recent unit cost estimate of £21,247 from NHS Reference Costs 2024/2025 (ASCT unit cost from NHS reference unit cost 2024/25 for Peripheral Blood Stem Cell Transplant, Autologous, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions).'	Page 100, Section 6.1.1.2 This issue should be captured within Section 6.1.1.3 (Matters of judgement) rather than 6.1.1.2 (Fixing violations).	This issue should not be considered a violation and instead a matter of judgement. The cost used in the Company model is based on NICE NG52 and prior NICE TAs in NHL, in which the cost was accepted as appropriate by both the EAG and the Committee.^{15, 16} While a cost for autologous peripheral stem cell transplant is available from the NHS Reference costs, as noted above, this cost is considered by clinical experts to be a considerable underestimate of the true unit cost for ASCT and as such, is not appropriate for use in the economic analysis.¹⁶ It is therefore a matter of judgement as to which cost is more appropriate.	Not a factual inaccuracy.

Issue 5 Incorrect description of subsequent treatment distributions elicitation

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 16, Section 1.5 ‘Company clinical experts indicated high variability in subsequent treatment options and distributions (second-line, third-line) for UK clinical practice, and the company’s base-case options and distributions do not match with those of the EAG clinical expert.’ Page 17, Section 1.6 ‘The EAG considers that the company’s CE results are subject to substantial uncertainty, primarily related to the modelling of ASCT, treatment effectiveness beyond first-line, and assumptions regarding subsequent treatment pathways.’ Page 93, Section 4.2.9.7 ‘Subsequent treatments (second-line and third-line) were informed	Please amend the text as follows: Page 16, Section 1.5 ‘Five company clinical experts indicated ~~high~~ some variability in subsequent treatment options and distributions (second-line, third-line) for UK clinical practice. These estimates were subsequently aggregated and unanimously validated as appropriate by all experts at a November 2025 advisory board; these estimates were used to inform the subsequent treatment distributions within the Company’s economic model, and the company’s base-case options and distributions do not match with those of the EAG clinical expert.’ It should be noted that ~~this~~ these distributions deviated from those of the one EAG clinical expert consulted.	The distribution of subsequent treatments received following failure on 1L or 2L treatment, respectively, in the economic model was informed by feedback received from UK clinical experts during the November 2025 advisory board.¹⁴ Five UK clinical experts independently provided their individual estimates, which inevitably were subject to some variability. These estimates were subsequently aggregated and the mean of these estimates was presented and unanimously validated as appropriate by all five UK clinical experts. Therefore, whilst some variation was present in the individual estimates, the experts reached consensus on the values informing the economic model. It is therefore factually inaccurate and misleading to state that the subsequent treatment distributions informing the economic model were based on ‘assumptions’. It	Not a factual inaccuracy.

by expert opinion and showed high variability in treatment options and distributions considered applicable for UK clinical practice.' Page 96, Section 5.2 'Although not listed by the company, the EAG further noticed that subsequent treatment distributions (although depicting considerable variation in estimates informed by clinical experts, see clarification response B20) ...' Page 107, Section 6.4 'These subsequent treatment assumptions, informed by the company's clinical experts, drive a large proportion of total costs and differed from the views of the EAG's clinical expert.'	Page 17, Section 1.6 'The EAG considers that the company's CE results are subject to ~~substantial~~ some uncertainty, primarily related to the modelling of ASCT, treatment effectiveness beyond first-line, and ~~assumptions regarding clinician-derived~~ subsequent treatment pathways estimates. Page 93, Section 4.2.9.7 'Subsequent treatments (second-line and third-line) were informed by expert opinion. While there was some ~~showed~~ high variability in treatment options and distributions considered applicable for UK clinical practice, ~~p~~Particularly in the company's clinical experts' expectations on second-line prescription of zanubrutinib to ibrutinib patients (varied from 20% to 80%¹⁷; clarification question B20), consensus was reached across clinicians on the most suitable subsequent treatment distributions.^{17, 18}	should be made clear in the relevant sections of the EAG report that the subsequent treatment distributions in the Company's economic model were informed by aggregated estimates from five UK clinical experts that were unanimously validated as appropriate by all experts. To aid interpretation, it should additionally be made clear that the EAG only consulted one expert. Furthermore, given that the clinical experts reached consensus on both the 2L and 3L subsequent treatment distributions included in the economic model, it is factually inaccurate to say that the distributions are associated with 'substantial uncertainty'.	

	Page 96, Section 5.2 ‘Although not listed by the company, the EAG further noticed that subsequent treatment distributions (although depicting ~~considerable~~ some variation in estimates informed by clinical experts, see clarification response B20¹⁷) ...’ Page 107, Section 6.4 ‘These subsequent treatment assumptions, informed by independent estimates from the company’s five clinical experts that were subsequently aggregated and unanimously validated, as appropriate by all clinical experts consulted by the Company, drive a large proportion of total costs and differed from the views of the EAG’s one clinical expert.’		
The EAG’s proposed scenario is clinically implausible. Page 20, Section 1.6, Table 1.13, Row: ‘EAG 10: Use	This scenario and all references to it should be removed from the EAG report.	In line with clinical expert opinion consulted by both the EAG and the company, subsequent treatment distributions would vary following receipt of the ibrutinib	Not a factual inaccuracy.

subsequent treatment distributions from ibrutinib for ASCT' The full row should be removed. Page 20, Section 1.6, Table 1.14, Row: 'EAG 10: Use subsequent treatment distributions from ibrutinib for ASCT' The full row should be removed. Page 101, Section 6.1.2.1 '10. Use subsequent treatment distributions from ibrutinib for ASCT (Section 4.2.9)' Page 104, Section 6.2, Table 6.4, Row: 'EAG 10: Use subsequent treatment distributions from ibrutinib for ASCT' The full row should be removed. Page 105, Section 6.2, Table 6.5, Row: 'EAG 10: Use subsequent treatment		regimen or the ASCT regimen. None of the five clinical experts consulted as part of this appraisal considered that the subsequent treatment distributions would be equal between the two regimens, nor did the expert consulted by the EAG. As such, this scenario analysis is not clinically plausible and should therefore be removed from the report as it is not informative for UK decision making.	

distributions from ibrutinib for ASCT' The full row should be removed.			

Issue 6 Inappropriate and clinically implausible survival extrapolation scenario analysis

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 84, Section 4.2.6 'The EAG explored a scenario analysis including the log-normal distribution (best statistical fit, more optimistic long-term estimates) for TTF for the ASCT regimen.' Page 20, Section 1.6, Table 1.13, Row: 'EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma"' Full row	The proposed scenario analysis should be removed.	The proposed scenario is clinically implausible and therefore should be removed as it is not informative for UK-decision making. As shown by the clinical expert and landmark estimates for the reconstructed FFS extrapolations presented in Table 36 of the CS, whilst the log-normal extrapolation for TTF (ASCT) provides the best statistical fit, it drastically overestimates long-term survival compared to clinician estimates and therefore lacks external validity. At 10, 15 and 20 years, the clinical experts estimated that 44.6%, 33.6% and 22.0% of patients who received the ASCT regimen would remain failure free, respectively. However, landmark estimates from the log-normal extrapolation indicate that [REDACTED],	Not a factual inaccuracy.

Page 20, Section 1.6, Table 1.14, Row: 'EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma" Full row Page 101, Section 6.1.2.1 '6. Use log-normal for extrapolation of TTF in ASCT regimen (Section 4.2.6)' Page 104, Section 6.2, Table 6.4, Row: 'EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma" Full row Page 104, Section 6.2, Table 6.5, Row: 'EAG_6: Use log-normal for extrapolation of TTF in ASCT regimen: set to "Log-normal" from "Gamma" Full row		■ and ■ of patients would be alive at those same time periods. Additionally, when using the EAG's proposed extrapolation (log-normal), the extrapolations of FFS for the ASCT regimen and the ibrutinib regimen cross at 120 months. In accordance with feedback received from five UK clinical experts who all indicated that the ibrutinib regimen would exhibit improved FFS versus the ASCT regimen at all timepoints, this is clinically implausible.¹⁴ According to the framework set out in DSU TSD 26, external validation of survival extrapolations is a fundamental criteria for selecting curves.¹⁹ The EAG's chosen extrapolation shows a marked deviation from the clinical expert estimates, indicating a lack of external validity and a breach of the guidance in DSU TSD 26. As such, this scenario should be removed from the EAG report as it is both misleading and not relevant for UK-decision making. The Company would additionally like to highlight that the landmark estimates from the Gamma	

		extrapolation selected to inform TTF for the ASCT regimen in the base case analysis already slightly overestimates FFS for the ASCT regimen versus the aggregated values provided by the clinical experts (predicting ■■■, ■■■ and ■■■ of patients would be failure-free at 10, 15 and 20 years, respectively). As such, the Company's base case modelling approach for the ASCT regimen is already optimistic for the ASCT regimen and therefore exploration of an even more optimistic, and clinically implausible, scenario is inappropriate.	

Issue 7 Incorrect reporting of the Company's cost effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG report presents the results of the company base case submitted prior to the clarification question phase. As such the results presented in the EAG report are outdated.	Please update the report to align the Company's base case, sensitivity and scenario analyses results to those included in the economic model submitted alongside the clarification question response.	The most up to date version of the Company's economic model and associated base case results should be presented within the EAG report to maintain factual accuracy.	Not a factual inaccuracy.

Minor Issues

Issue 8 Minor factual issues

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The wording used to describe the impact of ibrutinib on QALYs is misleading and is not an accurate representation of the Company's economic model. Page 13, Section 1.2 'Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by: - Time on first-line treatment - Second-line treatment effectiveness'	Please amend the text as follows: 'Overall, the technology is modelled to affect quality-adjusted life years (QALYs) by: First line-treatment effectiveness time on first-line treatment Second-line treatment effectiveness Distribution and efficacy of 2L treatment received'	It is misleading to state the ibrutinib regimen is modelled to affect QALYs by time on first-line treatment and second-line treatment effectiveness as it implies that first-line treatment effectiveness does not impact QALYs. The efficacy of first-line treatment impacts both pre-failure mortality and the time until failure on first-line treatment and therefore it would be more accurate to say that the technology affects QALYs by the efficacy of first-line treatment. Additionally, QALYs realised when patients receive second-line treatment are differentiated through the distribution of treatments received by patients. It should therefore be clarified in the report that it is combination of the distribution and efficacy of second-line treatments received	Adjusted accordingly.

		post the ibrutinib or ASCT regimen that impacts QALYs, not just the efficacy of second-line treatments, to ensure an accurate representation of the Company's economic model.	
The current wording in the report implies that the value of 85% of patients receiving rituximab maintenance treatment was arbitrarily selected which is factually inaccurate. Page 13, Section 1.3; Page 26, Section 2.2 'Rituximab maintenance is not mentioned in the NICE scope, but it is assumed to be given to 85% of patients in UK clinical practice, which caused the company to adjust OS and FFS outcomes from the TRIANGLE trial, where a smaller percentage of patient received it. '	Please amend the text as follows: Page 13, Section 1.3 "Rituximab maintenance is not mentioned in the NICE scope, but it is assumed to be given to 85% of patients in UK clinical practice, ~~which caused the company to adjust OS and FFS outcomes from the TRIANGLE trial, where a smaller percentage of patient received it~~ based on consultation with four UK clinical experts at the March advisory board and unanimously validated by five clinical experts at the November advisory board. IPCW adjusted analysis showed that FFS and OS HRs were highly consistent with those observed in the unadjusted analysis, as shown in Section 2.9 of the CS. Page 26, Section 2.2	This amendment clarifies how the 85% rituximab maintenance assumption was reached, thereby improving the transparency in data reporting. Furthermore, the amendment on the reporting of the impact of this adjustment should be made to improve the transparency of reporting results.	Not a factual inaccuracy. The EAG attributed it to consultation with clinical experts at the March 2025 Ad Board meeting.

	The company made an adjustment to the outcomes OS and FFS from the TRIANGLE trial to simulate the effectiveness with a higher percentage use of rituximab maintenance (85%, see also Section 3.2), which was based on aggregated estimates from UK clinical experts.		
The EAG could not identify the SmPC guidance on rituximab maintenance usage. Page 13, Section 1.3 'Use of rituximab maintenance is recommended in guidelines and confirmed by the EAG clinical expert, although the EAG cannot find a statement in the licence to support it.'	Please amend the text as follows: 'Use of rituximab maintenance is recommended in guidelines and confirmed by the EAG clinical expert, ~~although the EAG cannot find a statement in the licence to support it.~~	The MHRA SmPC states that rituximab maintenance can be taken daily for 24 months as part of the Part II treatment cycle, as shown in Table 1, Section 4.2, Page 2.²⁰ All sentences stating that the EAG could not locate the licence wording should therefore be removed throughout the EAG report, as it leaves doubt as to whether rituximab maintenance is licensed for use in clinical practice which is misleading.	Correction and clarification made to Table 1.2.
The wording used to describe the expected effect of uncertainties around the comparator induction regimen on CE estimates is misleading.	Please amend as follows: 'Probably small Minimal impact on ICER'	The impact of lower NORDIC usage was tested in clarification question 1fi, where 0% NORDIC usage was assumed in the ASCT model arm. The model results demonstrate that changing to 0% NORDIC usage has a minimal effect on the ICER. It is therefore	Adjusted accordingly

Page 14, Section 1.3, Table 1.3, Row: 'What is the expected effect on the CE estimates?' 'Probably small'		factually inaccurate and misleading to say that the impact of the NORDIC regimen assumption is 'probably' small given that the scenario analysis demonstrated that it has a minimal impact.	
The EAG should not consider Arm I+A as it is outside of the license for ibrutinib in untreated MCL. Page 14, Section 1.4 'However, the evidence of avoidance of ASCT toxicity is unclear with higher treatment duration than Arm A (ASCT only) not only for Arm I, but also Arm I+A, and increased rates of some AEs including infections in Arm I.' Page 66, Section 3.2.7 'However, the EAG note that the CSR shows that treatment duration in Arm A+I was almost identical to Arm I, at a median of 29.21 months. Therefore, although it is plausible that, as well as increased survival, HRQoL is improved, but it is unclear	Please amend the text as follows: Page 14, Section 1.4 However, the evidence of avoidance of ASCT toxicity is unclear with ~~higher treatment duration than Arm A (ASCT only) not only for Arm I, but also Arm I+A, and~~ increased rates of some AEs including infections in Arm I.' Page 66, Section 3.2.7 This sentence should be deleted. Page 69, Section 3.6 This sentence should be deleted.	As detailed elsewhere, Arm I+A is not relevant to this submission as it is outside of the license for ibrutinib in untreated MCL. As such, reference to this arm of the trial should be removed. This is reflected in the EAG report in Table 3.3, Section 3.2.1, where footnote c states that "Data for Arm A+I is not included beyond this point as it represents off-label treatment with ibrutinib and is therefore not relevant to clinical decision making in the UK". Additionally, given the duration of both the ibrutinib regimen is fixed, it is not pertinent to the arguments made in the EAG report to note that the treatment duration in Arm I was the same as that in Arm A+I.	Not a factual inaccuracy.

what the role of ASCT toxicity is in this.' Page 69, Section 3.6 'However, the EAG note that the CSR shows that treatment duration in Arm A+I was almost identical to Arm I, at a median of 29.21 months.'			
The wording used suggests that there is bias arising from the rituximab maintenance therapy subgroups in TRIANGLE is an oversimplification. Page 15, Section 1.4 'Subgroup analysis shows that the FFS HR does increase with rituximab maintenance, but the effect of rituximab is provably biased due to its choice occurring after induction/consolidation.'	Please amend as follows: 'Subgroup analysis shows that the FFS HR does increase with rituximab maintenance, but the effect of rituximab in these analyses is provably biased given that rituximab maintenance was only provided following completion of induction treatment in Arm I or consolidation ASCT in Arm A, meaning the subgroup represents an enriched population of patients that successfully completed induction with ibrutinib or consolidation with ASCT. As such, the subgroups are based on a selection of patients which can break the balance of populations that randomisation ensures, thus eliminating the guarantee that	The text in the EAG report represents an oversimplification of the bias arising from the rituximab maintenance therapy subgroups in TRIANGLE. The wording should be amended to improve clarity and factual accuracy.	Not a factual inaccuracy.

	treatment groups are comparable, introducing selection bias and confounding. due to its choice occurring after induction/consolidation.'		
The explanation of the proposed model structure update is misleading. Page 15, Section 1.5, Table 1.5; Row: 'What additional evidence or analyses might help to resolve this Key Issue?' 'An updated economic model and scenario analysis including ASCT-specific (tunnel) state(s) to reflect ASCT-related long-term benefits without extrapolating the short-term mortality risk associated with ASCT.'	Please amend the text as follows: 'An updated economic model and scenario analysis including ASCT-specific (tunnel) state(s) to reflect ASCT-related long-term benefits without assuming a constant pre-failure mortality risk derived from TRIANGLE. without extrapolating the short-term mortality risk associated with ASCT.'	It is misleading to imply that the short-term mortality risk of ASCT is extrapolated within the model. Instead, it is applied through a constant AMR which was derived from the gold standard of evidence; direct head-to-head data from TRIANGLE, validated as appropriate with UK clinical experts at the November 2025 advisory board.^{10, 14} Additionally, as highlighted by the EAG, given that the patient numbers informing pre-failure events are low, it should be noted that including ASCT-related mortality separately would further decrease the sample size informing this transition, introducing additional uncertainty with minimal improvement in granularity.	Not a factual inaccuracy.
The EAG's proposal of alternative data to inform second-line treatment	Page 16, Section 1.5, Table 1.7 This text should be removed.	The EAG has not identified any real-world or registry data to inform transitions beyond first-	Not a factual inaccuracy.

effectiveness is infeasible and therefore irrelevant. Page 16, Section 1.5, Table 1.8; Row: ‘What alternative approach has the EAG suggested?’ ‘Scenario analyses using alternative real-world and/or registry data to inform transitions beyond first-line.’ Page 79, Section 4.2.6.1 ‘The EAG questions the suitability of RAY-3001 to inform transitions beyond first-line treatment in the company’s economic model. Patients in RAY-3001 are not an appropriate reflection of patients entering second-line treatment in the economic model after being treated with the ibrutinib regimen, as all patients in RAY-3001 were ibrutinib-naïve at study entry. Likewise, patients in RAY-3001 are not reflective of patients entering second-line treatment in the economic model after being treated with the ASCT regimen, as prior ASCT treatment in RAY-3001 was limited to 23.7%. Consequently, the observed second line treatment effects in RAY 3001 are unlikely to	Page 79, Section 4.2.6.1 Please amend the text as follows: ‘The EAG questions the suitability of RAY-3001 to inform transitions beyond first-line treatment in the company’s economic model. Patients in RAY-3001 are not an appropriate reflection of patients entering second-line treatment in the economic model after being treated with the ibrutinib regimen, as all patients in RAY-3001 were ibrutinib-naïve at study entry. Likewise, patients in RAY-3001 are not reflective of patients entering second-line treatment in the economic model after being treated with the ASCT regimen, as prior ASCT treatment in RAY-3001 was limited to 23.7%. It is however acknowledged that owing to the paucity of available evidence in this setting, five UK clinical experts consulted by the Company unanimously validated that RAY-3001 was the most appropriate source to inform subsequent treatment-effectiveness in this setting.¹⁴ Consequently, the observed second line treatment	line. Given the requested scenario is therefore infeasible, this statement should be removed. Additionally, whilst the Company acknowledge that there are limitations associated with the use of RAY-3001 to inform the efficacy of later treatment lines in the economic model, these limitations should be appraised in the EAG report within the context of the paucity of available evidence in this setting and acknowledging the existing validation of the appropriateness of RAY-3001 from the Company’s clinical experts.	

reflect the outcomes of patients who have previously been exposed to ibrutinib or ASCT.'	~~effects in RAY 3001 are unlikely to reflect the outcomes of patients who have previously been exposed to ibrutinib or ASCT.~~		
The report implies that the Company's base case approach is not informative to the decision problem. Page 18, Section 1.5, Table 1.10, Row: 'What is the expected effect on the CE estimates?' 'Any cost effectiveness estimates produced by the health economic model would become more credible and thus informative to the DP.'	Please amend the text as follows: 'Any cost effectiveness estimates produced by the health economic model would become more credible ~~and thus informative to the DP.~~'	Given the model structure aligns with prior models within MCL and other NHLs, has been validated at an advisory board by an independent health economic expert and five UK clinical experts, and has undergone in-depth technical validation and quality control procedures, it is not accurate to imply that the current cost-effectiveness analyses provided are not informative to the decision problem.^{14, 21, 22} As such, this statement should be removed.	Not a factual inaccuracy.
The EAG report is missing key context regarding the choice of data to inform treatment efficacy within the model. Page 18, Section 1.6 'Evidence used to inform treatment effectiveness beyond first-line was drawn from clinically different populations...'	Please amend the text as follows: 'Evidence used to inform treatment effectiveness beyond first-line was drawn from clinically different populations, reflective of the different populations in the later line health states, ...'	As described in detail in the response to Clarification Question B7, the baseline characteristics between patients in TRIANGLE and RAY-3001 are intended to reflect the relevant populations for which they inform efficacy data for in the economic model. As such the trial populations are not intended to be aligned. This context should	Not a factual inaccuracy.

		be added to improve clarity as the current sentence is misleading.	
The EAG report states that it is off-license to receive ASCT alongside the ibrutinib regimen. Page 22, Section 2 'The intervention differs from the scope in that ASCT is removed as an optional addition (note that "with or without ASCT" was not included in the CS). The company have argued that the license is for without ASCT, but the SmPC does not explicitly state this, and the EAG clinical expert indicated that the option of ASCT for some patients could be valuable..'	Page 22, Section 2 Please amend the text as follows: 'The intervention differs from the scope in that ASCT is removed as an optional addition, in line with the SmPC (note that "with or without ASCT" was not included in the CS).²⁰ ~~The company have argued that the license is for without ASCT, but the SmPC does not explicitly state this, and the EAG clinical expert indicated that the option of ASCT for some patients could be valuable..~~	These statements are factually inaccurate; the UK license for the ibrutinib regimen does not include ASCT as is clear from Table 1, Section 4.2 of the SmPC.²⁰ It is factually inaccurate to suggest that because use of ASCT is not explicitly excluded in the license wording for ibrutinib that its use would not be off-label.	Not a factual inaccuracy.
The EAG report does not reference the consensus reached by UK clinical experts regarding the proportional use of rituximab maintenance in clinical practice. Page 26, Section 2.2 'The EAG can confirm that this was the figure reported for Arm A, and	Please amend the text as follows: Page 26, Section 2.2 'The EAG can confirm that this was the figure reported for Arm A, and 'NORDIC' in the Advisory Board report, with five UK clinical experts agreeing that 85% of patients in both arms would be anticipated to	It should be clarified that the proportion of 85% was unanimously validated by all 5 clinical experts at the November 2025 advisory board as being reflective of the anticipated rituximab maintenance use across both arms.¹⁴ The current wording in the EAG report	Not a factual inaccuracy.

'NORDIC' in the Advisory Board report, although a figure of 90% was reported for Arm I, and one expert stated that all patients in Arm I would receive rituximab maintenance, which was supported by the EAG clinical expert.'	receive rituximab maintenance in clinical practice. Prior to consensus, although a figure of 90% was reported for Arm I, and one expert stated that all patients in Arm I would receive rituximab maintenance, which was supported by the EAG clinical expert."	implies that it was only validated for Arm A which is factually inaccurate.	
The AE summary should be revised to accurately reflect the safety profiles of ibrutinib and ASCT. Page 67, Section 3.2.7.8 'Given the observation of worse AE profile for Arm I despite the argument that ASCT is best avoided because of its toxicity, following a meeting a meeting with the EAG clinical expert...'	Please amend the text as follows: ~~"Given the observation of worse AE profile for Arm I despite the argument that ASCT is best avoided because of its toxicity, f~~Following a meeting with the EAG clinical expert.,."	It is factually inaccurate to state that the AE profile of the ibrutinib regimen is worse than the ASCT regimen in TRIANGLE; TRIANGLE data demonstrated that patients can be exposed to the ibrutinib regimen for five times as long before experiencing a similar toxicity profile to the ASCT, regimen demonstrating the substantially increased acute toxicity associated with the ASCT regimen versus the ibrutinib regimen.	Not a factual inaccuracy.
The EAG incorrectly state that the PFS HR from MANTLE-FIRST used in the economic model does not align with published values. Page 83, Section 4.2.6	Page 83, Section 4.2.6 This text should be removed. Page 106, Section 6.4 Please amend the text as follows:	The PFS HR from MANTLE-FIRST used in the economic model can be found in Table S2 of the supplementary data of the Visco <i>et al.</i> (2021) paper.²³ It is therefore factually inaccurate to say that the value used in the	Adjusted accordingly

'First, the EAG was unable to identify the PFS HR of 1.26 (or the inverse 0.79 used by the company in its model) in the published MANTLE FIRST data that was used for modelling the relative treatment effect of ibrutinib versus R-BAC, BR and BSC. It is therefore unclear how this value was obtained or calculated.' Page 106, Section 6.4 'The EAG also questioned the company's approach to informing relative second-line treatment effectiveness from MANTLE-FIRST, because the HRs used in the model were not fully transparent, did not appear to align with the published results for all comparators, and did not capture potential treatment-effect modification by TTP'	'The EAG also questioned the company's approach to informing relative second-line treatment effectiveness from MANTLE-FIRST, because the HRs ~~used in the model were not fully transparent, did not appear to align with the published results for all comparators, and~~ did not capture potential treatment-effect modification by TTP'	economic model is misaligned with the value reported in the published literature and is not transparent.	
Further context is required to clarify that the per cycle pre-failure mortality probability was derived from TRIANGLE data. Page 73, Section 4.2.2 'The per cycle pre-failure mortality probability was assumed to be	Please amend the text as follows: 'The per cycle pre-failure mortality probability was derived from TRIANGLE data and assumed to be dependent of first-line treatment received (■■■■%) for the ibrutinib	Additional details are required to clarify that the pre-failure mortality probability used within the model was sourced from TRIANGLE data, given that multiple literature sources are used in the model.	Not a factual inaccuracy.

dependent of first-line treatment received (■■■■% for the ibrutinib regimen and ■■■■% for the ASCT regimen).	regimen and ■■■■% for the ASCT regimen).		
The wording asserting that the two induction regimens have equal efficacy should be revised to reflect the high degree of certainty surrounding their equivalence. Page 74, Section 4.2.2 'Both induction regimen were assumed to be equally effective (R-CHOP with R-DHAP or R-DHAox versus the NORDIC chemotherapy regimen, i.e. R-Maxi-CHOP alternating with R-cytarabine).'	Please amend the text as follows: 'Both induction regimen were considered assumed to be equally effective (R-CHOP with R-DHAP or R-DHAox versus the NORDIC chemotherapy regimen, i.e. R-Maxi-CHOP alternating with R-cytarabine), in line with BSH guidelines and validated by UK clinical experts.^{2, 14}	It is factually inaccurate to state that the clinical equivalence of induction regimens is an assumption when it is based on empirical evidence provided in the BSH guidelines. Specifically, the BSH guidelines state: "No specific induction regimen is clearly superior with overall response rates (ORRs) of >90% and CT-based complete response (CR) rates of >50% reported [across all regimens]."³ Additionally, five UK clinical experts consulted by the Company unanimously validated that all induction regimens are equally effective in UK clinical practice.^{2, 14}	Not a factual inaccuracy.
The EAG do not detail the impact of a scenario analysis on the cost-effectiveness conclusions which means the statement is misleading. Page 77, Section 4.2.4	Please amend the text as follows: 'Scenario analyses conducted by the company (clarification response Table 6) indicated that increasing the proportion of patients receiving alternating R-CHOP and R-DHAP (or R-DHAox) for the ASCT regimen	It is misleading to state only that incremental costs increased for the ibrutinib regimen, as this implies that the cost-effectiveness conclusions change in this scenario. In reality, the cost-effectiveness	Not a factual inaccuracy.

'Scenario analyses conducted by the company (clarification response Table 6) indicated that increasing the proportion of patients receiving alternating R-CHOP and R-DHAP (or R-DHA0x) for the ASCT regimen would reduce the costs of the ASCT regimen and thus increase the incremental costs for the ibrutinib regimen;'	would reduce the costs of the ASCT regimen and thus increase the incremental costs for the ibrutinib regimen; however, the ibrutinib regimen remains a cost-effective with no change to the cost effectiveness conclusions of the base case analysis.'	conclusions for the base case remained unchanged.	
The EAG incorrectly stated that there was no evidence to support the equal third-line treatment effectiveness of the ibrutinib regimen and ASCT regimen. Page 83, Section 4.2.6.3.1 'The company assumed equal third-line treatment effectiveness between the ibrutinib regimen and ASCT regimen (i.e. transition from PD to death). It is unclear to the EAG whether this assumption is appropriate, as it was not supported by evidence and deviated from the company's approach of modelling second-line treatment effectiveness.'	Please amend the text as follows: 'The company assumed equal third-line treatment effectiveness between the ibrutinib regimen and ASCT regimen (i.e. transition from PD to death); this pragmatic assumption is unlikely to meaningfully impact cost-effectiveness results and was considered appropriate by five UK clinical experts and a health economic expert at the November 2025 advisory board.¹⁴ It is unclear to the EAG whether this assumption is appropriate, as it was not supported by evidence and deviated from the company's approach of modelling second-line treatment effectiveness. Hence, the EAG believes it would have been informative if the company explored scenarios assuming	It is factually inaccurate to state that it is unclear whether this assumption is appropriate, given that Section 3.5.2 of the CS clarifies that the assumption of equal efficacy of third-line treatments for the ibrutinib and ASCT regimen was unanimously validated as appropriate by five UK clinical experts. Furthermore, feedback received from an independent health economic expert noted that it represents an appropriate pragmatic assumption to minimise model complexity given it was unlikely to meaningfully impact results.¹⁴ The Company would also like to highlight that this simplifying assumption aligns with advice the Company received from both	Not a factual inaccuracy.

	~~differential third-line treatment effectiveness and/or evidence to support the current assumptions related to third-line treatment.~~	NICE and the EAG at the decision problem meeting to refrain from overly complicating the model in the third-line setting.	
It should be clarified that the Company's approach to modelling ICU is conservative. Page 92, Section 4.2.9.7 'The company costed ICU events for 5% of ASCT patients, based on literature and clinical expert feedback indicating a range of 5-11%.^{18, 24, 25}	Please amend the text as follows: 'The company conservatively costed ICU events for 5% of ASCT patients, based on literature and clinical expert feedback indicating a range of 5-11%.^{18, 24, 25}	The text should be revised to reflect that the Company conservatively aligned with the literature-derived estimates of 5%, which is lower than the clinician-derived estimate of 10%.	Not a factual inaccuracy.
The EAG's statement is misleading in omitting that this approach is standard for CE analyses. Page 96, Section 5.2 'According to the CS, parameters missing information on credibility intervals were assigned $\pm 10\%$ (lower/upper limit) of the deterministic value. '	Please add additional context to this statement as follows: 'According to the CS, parameters missing information on credibility intervals were assigned $\pm 10\%$ (lower/upper limit) of the deterministic value, as is standard for cost-effectiveness analyses. '	This statement should be added to aid interpretation of the rationale for the approach adopted by the Company.	Not a factual inaccuracy.
The EAG's interpretation of variation of subsequent treatment inputs in sensitivity analyses is inaccurate and misleading.	This statement should be removed.	The statement is factually inaccurate and should be deleted. Whilst the subsequent treatment distributions were not varied, the	Not a factual inaccuracy.

Page 96, Section 5.2 ‘Although not listed by the company, the EAG further noticed that subsequent treatment distributions (although depicting considerable variation in estimates informed by clinical experts, see clarification response B20) were neither reported in the “Parameter” sheet (which details inclusion in DSA/PSA) nor varied (presumably).’		weighted 2L HRs (calculated using the subsequent treatment distributions) were included in the “Parameter” sheet and were varied. As such, the subsequent treatment distributions were implicitly varied. Varying the subsequent treatment distributions separately would lead to varying this input twice in the analyses and therefore would be inappropriate.	
The EAG’s statement is misleading in omitting that this approach is standard for CE analyses. Page 96/97, Section 5.2 ‘In summary, the EAG is concerned about the large, disproportional impact of second-line costs in light of the CS DP addressing a first-line treatment...’	Please add additional context to this statement as follows: ‘In summary, the EAG is concerned about the large, disproportional impact of second-line costs in light of the CS DP addressing a first-line treatment. However, it is recognised that this is not uncommon when assessing efficacious first-line treatment options, given that the improved outcomes at first-line often translate into improved survival and cost-savings at later lines....’	This statement overlooks key context that should be stated alongside the concerns around the disproportional impact of second-line costs. Whilst the Company recognise that second-line costs are influential in the model, this is not uncommon when assessing first-line treatments. It reflects a key benefit of bringing an efficacious treatment option earlier in the treatment pathway. This ultimately improves patient survival and reduces costs during later lines of treatment. As such, this context should be provided to aid interpretation of the	Not a factual inaccuracy.

		rationale for the approach adopted by the Company.	
The EAG's suggestion that external validation of the model was not conducted is inaccurate. Page 97, Section 5.3.5 'The CS further mentions "long-term studies" which were used for model outcome validation, yet no reference was provided for these. No further UK sources used were specified in this Section.'	This statement should be removed.	This statement is factually inaccurate and should be deleted; external validation against long-term studies was provided against the MCL2 trial and LyMA trial in Section 3.1.4 of the CS.^{7, 9}	Not a factual inaccuracy
The EAG's statement that the Company did not explore whether the model can reproduce the observed TTF/FFS curve from TRIANGLE when the transitions are recombined is factually inaccurate. Page 98, Section 5.3.5 'Unfortunately, the company did not explore whether the model can reproduce the observed TTF/TFFS curve from TRIANGLE when the transitions are recombined, as requested by the EAG.'	This statement should be removed.	The statement is factually inaccurate. A comparison of the observed FFS from TRIANGLE versus the model predicted reconstructed FFS is provided in Section 3.14 of the CS and in response to question B30ci of the clarification question response. In short, this showed that the model-predicted FFS curve is highly aligned with the observed FFS KM data from TRIANGLE, clearly demonstrating that the base case modelling approach produced	

		clinical efficacy estimates that accurately reflect the empirical data informing the model.	
The EAG report incorrectly insinuates that external validation was not conducted versus the HMRN study. Page 98, Section 5.3.2 'The company did not perform an external validation with this population, flagging the mismatch in patient populations with HMRN capturing all MCL patients, thus likely more frail and older ones with less use of ASCT, and the considerable difference in 5-year OS.'	Please amend the text as follows: 'The company did not perform an external validation with this overall population, flagging the mismatch in overall patient population with HMRN capturing all MCL patients, thus likely more frail and older ones with less use of ASCT, and the considerable difference in 5-year OS.'	Given that, as noted later in the same section of the EAG report, the Company provided a comparison versus a relevant subgroup of the HMRN study, the text should be amended to improve clarity that the lack of comparison was versus the overall study population specifically.	Not a factual inaccuracy

There is an issue in the implementation of scenario 5 in the EAG model. EAG Economic Model Drop-down for EAG scenario 5 (adjusting 2L HRs for RBAC, BR and BSC) is also linked to whether IV vial wastage is included (sets IV wastage to 'Yes').	Remove the 'IF' statement in cell D9 of the 'Drug and Admin Cost' tab	To ensure the scenario 5 drop-down is not influencing IV wastage settings.	Not a factual inaccuracy

Issue 9 Data and reporting errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 28, Section 3.1.1, EAG Comments The conference abstract date limit is incorrectly reported for the clinical SLR.	Please amend the text as follows: 'No date limits were used in the original search, except for limiting conference abstracts to those published from ~~2021~~ 2022 to the date of the search.'	The date limits included within the SLR searches should be accurately reported.	Corrected.
Page 45, Section 3.2.4.1 The text could be misinterpreted.	Please amend the text as follows: 'There was a greater proportion of patients who had experienced disease progression in Arm A versus Arm I₇; 60 (22.3%) and 49 (18.3%) respectively'	This amendment should be made to improve clarity.	Amended.
Page 45, Section 3.2.4.1	Please amend the text as follows:	The confidence interval should be accurately reported.	Corrected.

The text incorrectly reports the confidence interval for FFS.	'Kaplan-Meier (K-M) estimates provided a HR of 0.639 (~~95~~ 98.33 % CI 0.428 to 0.953; p=0.0068).'		
Page 46, Section 3.2.4.2, Table 3.8 caption The table caption is incorrect.	Please amend the text as follows: 'Table 3.8: ~~FFS~~ OS (FAS)'	The table caption should be accurate.	Corrected.
Page 47, Section 3.2.4.3 The text incorrectly reports the confidence interval for PFS as being the 95% confidence interval when it is the 98.33% confidence interval.	Please amend the text as follows: 'K-M estimates provided a HR of 0.633 (~~95~~ 98.33 % CI 0.424 to 0.946; p=0.0060).'	The confidence interval should be accurately reported.	Corrected.
Page 48, Section 3.2.4.4 The text incorrectly defines the abbreviation 'SD'.	Please amend the text as follows: '...PR was [REDACTED] in Arm I compared to [REDACTED] in Arm A. Arm I demonstrated lower ~~standard deviation~~ stable disease (SD) ([REDACTED]).'	The definition of SD should be accurately reported.	Corrected.
Page 49, Section 3.2.4.4 The confidence interval for the PR to CR conversion rate is incorrectly reported and the text is missing a space between '95%' and 'CI'.	Please amend the text as follows: 'The conversion rate was 60 (43.5%) in Arm I compared to 76 (50.7%) in Arm A (RR = 0.858, ~~85~~ 95 % CI 0.67 to 1.099; p = 0.2389).'	The confidence interval should be accurately reported.	Corrected.

Page 57, Section 3.2.5.3 The text reporting on the results of the rituximab IPCW analyses incorrectly refers to 'PFS' instead of 'FFS'.	Please amend the text as follows: 'The results of TSE analyses showed that these results of HRs for PFS FFS and OS were generally consistent with those results...'	The outcomes adjusted in the IPCW analyses should be accurately reported.	Corrected.
Page 58, Section 3.2.7.2 The text is unclear as to what data are being reported as the percentage sign is missing for the rate in Arm I.	Please amend the text as follows: 'The number of treatment emergent adverse events (TEAEs) during the induction phase was 259 (97.7%) in Arm I and 262 (97.8%) in Arm A.'	This amendment should be made to provide clarity.	Corrected.
Page 59, Section 3.2.7.2, Table 3.18 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Table ~~18~~ 21, CS.'	References to tables in the CS should be accurate.	Corrected.
Page 59, Section 3.2.7.2 The text is unclear as to what safety data are being reported.	Please amend the text as follows: 'There were 263 (99.2%) TEAEs in Arm I compared to 267 (99.6%) in Arm A.'	This amendment should be made to provide clarity.	Corrected.
Page 60, Section 3.2.7.2, Table 3.19 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Table ~~19~~ 22, CS.'	References to tables in the CS should be accurate.	Corrected.
Page 61, Section 3.2.7.3, Table 3.20 footnotes	Please amend the text as follows: 'Source: Table ~~20~~ 23, CS.'	References to tables in the CS should be accurate.	Corrected.

The source listed refers to the incorrect table in the CS.			
Page 62, Section 3.2.7.4, Table 3.21 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Table 21 24 , CS.'	References to tables in the CS should be accurate.	Corrected.
Page 63, Section 3.2.7.5 The text is unclear as to which data are being reported.	Please amend the text as follows: There was 1 grade 5 event in Arm A versus 0 in Arm I.	This amendment should be made to provide clarity.	Corrected.
Page 64, Section 3.2.7.5, Table 3.22 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Table 22 25 , CS.'	References to tables in the CS should be accurate.	Corrected.
Page 65, Section 3.2.7.6, Table 3.23 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Table 23 26 , CS.'	References to tables in the CS should be accurate.	Corrected.
Page 65, Section 3.2.7.7 The data reported are incorrect.	Please amend the text as follows: 'There was a greater number of all grades, other cardiac arrhythmia (excluding atrial fibrillation) in Arm I versus Arm A (34, 12.8% versus 34 24 , 9%).'	Data should be accurately reported.	Corrected.

Page 65, Section 3.2.7.7 The data reported are incorrect.	Please amend the text as follows: ‘There was a greater number of hypertension events (all grades) in Arm I versus Arm A (36, 13.6% versus 34 24, 9.0%)...’	Data should be accurately reported.	Corrected.												
Page 65, Section 3.2.7.7 The data reported are incorrect.	Please amend the text as follows: ‘There were fewer cytopenic AEs in Arm I versus Arm A (all grades; 224, 84.5% versus 233, 84.0 86.9%. grade 3/4; 209, 78.9% versus 225, 84.0%).’	Data should be accurately reported.	Corrected.												
Page 66, Section 3.2.7.8, Table 3.25, column headers The analysis set and header n numbers are missing.	Please could the table caption and column headers be updated to include the analysis set and n numbers, respectively, as outlined below: Table 3.25: Number of deaths (SAS) <table><tr><th></th><th>Arm I (n=265)</th><th>Arm A (n=268)</th></tr><tr><td>Deaths n (%)</td><td>33 (12.5%)</td><td>60 (22.4%)</td></tr><tr><td>Deaths attributed to PD n (%)</td><td>14 (5.3%)</td><td>30 (11.2%)</td></tr><tr><td>COVID-19 related</td><td>4 (1.5%)</td><td>2 (0.7%)</td></tr></table>		Arm I (n=265)	Arm A (n=268)	Deaths n (%)	33 (12.5%)	60 (22.4%)	Deaths attributed to PD n (%)	14 (5.3%)	30 (11.2%)	COVID-19 related	4 (1.5%)	2 (0.7%)	Data should be accurately reported.	Corrected.
	Arm I (n=265)	Arm A (n=268)													
Deaths n (%)	33 (12.5%)	60 (22.4%)													
Deaths attributed to PD n (%)	14 (5.3%)	30 (11.2%)													
COVID-19 related	4 (1.5%)	2 (0.7%)													

	deaths n (%) Based on CS, Table 22 and Section 2.12.8.²⁶ CS = company submission; PD = progressed disease		
Page 66, Section 3.2.7.8, Table 3.25 footnotes The source listed refers to the incorrect table in the CS.	Please amend the text as follows: 'Source: Based on CS, Table 224 and Section 2.12.8.'	References to tables in the CS should be accurate.	Corrected.
Page 70, Section 4.1.1 The date of the economic SLR searches are incorrectly reported.	Please amend the text as follows: 'The CE and resource use searches were conducted in May December 2023 and the HRQoL searches were conducted in June December 2023. Both sets of searches were updated in October 2024 2025 .'	The date of the SLR searches should be accurately reported.	Corrected.
Page 70, Section 4.1.1 The number of HTA sources searched is incorrectly reported for the economic searches.	Please amend the text as follows: 'For the economic searches, 15 14 HTA sources were searched. The date of the original search is not known, and updates were performed in May and November 2025, with the date ranges detailed in the CS appendices.'	The details of SLR searches should be accurately reported.	Corrected.

Page 80, Section 4.2.6.2.2, Table 4.2 footnotes The source incorrectly refers to only one table in the CS.	Please amend the text as follows: 'Based on CS Table 39, Table 40 and Table 41.'	References to tables in the CS should be accurate and include all tables of relevance.	Corrected.
Page 87, Section 4.2.8.3 The source does not provide the values stated.	Please revise the reference provided for the statement below, as the pre- and post-observation numbers for RAY-3001 and SPARK are not provided in TA502 CS Table 63. 'Specifically, pooled EQ-5D-5L data (████ pre-progression and █████ post-progression observations) from the RAY-3001 (████) and SPARK (████) trials were used (retrieved from TA502 CS Table 63)'	Data references should be accurately reported.	Adjusted accordingly

Issue 10 Minor typographical and grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Page 25, Section 2.1 The spelling of Mantle Cell Lymphoma is incorrect.	Please amend the text as follows: '...i.e. Adults with untreated ~~Mantel~~ Mantle cell lymphoma (MCL)...'	The disease should be correctly spelled.	Corrected.

Page 26, Section 2.2 The sentence has an open quotation mark but not a closing quotation mark.	Please amend the text as follows: ‘However, the Clinical Study Report (CSR) did conclude “no meaningful differences in the hazard rates of the primary outcome failure-free survival (FFS) (1-sided [REDACTED] confidence interval [CI]): [REDACTED], overall survival [OS] [Cox regression hazard ratio [HR] [(REDACTED)] or progression-free survival [PFS] HR [(REDACTED)].” ’	This amendment should be made to improve clarity on which text was taken directly from the CSR.	Corrected.
Page 29–30, Section 3.1.2, Table 3.1, Row: Intervention/comparator, Column: Inclusion The lack of sub-bullets makes the inclusion criteria difficult to understand.	Please amend the text as follows: ‘Induction regimens (with or without consolidation/maintenance) including, but not limited to those recommended by NCCN, ESMO and BSH: • High-dose Ara-C based regimens including: ○ R- plus maxiCHOP alternating with R plus high dose cytosine arabinoside (Ara-	This amendment should be made to provide clarity on which regimens are high-dose Ara-C based regimens.	Corrected.

	C) (NORDIC regimen) ○ R plus bendamustine followed by R plus high dose Ara-C ○ Hyper cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD) alternating with high-dose methotrexate (MTX) and Ara-C, plus R or another anti-CD20 mAb ○ R-DHAP followed by R-CHOP (LyMA regimen) ○ Alternating R-CHOP and R-DHA(P/Ox) ○ Alternating R-CHOP and R-DHA(P/Ox), with BTKi added to the R-DHA(P/Ox) cycles		

	(TRIANGLE regimen) ○ Rituximab, bendamustine and cytarabine (R-BAC500) ○ VR-doxorubicin, cyclophosphamide and cisplatin (CAP) alternating with R plus high dose Ara-C ○ R-CHOP followed by R-BAC • CHOP in combination with R or another anti-CD20 mAb • Zanubrutinib/obinutuzumab/venetoclax'		
Page 31, Section 3.1.2, Table 3.1, Row: Outcomes, Column: Inclusion HRQoL outcomes are incorrectly listed under the safety heading.	Please amend the text as follows:	HRQoL outcomes are not safety outcomes and therefore should not be included within the bullet list below the 'safety' heading.	Corrected.

	'Safety: • Overall AEs • TEAEs • TRAEs • Grade 3+ AEs • Grade 3+ TEAEs • Grade 3+ TRAEs • SAEs • Discontinuations due to AEs HRQoL outcomes (measured using generic or disease-specific instruments/questionnaires)'		
Page 37, Section 3.2.1, Table 3.4, Row: Key eligibility criteria for patients, Column: second column The statement incorrectly implies that the CSR for TRIANGLE is included in the reference pack accompanying the EAG report.	Please could the following text be updated: 'A full list of inclusion and exclusion are provided within the CSR, included in the reference pack ~~accompanying this submission~~ provided alongside the Company Submission.'	This amendment should be made to ensure the correct document is referenced.	Amended.
Page 38, Section 3.2.1, Table 3.4, Row: Method of study	Please amend the text as follows:	This amendment should be made to provide clarity.	Corrected.

drug administration, Column: second column The dosing of IV vincristine incorrectly uses a comma rather than a full stop.	'R-CHOP: Induction: IV rituximab 375 mg/m² on day 0 or 1, IV cyclophosphamide 750 mg/m² on day 1, IV doxorubicin 50 mg/m² on day 1, IV vincristine 1,4 mg/m² on day 1, and oral predniso(lo)ne 100 mg on days 1–5'		
Page 38, Section 3.2.1, Table 3.4, footnotes The text is grammatically incorrect.	Please amend the text as follows: '^aThe FAS does not include patients from the ITT in the ~~Israeli~~ Israeli study group as it was not possible to re-consent these patients due to the ongoing geopolitical situation.'	This amendment should be made so the sentence is grammatically correct.	Corrected.
Page 46, Section 3.2.4.2 The text is missing a space between '95%' and 'CI'.	Please amend the text as follows: 'K-M estimates provided a HR of 0.522 (95% CI 0.341 to 0.799; p=0.0023).'	This amendment should be made to provide clarity.	Corrected.
Page 46, Section 3.2.4.2, Table 3.9, Row: Median (95% CI), Column: Arm A (N=269)	Please amend the text as follows: 'NE (77.44, NE)'	This amendment should be made to improve clarity.	Corrected.

The 95% CI is missing a comma to separate the range.			
Page 48, Section 3.2.4.4 The text refers to the wrong table number.	Please amend the text as follows: 'Table ~~3.7~~ 3.11 provides a summary of overall CRR and ORR.'	This amendment should be made to ensure the correct table is referenced.	Corrected.
Page 48, Section 3.2.4.4 The text is missing a space between '95%' and 'CI'.	Please amend the text as follows: 'For ORR, response in Arm I was 258 (96.3%) compared to 248 (92.2%) in Arm A (RR = 1.044, 95% CI 1.001 to 1.089; p = 0.0297).'	This amendment should be made to provide clarity.	Corrected.
Page 48, Section 3.2.4.4 The text refers to the wrong table number.	Please amend the text as follows: Table ~~3.8~~ 3.12 provides a summary of PR to CR conversion rates after the end of induction therapy.	This amendment should be made to ensure the correct table is referenced.	Corrected.
Page 53, Section 3.2.5.1, Table 3.15, Row: FFS HR (95% CI), Column: Unadjusted analysis	Please amend the text as follows: '  a'	This amendment should be made to provide clarity.	Corrected.

The footnote should be superscript.			
Page 56, Section 3.2.5.3 and Page 77, Section 4.2.4 The trial name is spelt incorrectly.	Page 56, Section 3.2.5.3: Please amend the text as follows: 'The EAG also asked the company to consider using alternative statistical approaches (e.g. two-stage estimation [TSE] approach), given the analogy of the movement to maintenance in TRIANGLY TRIANGLE with that to progression, which is often the basis for choosing this method.' Page 77, Section 4.2.4: Please amend the text as follows: 'Hence, it is likely that ibrutinib will be used as per the TRIANGL TRIANGLE trial protocol'	The typographical error should be corrected.	Corrected.
Page 59, Section 3.2.7.2, Table 3.18 Without indentations it is unclear which data are being reported.	Please could the first column of the table be updated to have the following indentation:	This amendment should be made to improve clarity.	Corrected.

	TEAEs, n (%)	Arm I N=265	Arm A N=268		
	Any TEAE	259 (97.7 %)	262 (97.8 %)		
	Grade ≥3	228 (86.0 %)	220 (82.1 %)		
	Ibrutinib-related^a	148 (55.8 %)	-		
	Any serious TEAE	119 (44.9 %)	110 (41.0 %)		
	Grade ≥3	90 (34.0 %)	89 (33.2 %)		
	Ibrutinib-related^a	22 (8.3%)	-		
	TEAEs leading to death ^b	1 (0.4%)	3 (1.1%)		
	Within 30 days of last dose	1 (0.4%)	0		

	<table><tr><th>of study treatment</th><td></td><td></td></tr><tr><td>TEAE leading to ibrutinib discontinuation^c</td><td>13 (4.9%)</td><td>-</td></tr><tr><td>TEAE leading to ibrutinib dose reduction^c</td><td>10 (3.8%)</td><td>-</td></tr><tr><td colspan="3"></td></tr></table>	of study treatment			TEAE leading to ibrutinib discontinuation ^c	13 (4.9%)	-	TEAE leading to ibrutinib dose reduction ^c	10 (3.8%)	-					
of study treatment															
TEAE leading to ibrutinib discontinuation ^c	13 (4.9%)	-													
TEAE leading to ibrutinib dose reduction ^c	10 (3.8%)	-													
Page 59, Section 3.2.7.2 The spelling of TEAE is incorrect.	Please amend the text as follows: ‘Table 3.19 provides a summary of ~~TAEs~~ TEAEs for the for the overall study period. There were 263 (99.2%) in Arm I compared to 267 (99.6%) in Arm A.’	The typographical error should be corrected.	Corrected.												
Page 59, Section 3.2.7.2, Table 3.19 Without indentations it is unclear which data are being reported.	Please could the first column of the table be updated to have the following indentation: <table><tr><th>TEAEs, n (%)</th><th>Arm I N=265</th><th>Arm A N=268</th></tr><tr><td>Any TEAE</td><td>263 (99.2%)</td><td>267 (99.6%)</td></tr></table>	TEAEs, n (%)	Arm I N=265	Arm A N=268	Any TEAE	263 (99.2%)	267 (99.6%)	This amendment should be made to provide clarity.	Corrected.						
TEAEs, n (%)	Arm I N=265	Arm A N=268													
Any TEAE	263 (99.2%)	267 (99.6%)													

	Grade ≥3	247 (93.2 %)	250 (93.3 %)		
	Ibrutinib-related^a	212 (80.0 %)	-		
	Any serious TEAE	171 (64.5 %)	123 (45.9 %)		
	Grade ≥3	146 (55.1 %)	105 (39.2 %)		
	Ibrutinib-related^a	50 (18.9 %)	-		
	TEAE leading to death ^b	6 (2.3%)	11 (4.1%)		
	Within 30 days of last dose of study treatment	4 (1.5%)	5 (1.9%)		
	TEAE leading to ibrutinib discontinuation ^c	61 (23.0 %)	-		

	<table><tr><td>TEAE leading to ibrutinib dose reduction^c</td><td>43 (16.2%)</td><td>-</td></tr><tr><td>COVID-19 TEAE</td><td>52 (19.6%)</td><td>5 (1.9%)</td></tr><tr><td>COVID-19 serious TEAE</td><td>23 (8.7%)</td><td>4 (1.5%)</td></tr><tr><td>COVID-19 TEAE leading to death</td><td>4 (1.5%)</td><td>2 (0.7%)</td></tr><tr><td></td><td></td><td></td></tr></table>	TEAE leading to ibrutinib dose reduction ^c	43 (16.2%)	-	COVID-19 TEAE	52 (19.6%)	5 (1.9%)	COVID-19 serious TEAE	23 (8.7%)	4 (1.5%)	COVID-19 TEAE leading to death	4 (1.5%)	2 (0.7%)					
TEAE leading to ibrutinib dose reduction ^c	43 (16.2%)	-																
COVID-19 TEAE	52 (19.6%)	5 (1.9%)																
COVID-19 serious TEAE	23 (8.7%)	4 (1.5%)																
COVID-19 TEAE leading to death	4 (1.5%)	2 (0.7%)																
Page 59, Section 3.2.7.2 The text incorrectly refers to ‘series’ TEAEs rather than ‘serious’ TEAEs.	Please amend the text as follows: ‘There were a greater number of series serious TEAEs in Arm I (171, 64.5%) compared to Arm A (123, 45.9%).’	The typographical error should be corrected.	Corrected.															
Page 63, Section 3.2.7.5 The text is grammatically incorrect.	Please amend the text as follows: ‘There was a greater number of general disorders and administration site conditions in Arm I versus Arm A for grade ≥3 (18, 6.8% versus 13, 4.9%) however a similar number of	The grammatical error should be corrected.																

	grade 3/4 across the two groups and ~~a~~ 1 grade 5 in Arm A and 0 in Arm I.'									
Page 63, Section 3.2.7.5 The text is grammatically incorrect.	Please amend the text as follows: 'There was a smaller number of respiratory, thoracic, and mediastinal disorders in Arm I versus Arm A for grade ≥3 (3, 1.1% versus 7, 2.6%) and grade 3/4 (2, 0.8% versus 5, 1.9%). ~~†~~ There were 2 (0.7%) grade 5 events in Arm A compared to 0 in Arm I.'	The grammatical error should be corrected.	Corrected.							
Page 63, Section 3.2.7.5, Table 3.22 Indentations are not used consistently throughout the table.	Please could the first column of the table be updated to have the following indentation: <table><tr><td>TESAE, n (%)</td></tr><tr><td>Blood and lymphatic system disorders</td></tr><tr><td>Thrombocytopenia</td></tr><tr><td>Febrile neutropenia</td></tr><tr><td>Infections and infestations</td></tr><tr><td>Pneumonia</td></tr><tr><td>COVID-19</td></tr></table>	TESAE, n (%)	Blood and lymphatic system disorders	Thrombocytopenia	Febrile neutropenia	Infections and infestations	Pneumonia	COVID-19	This amendment should be made to ensure consistency throughout the table and improve clarity of the data being presented.	Corrected.
TESAE, n (%)										
Blood and lymphatic system disorders										
Thrombocytopenia										
Febrile neutropenia										
Infections and infestations										
Pneumonia										
COVID-19										

	Sepsis		
	COVID-19 pneumonia		
	Device related infection		
	Herpes zoster		
	Gastrointestinal disorders		
	Diarrhoea		
	Vomiting		
	General disorders and administration site conditions		
	Pyrexia		
	Investigations		
	Platelet count decreased		
	Blood creatinine increased		
	Nervous system disorders		
	Respiratory, thoracic, and mediastinal disorders		
	Metabolism and nutrition disorders		
	Vascular disorders		
	Renal and urinary disorders		
	Acute kidney injury		
	Renal failure		

	Cardiac disorders		
	Atrial fibrillation		
	Injury, poisoning, and procedural complications		
	Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Page 65, Section 3.2.7.7 The text is grammatically incorrect.	Please amend the text as follows: ‘However ~~similar~~ the same number of grade 3/4 events were reported in both arms , and 1 grade 5 event in Arm A and 0 in Arm I.’	The grammatical error should be corrected.	Corrected.
Page 66, Section 3.2.7.8 The text is grammatically incorrect.	Please amend the text as follows: ‘There was a total of 93 deaths, with 60 (22.4%) in Arm A compared to 33 (12.5%) in Arm I. 30 (11.2%) deaths in Arm A and 14 (5.3%) in Arm I were attributed to PD.’	The grammatical error should be corrected.	Corrected.
Page 89, Section 4.2.9.2, Table 4.6, Row: R-DHAox, Column:	Please amend the text as follows:	The acquisition cost for R-DHAox should be reported with a comma to separate the 1 and	Corrected.

Acquisition cost (per administration) The acquisition cost for R-DHA0x is not reported to two decimal places	'£1,926.80'	9, and with two decimal places for consistency with the rest of the cost data reported in this table.	
Page 98, Section 5.3.5, EAG comment d) The outcome 'FFS' is incorrectly spelt as 'TFFS'	Please amend the text as follows: 'Unfortunately, the company did not explore whether the model can reproduce the observed TTF/ ~~TFFS~~ curve from TRIANGLE when the transitions are recombined, as requested by the EAG	The typographical error should be corrected.	Corrected.

Issue 1 Confidentiality highlighting errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG comment
Page 26, Section 2.2	Data comparing against the A+I arm of TRIANGLE are not publicly available and should therefore be marked as CIC.	'However, the Clinical Study Report (CSR) did conclude "no meaningful differences in the hazard rates of the primary outcome failure-free survival (FFS) (1-sided [REDACTED] confidence interval [CI]): [REDACTED], overall survival [OS] [Cox regression hazard ratio [HR] [(REDACTED)] or	Amended.

		progression-free survival [PFS] HR [REDACTED]).” ’	
Page 48, Section 3.2.4.4	CRR and ORR at the end of induction in TRIANGLE should be marked as CIC.	For ORR, response in Arm I was [REDACTED] compared to [REDACTED] in Arm A (relative risk [RR] = [REDACTED]). For CRR, response in Arm I was [REDACTED] compared to [REDACTED] in Arm A (RR = [REDACTED]). CR was [REDACTED] in Arm I compared to [REDACTED] in Arm A. PR was [REDACTED] in Arm I compared to [REDACTED] in Arm A. Arm I demonstrated [REDACTED] standard deviation (SD) ([REDACTED]) progressed disease (PD) ([REDACTED]) and not estimable (NE) [REDACTED] compared with Arm A, SD [REDACTED] PD ([REDACTED] and [REDACTED]).	Amended.
Page 65, Section 3.2.7.7	Tumour lysis syndrome events from TRIANGLE should be marked as CIC.	There was a [REDACTED] number of tumour lysis syndrome events in Arm I versus Arm A (all grades; [REDACTED] versus [REDACTED] grade 3/4; [REDACTED] versus [REDACTED]).	Amended.
Page 82, Section 4.2.6.3.1, EAG comment c)	The percentage of patients that received prior ASCT in RAY-3001 should be marked as CIC.	Likewise, patients in RAY-3001 are not reflective of patients entering second-line treatment in the economic model after being treated	

		with the ASCT regimen, as prior ASCT treatment in RAY-3001 was limited to [REDACTED]	
Page 82, Section 4.2.6.3.1, EAG comment d)	The percentage of patients that received prior ASCT in RAY-3001 should be marked as CIC.	Based on that, and the fact that [REDACTED] of the patients received prior ASCT...	Amended.

References

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2. Eyre TA, Bishton MJ, McCulloch R, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. *Br J Haematol* 2023;204:108-126.
3. Eyre TA, Cwynarski K, d'Amore F, et al. Lymphomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2025.
4. Keating SJ, Sushmitha I, Joyce Q, et al. Real-world treatment patterns, healthcare resource utilization and total cost of care in mantle cell lymphoma from US commercial claims. *International Journal of Hematologic Oncology* 2023;12:IJH45.
5. Jantunen E, Canals C, Attal M, et al. Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). *Annals of Oncology* 2012;23:166-171.
6. Stewart C, Owen C, Chua N, et al. Long-Term Remissions after First-Line Autologous Stem Cell Transplantation for Mantle Cell Lymphoma. *Blood* 2023;142:3599.
7. Eskelund CW, Kolstad A, Jerkeman M, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. *Br J Haematol* 2016;175:410-418.
8. Le Gouill S, Thieblemont C, Oberic L, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. *N Engl J Med* 2017;377:1250-1260.
9. Sarkozy C, Thieblemont C, Oberic L, et al. Long-Term Follow-Up of Rituximab Maintenance in Young Patients With Mantle-Cell Lymphoma Included in the LYMA Trial: A LYSA Study. *J Clin Oncol* 2024;42:769-773.
10. Johnson & Johnson Innovative Medicine. Clinical Study Report: Autologous Transplantation After a Rituximab/Ibrutinib/Ara-c Containing Induction in Generalized Mantle Cell Lymphoma –a Randomized European MCL Network Trial, 2024.
11. NICE. Zanubrutinib for treating relapsed or refractory mantle cell lymphoma [TA1081], 2025. Available at: <https://www.nice.org.uk/guidance/ta1081>. Last accessed: July 2025.
12. NICE. Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy [TA895], 2023. Available at: <https://www.nice.org.uk/guidance/ta895>. Last accessed: July 2025.
13. Di M, Ho CI, Smith SD, et al. Quality of Life during Survivorship Following Autologous Stem Cell Transplant for Mantle Cell Lymphoma. *Blood* 2024;144:5116-5116.
14. Johnson & Johnson Innovative Medicine. Advisory Board Meeting Report (November 2025).

15. NICE. Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable, 2025. Available at: <https://www.nice.org.uk/guidance/ta1048>. Last accessed: December 2025.
16. NICE. Non-Hodgkin's lymphoma: diagnosis and management [NG52], 2024. Available at: <https://www.nice.org.uk/guidance/ng52/resources/nonhodgkins-lymphoma-diagnosis-and-management-pdf-1837509936325>. Last accessed: June 2025.
17. National Institute for Health and Care Excellence. Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]: Response to request for clarification from the EAG. London: NICE, 2026:111.
18. Johnson & Johnson Innovative Medicine. Advisory Board Meeting report (November 2025) [Data on file], 2025.
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23. Visco C, Di Rocco A, Evangelista A, et al. Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: results from the MANTLE-FIRST study. *Leukemia* 2021;35:787-795.
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25. Kerhuel L, Amorim S, Azoulay E, et al. Clinical features of life-threatening complications following autologous stem cell transplantation in patients with lymphoma. *Leuk Lymphoma* 2015;56:3090-5.
26. Johnson & Johnson Innovative Medicine. Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable [ID6596]: Submission to National Institute of Health and Care Excellence. Single technology appraisal (STA): Document B - Company evidence submission: Johnson & Johnson Innovative Medicine, 2026:189.

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

Topic ID:

Managed Access Lead:

Date of assessment(s):

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable

6596

Milena Wobbe

20/04/2026

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	Rationale for rating	To consider managed access, a committee will need a managed access proposal, along with a feasibility assessment from the NICE managed access team. Currently no managed access proposal has been submitted. The managed access team should be contacted if a managed access proposal is expected to be requested or submitted at a later point in the NICE evaluation process.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	As there is no proposal, this can only enter CDF if a proposal is received after the first committee meeting

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	No	As a cancer drug, this technology is eligible for reimbursement through the CDF, though no proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	Low	The key uncertainties cannot be resolved through further data collection as it stands. Data from SACT could resolve uncertainty for subsequent treatments and maintenance treatment, but impacts on ICERs are low.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	No	As per company submission, no further data cuts will be available for the purpose of HTA. Primary completion was reached in May 2021.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	SACT dataset would be available.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	As there is no proposal, this has not been investigated in detail, but standard SACT logic has been applied.

Key questions for committee if Managed Access is considered	
1	N/A

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	N/A