Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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 Astrazeneca UK:**
   a. Full submission
   b. Submission addendum
   c. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Lymphoma Action
   b. The Royal College of Pathologists and University Hospitals Plymouth NHS Trust – written by clinical expert

4. **Expert personal perspectives** from:
   a. Rory McCulloch – clinical expert, nominated by NICE
   b. Clinical expert - nominated by The Royal College of Pathologists
   c. Patient expert - nominated by Lymphoma Action

5. **NDRS and NICE SACT report**:
   a. Bendamustine + Rituximab for mantle cell lymphoma (MCL)
   b. R-CHOP for mantle cell lymphoma (MCL)

6. **External Assessment Report** prepared by Aberdeen HTA Group
   a. External Assessment Report
   b. EAG critique of company addendum

7. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Document B

Company evidence submission

January 2025

File name	Version	Contains confidential information	Date
ID6155 Acalabrutinib MCL Document B vFINAL [redacted]	**V2.0**	**Yes (CIC)**	**8th January 2025**

Contents

Tables and figures

Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
ABR	Acalabrutinib, bendamustine, rituximab
Acala	Acalabrutinib
AE	Adverse event
AIC	Akaike information criteria
AIHA	Autoimmune haemolytic anaemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BR	Bendamustine + rituximab
BSA	Body surface area
BSH	British Society for Haematology
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR-T	Chimeric antigen receptor T-cell
cBTKi	Covalent Bruton's tyrosine kinase inhibitor
CC	Critical care
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMU	Commercial Medicines Unit
CNS	Central nervous system
CMV	Cytomegalovirus
CPI	Consumer price index
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report

DAPS	Directly accessed pathology services
DCO	Data cut-off
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC	European Organization for Research and Treatment of Cancer
ERG	Evidence Review Group
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FAS	Full analysis set
FCR	Fludarabine, cyclophosphamide, rituximab
HCP	Healthcare Professional
HCRU	Healthcare resource use
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INR	International normalised ratio
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice/web response system
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LY	Life year
LYMS	Lymphoma-specific subscale
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency

MIMS	Monthly Index of Medical Specialties
MIPI	Mantle Cell Lymphoma International Prognostic Index
MMRM	Mixed model for repeated measures
N/A	Not applicable
NE	Not estimable
NHB	Net health benefit
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NMA	Network meta-analysis
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PBR	Placebo, bendamustine, rituximab
PCR	Polymerase chain reaction
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazards
PO	Orally
PPAS	Per protocol analysis population
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of life
QTc	Corrected QT interval
R	Rituximab
R-BAC	Rituximab, bendamustine, cytarabine
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone
R-CVP	Rituximab, cyclophosphamide, vincristine, prednisolone
R/R	Relapsed/refractory
RCT	Randomised controlled trial

RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STM	State transition model
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TECH-VER	Technical verification
TLR	Targeted literature review
TOI	Trial outcome index
TP53	Tumour protein 53
TSD	Technical support document
TTD	Time to treatment discontinuation
TTR	Time to response
ULN	Upper limit of normal
VR-CAP	Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone

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

B.1.1 Decision problem

The submission focuses on part of the technology's anticipated marketing authorisation. The anticipated marketing authorisation indication is for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL). The proposed population considered in this submission is adult patients with previously untreated MCL *who are considered unsuitable candidates for autologous stem cell transplant (ASCT)*. The proposed population is narrower than the anticipated marketing authorisation because the evidence base on acalabrutinib in combination with bendamustine and rituximab (ABR) is limited to this population (see Table 1 for more information).

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 previously untreated MCL	Adults with previously untreated MCL who are considered unsuitable candidates for ASCT	Until now, 1L treatment for MCL has required dichotomising patients based on ASCT suitability based on a range of factors, including patient choice, the timing of relapse, age, previous treatment, and general health and fitness (1). Patients deemed suitable for a transplant typically receive aggressive chemoimmunotherapy, consolidative ASCT in first remission, and rituximab maintenance (2). For the older, less fit population who are unsuitable for aggressive induction therapy, BR and R-CHOP are recommended, with BR considered SoC for the majority of patients (2, 3). The evidence from the Phase 3 ECHO trial focuses on patients with untreated MCL who are considered unsuitable candidates for ASCT.
Intervention	Acalabrutinib with bendamustine and rituximab	As per NICE scope	-
Comparator(s)	Established clinical management without acalabrutinib, including: • Chemotherapy in combination with rituximab, including bendamustine with rituximab (BR) • Cytarabine-based immunochemotherapy • Radiotherapy • Bortezomib	• Chemotherapy in combination with rituximab: – BR – R-CHOP	To understand the standard treatments currently used in the NHS for this population and to identify appropriate comparators, AstraZeneca conducted one-to-one interviews with several haematology-oncology consultants in the UK who treat MCL (see Appendix N). All clinicians independently agreed that the treatments used in the UK for patients with untreated MCL who are considered unsuitable candidates for ASCT are **BR** and **R-CHOP**, with BR considered as the SoC (3). Although **VR-CAP** (**V = bortezomib**) is recommended in the guidelines for patients with 1L MCL who are unsuitable for ASCT, all clinicians stated that this therapy is rarely used in the UK due to increased toxicity versus R-CHOP and the need for frequent monitoring (2, 3). Similarly, with **R-BAC (cytarabine-based immunochemotherapy)**, this regimen is associated with

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			significant infective and haematological toxicity (2) and is therefore not frequently used (3). Finally, **radiotherapy** is reserved for patients with early-stage MCL and therefore falls outside the remit of the population in this submission which includes patients with advanced disease who are unsuitable for ASCT (2, 4). The insights gathered from the UK clinicians on the appropriate comparators align with the BSH guidelines for treating 1L MCL patients unsuitable for transplant, which describe the toxicity of both R-BAC and VR-CAP (2).
Outcomes	The outcome measures to be considered include: • PFS • OS • Response rates • Adverse effects of treatment • HRQoL	As per NICE scope	-

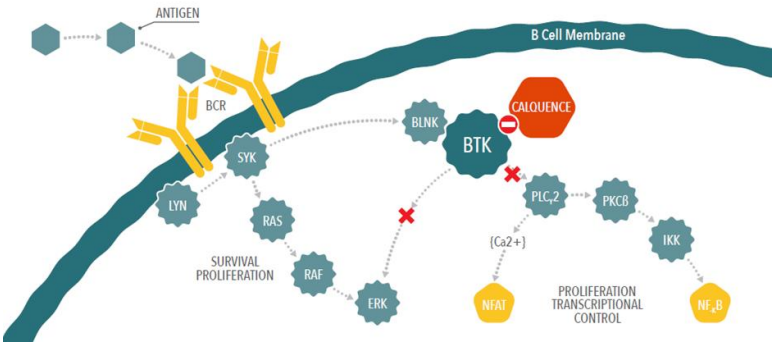
Abbreviations: 1L, first-line; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; BSH, British Society for Haematology; CAR-T, chimeric antigen receptor T-cell; HRQoL, health-related quality of life; MCL, mantle cell lymphoma; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission are provided in Table 2. The draft summary of product characteristics (SmPC) for acalabrutinib is provided in Appendix C.

Acalabrutinib is currently indicated as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (5), and as monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy (5). This submission is for ABR for the proposed indication of adult patients with previously untreated MCL who are considered unsuitable candidates for ASCT. Marketing authorisation for this indication is pending.

Table 2: Technology being evaluated

UK approved name and brand name	Calquence® (acalabrutinib) in combination with bendamustine and rituximab
Mechanism of action	Acalabrutinib is a selective inhibitor of BTK (5). BTK is a signalling molecule of the B-cell antigen receptor and cytokine receptor pathways. In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK with minimal off-target interactions (5).  Abbreviations: BCR, B cell receptor; BLNK, B cell linker; BTK, Bruton's tyrosine kinase; Ca2+, calcium ion; ERK, extracellular signal-regulated kinase; IKK, inhibitor of kappa-B kinase; LYN, Lck/Yes novel tyrosine kinase; NFAT, nuclear factor of activated T-cells; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PKCβ, protein kinase C beta; PLCγ2, phospholipase-gamma-2; RAF, rapidly accelerated fibrosarcoma; RAS, Rat sarcoma; SYK, spleen tyrosine kinase. Adapted from Hendriks et al. 2014 (6).
Marketing authorisation/CE mark status	A marketing authorisation application was submitted to the MHRA in September 2024. The anticipated date of UK regulatory approval is [redacted].

Indications and any restriction(s) as described in the SmPC	***Indication covered in this submission:*** Acalabrutinib in combination with bendamustine and rituximab (BR) is expected to be indicated for the treatment of adult patients with previously untreated MCL (5). The population for this submission is narrower; it includes adult patients with previously untreated MCL *who are considered unsuitable candidates for ASCT*. This is because the evidence base focuses on patients considered to be unsuitable for ASCT and aligns with how acalabrutinib is expected to be used in clinical practice (Table 1). ***Existing indications for acalabrutinib:*** Acalabrutinib as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL (5). Acalabrutinib as monotherapy is indicated for the treatment of adult patients with CLL who have received at least one prior therapy (5).
Method of administration and dosage	Acalabrutinib is for oral use (5). The tablets should be swallowed whole with water at approximately the same time each day. The recommended dose of acalabrutinib is 100 mg twice daily (equivalent to a total daily dose of 200 mg), with a dose interval of approximately 12 hours. Treatment should be continued until disease progression or unacceptable toxicity. For BR, the healthcare professional should refer to the prescribing information of each of these medicinal products for their dosing information (5). The dosing strategy adopted in the ECHO trial was as follows (7): • The dose of bendamustine was 90 mg/m^2 delivered intravenously on Days 1 and 2 of a 28-day cycle • The dose of rituximab was 375 mg/m^2 delivered intravenously on Day 1 of a 28-day cycle • BR was administered for a maximum of 6 cycles *Maintenance:* • Patients who achieved a response (PR or greater) received maintenance rituximab 375 mg/m^2 on Day 1 of every other cycle for a maximum of 12 additional doses (through no later than Cycle 30)
Additional tests or investigations	No additional tests or investigations are required.
List price and average cost of a course of treatment	Acalabrutinib is available at a list price of £5,059.00 per 60 tablets (8). Based on the median duration of treatment of 28.6 months in ECHO (5), the average cost of a course of treatment is £146,797.† Bendamustine is available at a list price of £65.59 for a pack of 5 x 100 mg solution for infusion, £53.37 for a pack of 1 x 100 mg solution for infusion, or £27.19 for a pack of 5 x 25 mg solution for infusion (9). Based on patients receiving bendamustine for a maximum of 6 cycles, the average cost of a course of treatment is £301.38.‡,§ Rituximab is available at a list price of £1,344.65 for a pack of 1 x 1,400 mg solution for injection, £785.84 for a pack of 1 x 500 mg solution for injection, or £314.33 for a pack of 2 x 100 mg solution for injection (10). The average cost of a course of treatment (excluding maintenance) is £7,544.04.‡,§ *Maintenance:* The average cost of maintenance rituximab is £15,088.08.¶,§
Patient access scheme (if applicable)	A PAS of [redacted] on the list price of acalabrutinib is already in place. For the purposes of the submission, the existing simple discount patient access scheme for acalabrutinib is used.

Abbreviations: BR, bendamustine + rituximab; BSA, body surface area; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; MHRA, Medicines and Healthcare products Regulatory Agency; PAS, patient access scheme; PR, partial response; SmPC, summary of product characteristics.

† Assuming an average of 30.4375 days in a month.

‡ Assuming no vial sharing, and an average BSA of 1.898 (based on ECHO trial data) (11).

§ Price calculated based on the cheapest combination of available pack sizes.

¶ Based on a maximum of 12 doses.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 MCL overview

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers of the lymphatic system. MCL is a rare subtype of NHL, accounting for approximately 3–10% of all NHL in Western countries (12, 13), with its name derived from the accumulation of abnormal B-cells in the mantle zone of lymph nodes (13).

MCL accounts for 1.6% of diagnosed haematological malignancies in the UK, with an annual incidence of 0.9 per 100,000, equating to approximately 590 new cases diagnosed each year (14). It occurs more frequently in males than females (2.4:1 ratio) and is more likely to occur at older ages (median age at diagnosis: 72 years) (14). While specific risk factors or predispositions for MCL have not been identified, overexpression of cyclin D1 is a key event in the pathogenesis of MCL and is most commonly the result of the chromosome translocation t [11;14] (q13;q32) (12). ATM (DNA damage response) is the most frequent mutation (43.5% of patients), whilst mutation of tumour protein 53 (TP53; a tumour suppressor gene) is also common (26.8% of patients) (15). Mutated TP53 is typically associated with an aggressive disease course, poor response to chemotherapy, and high mortality (2, 12). Morphological subgroups of MCL include classic, blastoid, pleomorphic, marginal zone-like and small cell types (2). Blastoid and pleomorphic types are associated with poorer survival (2). Finally, Ki-67 is a protein that is a marker of proliferation, and a Ki-67 of less than 30% has been associated with a more favourable prognosis (16).

Staging in lymphoma is based on the Lugano classification, where Stage I represents localised lymphoma, and Stage IV indicates spread to distant extranodal sites (17). MCL typically presents as a high grade (fast growing) lymphoma; most patients are therefore diagnosed at advanced stages (13). Estimates suggest that 87.9% of patients with MCL are diagnosed with Stage IV disease (18).

Patients with MCL have varied clinical presentations, with a small number (10–15%) of patients experiencing an asymptomatic, indolent disease course (2, 12). The most common symptom is painless swelling in the lymph nodes, though patients may

experience reduced appetite, pain in the abdomen, fatigue, thrombocytopenia, or diarrhoea and sickness, depending on the lymphatic sites affected (13, 19). Some patients may also experience ‘B symptoms’, including unexplained weight loss, night sweats, or fever (19).

Despite available treatments, MCL is generally incurable, with patients typically experiencing a relapsing disease course. The median duration of remission has been reported to be between 1.5 and 3 years (20). Survival is poor, with an overall 5-year survival rate from diagnosis of 47.4% across all patients with MCL (14). The Mantle Cell Lymphoma International Prognostic Index (MIPI), developed as a prognostic tool to identify the risk categories to which patients with MCL belong, and aid treatment decisions, categorises patients into ‘low-risk’ (33% of patients), ‘intermediate-risk’ (32%), and ‘high-risk’ (35%) subgroups (21). Based on these risk categories, 5-year overall survival (OS) was estimated at 83% for ‘low-risk’, 63% for ‘intermediate risk’, and 34% for ‘high-risk’ patients (22).

B.1.3.2 Current clinical care pathway

Guidelines for the management of MCL are available from NICE (NG52) (4) and the British Society for Haematology (BSH) (2), with strong alignment between the two guidelines.

The current treatment pathway in England for patients with MCL is dependent on the stage of disease and presentation of symptoms. Options for patients with early stage, non-progressive, asymptomatic MCL include radiotherapy, or a ‘watch and wait’ approach of active monitoring (2, 4).

For advanced MCL, the treatment pathway is further segmented based on suitability for ASCT. Suitability for ASCT is determined by clinical experts on an individual patient basis, taking into account a range of factors including patient choice, the timing of relapse, age, previous treatment, comorbidities, and general health and fitness (1, 3).

Patients deemed transplant-suitable typically receive aggressive chemoimmunotherapy, consolidative ASCT in first remission, and rituximab

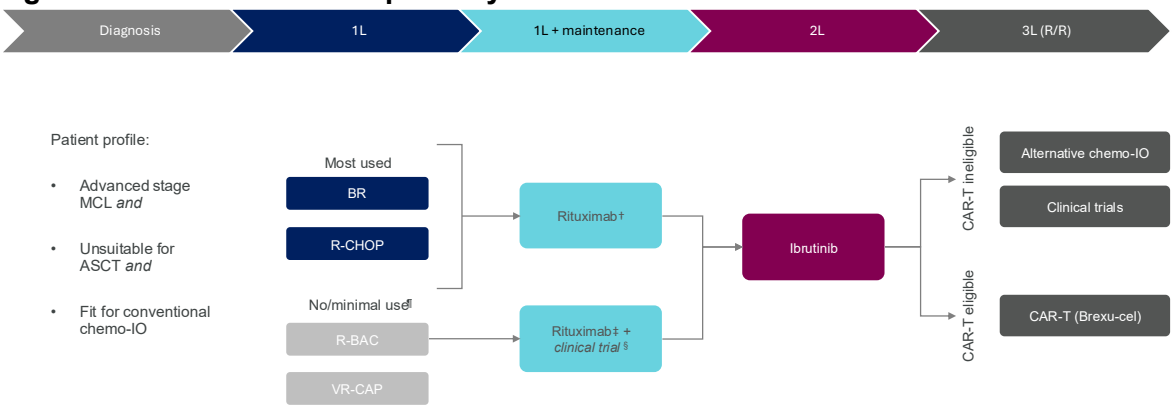
maintenance (2, 4). Despite clear progression-free survival (PFS) and OS benefits from such an approach, patients eventually relapse.

The group of patients who are not deemed fit for ASCT (typically older, less fit patients) are the focus of this submission. An overview of the treatment pathway for this population is presented in Figure 1.

In first-line (1L) treatment, guidelines recommend that patients with previously untreated MCL unsuitable for ASCT should be offered chemotherapy with bendamustine plus rituximab (BR), rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), rituximab, bendamustine and cytarabine (R-BAC), or bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone (VR-CAP), taking patient fitness into consideration (2, 4). Input from clinicians (see Expert Input, Appendix N) highlighted that BR and R-CHOP are the predominant treatment options used in the UK, with over 90% of patients on active 1L treatment receiving these therapies (3). Based on increased efficacy (2, 3), BR is more commonly used than R-CHOP (60–75% of patients treated with BR versus approximately 25–30% treated with R-CHOP) (3). Despite being recommended by NICE (23), UK clinical experts experienced in managing patients with previously untreated MCL highlighted that VR-CAP is not considered a treatment option for 1L treatment of MCL in the UK due to increased toxicity versus R-CHOP and the need for frequent monitoring (3). R-BAC is reserved for patients who are ineligible for R-CHOP but able to tolerate a more aggressive regimen than BR, though this represents a minority (less than 3%) of the population (3). These insights gathered from UK clinicians align with BSH guidelines, which describe the high toxicity of both R-BAC and VR-CAP (2).

Following 1L chemotherapy with BR or R-CHOP, maintenance rituximab is recommended every 2 months (following chemotherapy with R-BAC, this is only recommended in a clinical trial setting). Maintenance rituximab has demonstrated significant real-world improvements in outcomes, including longer time to next treatment and overall survival (OS), versus 1L chemotherapy alone (24, 25). In the second-line (2L) setting, ibrutinib (a Bruton’s tyrosine kinase inhibitor [BTKi]) is recommended, before chimeric antigen receptor T-cell (CAR-T) therapy with brexucabtagene autoleucel in third-line (3L) for those who are eligible.

Figure 1: Current treatment pathway for advanced MCL unsuitable for ASCT



Abbreviations: 1/2/3L, first-/second-/third-line; ASCT, autologous stem cell transplant; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor T-cell; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
† For patients with newly diagnosed MCL who are not fit enough for high-dose chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy, rituximab maintenance may be given every 2 months until disease progression.
‡ For patients with newly diagnosed MCL who are in remission after cytarabine-based induction and high-dose chemotherapy, rituximab maintenance may be given every 2 months for 3 years.
§ BSH guidelines suggest that rituximab maintenance following R-BAC should not be offered outside of a clinical trial.
¶ Used in less than 3% of patients.
References: Eyre T et al. 2024 (2); NICE NG52 (4); AstraZeneca Data on File REF-251322, 2024 (3).

B.1.3.3 Unmet need

Despite high response rates with available chemoimmunotherapy, MCL remains incurable, with poor survival and high relapse rates placing a high burden on patients. Patients who are unsuitable for aggressive regimens (intensive chemotherapy induction and ASCT) are restricted to chemotherapy options that have limited efficacy in preventing relapses, in turn leading to high mortality (26-28).

In 1L, clinicians also cite a lack of tolerable treatment options for elderly, unfit, or comorbid patients (see Expert Input, Appendix N). Patients with MCL who are unsuitable for ASCT typically have comorbidities, meaning they cannot tolerate treatments with high toxicity rates. As such, the safety profile of future therapies is of particular importance.

Given that the management of patients with relapsed/refractory (R/R) MCL is particularly challenging due to limited treatment options and poor response durability (29), improving the efficacy of 1L treatment, and specifically maximising the duration of first remission, remains of critical importance to obtain favourable long-term

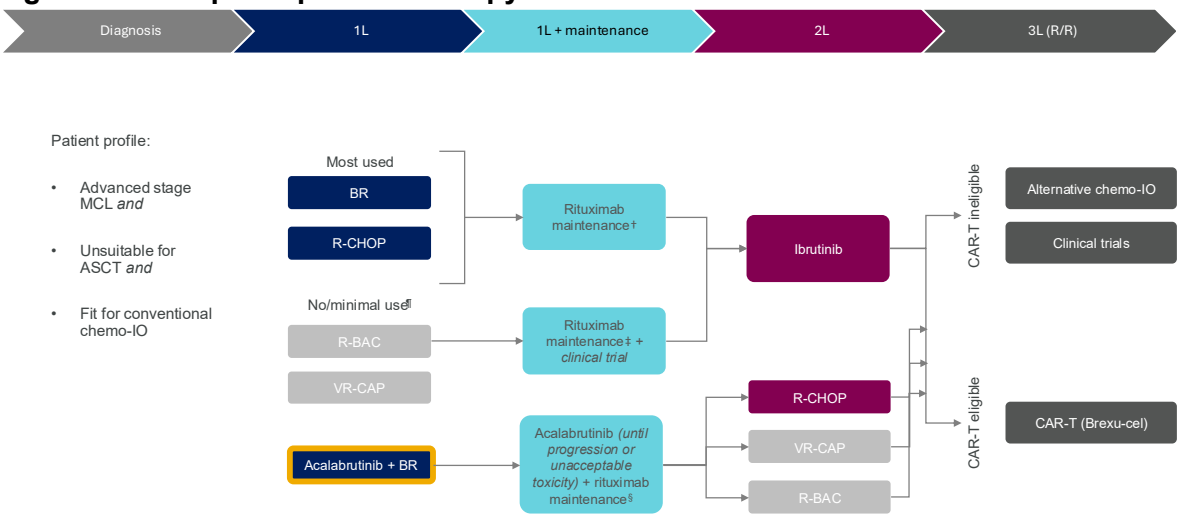
outcomes. Published estimates for the number of relapsed patients who receive a subsequent (2L treatment) range between 49 and 87%, based on data from the US and Sweden (25, 30).

B.1.3.4 Acalabrutinib place in therapy

One of the main areas of possible focus for advancement of 1L management is adding targeted agents to immunochemotherapy. Targeted agents, which are now mainstays of treatment in later-line R/R MCL, are establishing new, paradigm-changing roles in 1L treatment. In particular, BTKis have transformed the treatment of MCL; given their improved single-agent activity in R/R disease versus standard of care (SoC), their use is being explored in 1L, with the aim of achieving significant long-term benefit while limiting toxicity, which is also an important goal in patients who are unsuitable for ASCT.

Acalabrutinib (a BTKi) + BR is anticipated to be used in the 1L treatment of ASCT -unsuitable patients with MCL, who would otherwise be considered for BR or R-CHOP (Figure 2). Following the use of ABR in the 1L setting, 2L treatment options would include R-CHOP, R-BAC, and VR-CAP, with no anticipated change to 3L treatment.

Figure 2: Anticipated place in therapy for ABR



Abbreviations: 1/2/3L, first-/second-/third-line; ABR, acalabrutinib, bendamustine, rituximab; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor T-cell; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
† For patients with newly diagnosed MCL who are not fit enough for high-dose chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy, rituximab maintenance may be given every 2 months until disease progression.
‡ For patients with newly diagnosed MCL who are in remission after cytarabine-based induction and high-dose chemotherapy, rituximab maintenance may be given every 2 months for 3 years.
§ For patients treated with ABR, acalabrutinib may be given until progression or unacceptable toxicity. Rituximab maintenance may be given every 2 months for 2 years.
¶ Used in less than 3% of patients.
References: Eyre T et al. 2024 (2); NICE NG52 (4); AstraZeneca Data on File REF-251322, 2024 (3).

B.1.4 Equality considerations

Use of ABR is not expected to raise any equality issues.

B.2 Clinical effectiveness

Overview

- ECHO is an ongoing, global, Phase 3 randomised, double-blind, multi-centre study to assess the efficacy and safety of ABR compared with placebo plus BR (PBR) in previously untreated adult patients with MCL
- Patients had a median age of 71.0 years, 70.7% were male and most patients were classified as having either low (33.4%) or intermediate (42.3%) risk, as per the MIPI. The most common Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0 (49.5% of patients)
- Patient demographics and disease baseline characteristics were similar between the two treatment arms and were representative of the target population of adult patients with previously untreated MCL who are unsuitable for ASCT
- At the data cut-off (DCO) for the primary Independent Review Committee (IRC)-assessed PFS analysis (15th February 2024), ECHO met the primary endpoint, and demonstrated that ABR resulted in a statistically significant reduction in the risk of progressed disease (PD) or death by 27% relative to PBR (PFS hazard ratio [HR]: 0.73; 95% CI: 0.57, 0.94; 2-sided log-rank p=0.0160)
- The median estimated PFS (based on 247 PFS events) in the ABR arm was 66.4 months (95% CI: 55.1, not estimable [NE]) compared with 49.6 months in the PBR arm (95% CI: 36.0, 64.1), corresponding to an approximate 17-month increase in median PFS
- PFS outcome from ECHO included patients who did not experience disease progression prior to death. When COVID-19 deaths were censored, median PFS improved in both arms (NE vs 61.6 months for ABR and PBR, respectively). ABR reduced the risk of PD or death by 36% versus PBR (HR: 0.64; 95% CI: 0.48, 0.84; p=0.0017)
- OS data showed a positive trend favouring the ABR arm (HR: 0.86; 95% CI: 0.65, 1.13; p=0.2743); however, the median OS was not reached at the DCO (34% maturity reached [203 of 598 target OS events met])

- The trend for OS improved when COVID-19 deaths were censored (HR: 0.75, 95% CI: 0.53, 1.04; p=0.0797 in favour of ABR)
- High response rates (≥88.0%) were observed in both treatment arms, with a numerically higher complete response (CR) rate in the ABR arm. Likewise, more durable responses were observed in those treated with ABR versus PBR, with a median duration of response (DOR) of 63.5 months (95% CI: 52.5, NE) versus 53.8 months (95% CI: 37.5, 66.1), respectively
- The patient-reported outcome (PRO) data demonstrated [redacted]
- The safety profile of ABR was consistent with the known safety profile of the individual treatments used in each arm. Any grade treatment-emergent adverse events (TEAEs) were reported in 99.7% of patients in the ABR arm and 99.0% of patients in the PBR arm. The reported Grade ≥3 TEAEs (88.9% with ABR vs 88.2% with PBR) and Grade ≥3 serious adverse events (SAEs) (64.3% with ABR vs 55.9% with PBR) were comparable between the two arms. At the DCO, a greater number of patients remained on ABR compared with PBR, making the number of patients at risk of adverse events (AEs) higher in the ABR arm

Clinical effectiveness conclusions

- The ECHO efficacy and safety data confirm that ABR significantly improves PFS versus currently available SoC for patients with previously untreated MCL, with a trend towards improved OS and [redacted]
  - The improvement in PFS with ABR is statistically significant and clinically meaningful
- No additional safety concerns outside the known tolerability profiles of the individual treatments used were identified
- In the context of a disease which remains incurable, this substantial increase in median PFS represents a significant improvement in the treatment of patients with previously untreated MCL

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to ABR in patients with previously untreated MCL.

A systematic literature review (SLR) was conducted to identify clinical evidence for the efficacy and safety of ABR and potential comparators in previously untreated patients with MCL who are unsuitable for aggressive induction therapy and/or stem cell transplant (SCT).

An overview of the methodology, including search strategy, Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram, list of included studies and list of excluded studies at full paper review is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one relevant randomised controlled trial (RCT) (ECHO) reporting on the clinical effectiveness of ABR in previously untreated MCL (Table 3).

Table 3: Clinical effectiveness evidence

Study	ECHO
Study design	Phase 3, randomised, double-blind, placebo-controlled, multi-centre study Interim analysis DCO: 15th February 2024 Final analysis planned when approximately 268 IRC-assessed PFS events have been observed
Population	Adults with previously untreated MCL
Intervention(s)	Acalabrutinib in combination with bendamustine and rituximab
Comparator(s)	Placebo in combination with bendamustine and rituximab
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	NA
Reported outcomes specified in the decision problem	**PFS**, **OS**, response rates (ORR, DOR, TTR), **AEs of treatment**, **HRQoL**

Abbreviations: AE, adverse event; DCO, data cut-off; DOR, duration of response; HRQoL, health-related quality of life; IRC, Independent Review Committee; MCL, mantle cell lymphoma; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Summary of trial methodology – ECHO

ECHO is an ongoing, global, Phase 3, randomised, double-blind, multicentre study to assess the efficacy and safety of ABR compared with PBR in patients with previously untreated MCL.

The methodology for, and data from, ECHO are drawn from multiple sources. These include:

- ECHO interim clinical study report (CSR) (11)
- ECHO clinical study protocol (CSP) (7)
- ECHO statistical analysis plan (SAP) (31)

B.2.3.1.1 Data cut-off

The interim analysis for PFS was initially planned to take place when approximately 227 IRC-assessed PFS events were observed. In light of the potential impact of COVID-19 on the primary analysis, the DCO was determined to allow for an additional 10% IRC-PFS events. The results of the interim analysis were based on a DCO of 15th February 2024. A final analysis is planned to occur when approximately 268 IRC-assessed PFS events (~49% data maturity) have been observed.

B.2.3.2 Study objectives

The primary objective of the study was to evaluate the efficacy of ABR compared with PBR based on IRC assessment of PFS per the Lugano Classification for NHL in patients with previously untreated MCL.

B.2.3.3 Study locations

The study included 189 sites in 26 countries: Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Greece, Hungary, Israel, Italy, Japan, Mexico, New Zealand, Peru, Poland, Republic of Korea, Romania, Russia, Spain, Taiwan, Ukraine, United States, Vietnam.

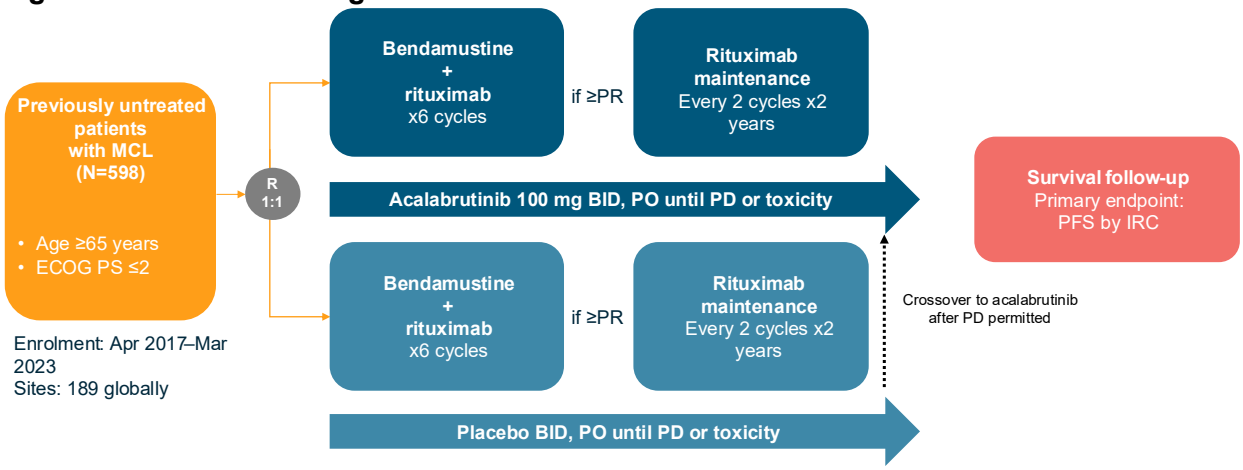
B.2.3.4 Trial design

Patients meeting the eligibility criteria were randomised 1:1 to the following arms:

- Arm 1: Acalabrutinib + six cycles of BR
- Arm 2: Matching placebo + six cycles of BR

BR can only be administered for a maximum of six cycles. After this point, patients who achieved at least a partial response (PR) continued to receive rituximab maintenance every two cycles for a maximum of 12 additional doses (through no later than Cycle 30), alongside daily acalabrutinib or placebo. An overview of the trial design is presented in Figure 3.

Figure 3: ECHO trial design



Abbreviations: BID, twice daily; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; MCL, mantle cell lymphoma; PD, progressed disease; PFS, progression-free survival; PO, orally; PR, partial response; PS, performance status.

B.2.3.4.1 Method of randomisation and blinding

Patients meeting the eligibility criteria for the study were randomised 1:1 using an interactive voice/web response system (IXRS) to one of the two study arms. Randomisation was stratified by:

- Geographic region (North America, Western Europe, or Other)
- Simplified MIPI score (low risk [0–3], immediate risk [4–5], or high risk [6–11])

ECHO is a double-blind trial. The sponsor, investigator, site staff, and subject were blinded to the treatment, and the subject was randomised.

B.2.3.4.2 Eligibility criteria

Details of key inclusion and exclusion criteria for ECHO are presented in Table 4.

Table 4: Eligibility criteria – ECHO

Inclusion	Exclusion
• Men and women, ≥65 years of age • Pathologically confirmed MCL, with documentation of chromosome translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1 in association with other relevant markers (e.g. CD5, CD19, CD20, PAX5) • MCL requiring treatment and for which no prior systemic anticancer therapies have been received • Presence of radiologically measurable lymphadenopathy and/or extranodal lymphoid malignancy • ECOG PS ≤2 • Men who are sexually active and can beget children must agree to use highly effective forms of contraception during the study and for 6 months after the last dose of bendamustine, or 12 months after the last dose of rituximab, whichever is longest • Men must agree to refrain from sperm donation during the study and for 6 months after the last dose of bendamustine or 12 months after the last dose of rituximab, whichever is longest • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorisation to use protected health information (in accordance with national and local patient privacy regulations)	• History of prior malignancy except for the following: – Malignancy treated with curative intent and with no evidence of active disease present for more than 2 years before screening and felt to be at low risk for recurrence by treating physician† – Adequately treated lentigo maligna melanoma without current evidence of disease or adequately controlled non-melanomatous skin cancer – Adequately treated carcinoma *in situ* without current evidence of disease • Patients for whom the goal of therapy is tumour debulking before SCT • Any history of CNS lymphoma or leptomeningeal disease • Uncontrolled AIHA or ITP • Major surgical procedure within 28 days before first dose of study drug‡ • Significant cardiovascular disease§ • ANC <1.0 × 10^9/L or platelet count <75 x 10^9/L; for patients with disease involvement in the bone marrow, ANC <0.75 x 10^9/L or platelet count <50 x 10^9/L. Patients were only be considered eligible if peripheral blood counts could be maintained independent of growth factors or transfusions during the screening period • Total bilirubin >1.5 x ULN; or AST or ALT >2.5 x ULN • Estimated creatinine clearance of <50 mL/min calculated using the formula of Cockcroft and Gault ([140-age] x mass [kg]/[72 x creatinine mg/dL] x multiply by 0.85 if female) • Prothrombin time/INR or aPTT (in the absence of a lupus anticoagulant) >2.0 x ULN. Exception: Patients receiving warfarin were excluded; however, those receiving other anticoagulant therapy who had a higher INR/aPTT could be permitted to enrol in this study following discussion with the medical monitor • Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel

Inclusion	Exclusion
	disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass • Uncontrolled active systemic fungal, bacterial, viral, or other infection, or intravenous anti-infective treatment within 2 weeks before first dose of study drug • Known history of infection with HIV • Ongoing immunosuppressive therapy, including systemic (e.g. IV or oral) corticosteroids within 2 weeks before the first dose of study drug¶ • Known history of anaphylaxis or hypersensitivity to bendamustine, rituximab, or any of their components • Serologic status reflecting active hepatitis B or C infection†† • Received a live virus vaccination within 28 days of first dose of study drug • History of stroke or intracranial haemorrhage within 6 months of first dose of study drug • History of bleeding diathesis (e.g. haemophilia or von Willebrand disease) • Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before first dose of study drug • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon) within 7 days of first dose of study drug • Requires treatment with a strong CYP3A inhibitor/inducer • Requires treatment with proton pump inhibitors (e.g. omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids were eligible for enrolment to this study • Concurrent participation in another therapeutic clinical trial • Active CMV infection (active viremia as evidenced by positive PCR result for CMV DNA) • History of confirmed progressive multifocal leukoencephalopathy

Abbreviations: AIHA, autoimmune haemolytic anaemia; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CMV, cytomegalovirus; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; INR, international normalised ratio; ITP, idiopathic thrombocytopenic purpura; IV, intravenous; MCL, mantle cell lymphoma; PCR, polymerase chain reaction; PS, performance status; QTc, corrected QT interval; SCT, stem cell transplant; ULN, upper limit of normal.

† Provided they meet other eligibility criteria, patients who were receiving hormonal therapy alone were allowed to enrol on study.

‡ If a patient had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
§ Such as uncontrolled or untreated symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of first dose of study drug, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec (calculated using Fridericia's formula: QT/RR0.33) at screening. Patients with controlled, asymptomatic atrial fibrillation during screening were allowed to enrol on study.
¶ Patients may have used topical or inhaled corticosteroids or low-dose steroids (≤20 mg prednisone equivalent/day for ≤2 weeks) as a therapy for comorbid conditions. During study participation, patients may have also received systemic (e.g. IV or oral) corticosteroids as needed for treatment-emergent comorbid conditions.
†† Patients who were anti-HBc positive and who were surface antigen negative needed to have a negative PCR result before randomisation. Those who were hepatitis B surface antigen positive or hepatitis B PCR positive were excluded. Patients who were hepatitis C antibody positive needed to have a negative PCR result before randomisation. Those who were hepatitis C PCR positive were excluded.

B.2.3.4.3 Trial drugs

A summary of the study treatments administered is provided in Table 5.

Table 5: Study treatments, dosage, and administration

	Drug	Dosing schedule	
Arm 1	Acalabrutinib	100 mg BID PO	• Cycles repeated every 28 days • BR can be administered for a maximum of 6 cycles • After 6 cycles, patients who were tolerating treatment and not progressing then received monotherapy acalabrutinib 100 mg BID • Patients who had achieved a response (PR or greater) received maintenance rituximab 375 mg/m^2 on Day 1 of every other cycle for a maximum of 12 additional doses
	Bendamustine	90 mg/m^2 IV on Days 1 and 2	
	Rituximab	375 mg/m^2 IV on Day 1	
Arm 2	Placebo	BID PO	• Cycles repeated every 28 days • BR can be administered for a maximum of 6 cycles • After 6 cycles, patients who were tolerating treatment and not progressing then receive placebo BID • Patients who had achieved a response (PR or greater) received maintenance rituximab 375 mg/m^2 on Day 1 of every other cycle for a maximum of 12 additional doses
	Bendamustine	90 mg/m^2 IV on Days 1 and 2	
	Rituximab	375 mg/m^2 IV on Day 1	

Abbreviations: BID, twice daily; BR, bendamustine + rituximab; IV, intravenous; PO, orally; PR, partial response.

B.2.3.4.3.1 Crossover

Patients randomised to the control arm (PBR) who had disease progression assessed by the investigator and confirmed by an unblinded non-study team physician, were permitted to cross over to receive acalabrutinib monotherapy until disease progression or unacceptable toxicity.

B.2.3.4.3.2 Dose delays and modifications

Modifications to treatment dosing for study drugs in the case of toxicity are outlined in Table 6.

Table 6: Dose levels

Dose level	Acalabrutinib/placebo†	Bendamustine‡	Rituximab§
Starting dose	100 mg BID	90 mg/m^2 IV	375 mg/m^2 IV
Level-1	100 mg QD	70 mg/m^2 IV	Discontinue
If additional dose reduction is required	Discontinue	Discontinue	Discontinue

Abbreviations: AE, adverse event; BID, twice daily; BR, bendamustine + rituximab; IV, intravenous; QD, once daily.
† Acalabrutinib/placebo may have been held for a maximum of 28 consecutive days from expected dose due to toxicity. In the event of a toxicity lasting >28 days, acalabrutinib/placebo was to be discontinued, unless reviewed and approved by the medical monitor. If acalabrutinib/placebo was reduced for apparent treatment-related toxicity, the dose did not need to be re-escalated, even if there was minimal or no toxicity with the reduced dose. However, if the patient tolerated a reduced dose of acalabrutinib/placebo for ≥4 weeks then the dose may have been increased to the next higher dose level, at the discretion of the investigator.
‡ A 28-day cycle length was maintained, if possible. A bendamustine dose delay of up to 28 days was acceptable. Every attempt was made to complete 6 cycles of bendamustine and rituximab. Following dose reduction, re-escalation of bendamustine may have been considered after consultation with the medical monitor and in accordance with local regulations/prescribing information.
§ No dose reductions for rituximab were allowed. A rituximab dose delay of up to 28 days was acceptable.
Note: If bendamustine was delayed due to toxicity, rituximab was to be withheld as well, or vice versa. If BR was held or bendamustine dose reduced due to an AE thought to be related to BR, treatment with acalabrutinib/placebo was to be continued. In the event of a toxicity lasting >28 days, bendamustine and rituximab should have been discontinued, unless reviewed and approved by the medical monitor.

B.2.3.4.4 Concomitant medications

B.2.3.4.4.1 Permitted concomitant therapy

Standard supportive care medications were permitted as per institutional standards (e.g. antiemetics, antipyretics, antibiotics, transfusion of blood products). Prophylactic use of growth factors or administration in response to severe myelosuppression was permitted in accordance with American Society of Clinical Oncology (ASCO) guidelines (32). During the study, a short course (e.g. ≤2 weeks) of high-dose corticosteroids (>20 mg/day) was permitted for premedication to manage infusion-related reactions or to manage other inflammatory reactions. Corticosteroids to treat the underlying MCL were not allowed during the study.

Prophylaxis for opportunistic infections in patients who were at increased risk was recommended in the protocol, with the importance of prophylaxis for herpes zoster infection emphasised.

Patients considered at risk for TLS (e.g. presence of bulky disease at baseline, compromised renal function at baseline) were permitted administration of appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

Patients considered at risk for central nervous system (CNS) involvement of MCL (e.g. blastic variant) were permitted prophylaxis with intrathecal chemotherapy in accordance with institutional standards.

B.2.3.4.4.2 Prohibited concomitant therapy

Any anti-cancer therapies including chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy were prohibited. Warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon) were also prohibited.

Acalabrutinib and concomitant therapy

Concomitant administration of strong inhibitors/inducers of CYP3A was to be avoided when possible.

The use of calcium carbonate-containing drugs or supplements was to be avoided for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole, or any other proton pump inhibitors while taking acalabrutinib was not recommended due to a potential decrease in study drug exposure. Although the effect of H_2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H_2-receptor antagonist was required, the H_2-receptor antagonist should have been taken approximately 2 hours after an acalabrutinib dose.

B.2.3.5 Outcomes

B.2.3.5.1 Primary outcome

The primary outcome was PFS, defined as the time from the date of randomisation until disease progression (per the Lugano Classification for NHL [Appendix M], based on IRC assessment) or death from any cause, whichever occurred first.

B.2.3.5.2 Other outcomes used in the economic model and/or specified in the scope

B.2.3.5.2.1 Secondary efficacy outcomes

Key secondary efficacy outcomes included investigator-assessed PFS, overall response rate (ORR) (investigator- and IRC-assessed), OS, DOR (investigator- and IRC-assessed), and time to response (TTR) (investigator- and IRC-assessed), as defined in Table 7.

Table 7: Key secondary efficacy outcomes

Outcome	Definition
Investigator-assessed PFS	The time from the date of randomisation until disease progression assessed by the investigator per the Lugano Classification for NHL, or death from any cause, whichever occurs first.
Investigator-assessed ORR	The proportion of patients who achieve either PR or CR as best overall response according to the Lugano Classification for NHL as assessed by investigator.
IRC-assessed ORR	The proportion of patients who achieve either PR or CR as best overall response according to the Lugano Classification for NHL as assessed by IRC.
OS	The time from randomisation until the date of death from any cause.
IRC-assessed and investigator-assessed DOR	The time from the first documentation of CR or PR to disease progression per the Lugano Classification for NHL, or death from any cause, whichever occurs first.
IRC-assessed and investigator-assessed TTR	The time from randomisation to the first CR or PR per the Lugano Classification for NHL.

Abbreviations: CR, complete response; DOR, duration of response; IRC, Independent Review Committee; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TTR, time to response.

B.2.3.5.2.2 Safety

Key safety outcomes included the incidence of AEs, SAEs, and AEs leading to study drug dose modification or treatment discontinuation. Safety data were summarised for the main study period and crossover period separately, unless otherwise specified.

B.2.3.5.2.3 HRQoL

PROs were assessed using three measures:

- EQ-5D-5L index score: includes mobility, self-care, usual activities, pain/discomfort and anxiety/depression. EQ-5D-5L index and EQ-5D-VAS

scores and score change from the baseline were summarised using descriptive statistics

- Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) scale score: includes physical well-being, social/family well-being, emotional well-being, functional well-being, as well as the lymphoma subscale. Trial outcome index (TOI), Functional Assessment of Cancer Therapy – General (FACT-G), and FACT-Lym scores and score change from the baseline were summarised using descriptive statistics
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) score: global health status/QoL scale, includes five functional scales (physical, role, emotional, cognitive, and social), five standalone symptom items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), and one financial impact item. Scores and score change from baseline were summarised using descriptive statistics

B.2.3.6 Pre-planned subgroups

Subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms. Details are provided in Section B.2.7.

B.2.3.7 Baseline characteristics and demographics

Patient demographics and disease characteristics at baseline were well balanced between the two treatment arms and are summarised in Table 8.

Demographics were representative of the targeted patient population of patients with untreated MCL who are considered to be unsuitable for ASCT. The median age was 71.0 years (range: 65 to 86 years), with 59.9% of patients aged 70 years or older, and 70.7% of participants were male (Table 8).

With respect to baseline disease characteristics, the majority of patients were in either low (33.4%) or intermediate (42.3%) MIPI risk groups. Most patients had a diagnosis of classic MCL histology subtype (80.4%), with extranodal disease in 90.5%, and bulky disease (≥5 cm) in 37.6%.

Ann Arbor Stage IV MCL was reported in 83.9% and 88.0% of patients in the ABR and PBR arms, respectively. The median time from initial MCL diagnosis to randomisation was 1.68 months (range: 0–116.4 months) and 1.54 months (range: 0.1–142.4 months) for patients in the ABR and PBR arms, respectively (Table 8). Further details of baseline disease characteristics are provided in Appendix M.

Table 8: Demographics of participants in ECHO (FAS)

	ABR (N=299)	PBR (N=299)	Total (N=598)
Age, years			
Mean (SD)	71.6 (4.73)	71.6 (4.60)	71.6 (4.66)
Median	71.0	71.0	71.0
Min, max	65, 85	65, 86	65, 86
Age group, n (%)			
65–<70	123 (41.1)	117 (39.1)	240 (40.1)
≥70	176 (58.9)	182 (60.9)	358 (59.9)
65–<75	215 (71.9)	222 (74.2)	437 (73.1)
≥75	84 (28.1)	77 (25.8)	161 (26.9)
Sex, n (%)			
Male	214 (71.6)	209 (69.9)	423 (70.7)
Female	85 (28.4)	90 (30.1)	175 (29.3)
Race, n (%)			
White	233 (77.9)	235 (78.6)	468 (78.3)
Asian	44 (14.7)	49 (16.4)	93 (15.6)
American Indian or Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)
Black or African American	1 (0.3)	2 (0.7)	3 (0.5)
Multiple	5 (1.7)	0	5 (0.8)
Not reported	14 (4.7)	11 (3.7)	25 (4.2)
Ethnicity, n (%)			
Hispanic or Latino	34 (11.4)	33 (11.0)	67 (11.2)
Not Hispanic or Latino	245 (81.9)	252 (84.3)	497 (83.1)
Not reported	20 (6.7)	14 (4.7)	34 (5.7)
BMI, kg/m^2			
Mean (SD)	27.05 (4.70)	27.01 (4.73)	27.03 (4.71)
Median	26.40	26.30	26.35
Min, max	16.2, 44.8	14.9, 41.8	14.9, 44.8
ECOG performance status, n (%)			
0	156 (52.2)	140 (46.8)	296 (49.5)

	ABR (N=299)	PBR (N=299)	Total (N=598)
1	129 (43.1)	132 (44.1)	261 (43.6)
2	12 (4.0)	23 (7.7)	35 (5.9)
3	0 (0.0)	2 (0.7)	2 (0.3)
Missing	2 (0.7)	2 (0.7)	4 (0.7)
Tumour bulk,† n (%)			
<5 cm	187 (62.5)	186 (62.2)	373 (62.4)
≥5 cm and <10 cm	92 (30.8)	92 (30.8)	184 (30.8)
≥10 cm	20 (6.7)	21 (7.0)	41 (6.9)
Ann Arbor staging for lymphoma, n (%)			
I	2 (0.7)	1 (0.3)	3 (0.5)
II	15 (5.0)	11 (3.7)	26 (4.3)
III	31 (10.4)	24 (8.0)	55 (9.2)
IV	251 (83.9)	263 (88.0)	514 (86.0)
Patients with extranodal disease, n (%)			
1 site	155 (51.8)	155 (51.8)	310 (51.8)
2 or more sites	109 (36.5)	122 (40.8)	231 (38.6)
Simplified MIPI score, n (%)			
Low risk, i.e. 0–3	99 (33.1)	101 (33.8)	200 (33.4)
Intermediate risk, i.e. 4–5	128 (42.8)	125 (41.8)	253 (42.3)
High risk, i.e. 6–11	72 (24.1)	73 (24.4)	145 (24.2)
Time from diagnosis to randomisation, months			
Mean (SD)	3.91 (10.10)	4.27 (12.46)	4.09 (11.34)
Median	1.68	1.54	1.64
Min, max	0.0, 116.4	0.1, 142.4	0.0, 142.4

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; MIPI, Mantle Cell Lymphoma International Prognostic Index; PBR, placebo, bendamustine, rituximab; PS, performance status; SD, standard deviation.
† For target lesions at baseline, investigator assessment was used. Tumour bulk was defined as the largest diameter of a nodal or extranodal lesion.

B.2.3.7.1 Subsequent anti-MCL therapy

A total of [redacted] patients in the ABR arm and [redacted] patients in the PBR arm received at least one subsequent anti-MCL therapy (Table 9). Among these patients, [redacted] in the ABR arm and [redacted] in the PBR arm received a BTKi including crossover to acalabrutinib monotherapy after experiencing PD.

Table 9: Subsequent anti-MCL therapy (FAS)

	ABR (N=299)	PBR (N=299)
Patients with at least 1 subsequent anti-MCL therapy, n (%)†	[redacted]	[redacted]
Patients with at least 1 BTKi type of subsequent anti-MCL treatment, n (%)	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BTKi, Bruton's tyrosine kinase inhibitor; FAS, full analysis set; MCL, mantle cell lymphoma; PBR, placebo, bendamustine, rituximab.
† A patient was only counted once for each category.

B.2.3.8 Expert elicitation/opinion

An advisory board was conducted in July 2024 with three healthcare professionals (HCPs) and three health economists based in the UK, Canada, and Sweden (33). The objective of the advisory board was to review and appraise the clinical evidence and health economic models for ABR in previously untreated MCL, including discussion of:

- The treatment pathway for patients with previously untreated MCL
- ECHO trial results and the positioning of ABR in the treatment pathway
- Model structure, health states of interest, key modelling assumptions, and missing model inputs

A further four one-to-one interviews were conducted with clinical experts (consultant haematologists) based in England to support clinical assumptions and statements used for this submission (3).

Insights from the advisory board and clinician interviews are provided throughout the dossier. The reports, which are qualitative in nature, are provided as confidential 'Data on File' references. Further details are provided in Appendix N.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Populations analysed

Details of the population analysis sets defined in ECHO along with their use in the study are presented in Table 10.

Table 10: Population analysis sets

Analysis set	Definition	Purpose
FAS	All patients randomised at least 24 months prior to the DCO of interim analysis. Includes patients who were randomised but did not subsequently receive treatment.	Used for interim and final analysis, and to summarise demographics, baseline characteristics, and disease characteristics.
SAS	All randomised patients who received at least one dose of study drug.	Used for safety analyses, summarised for the main study period and crossover period separately.
PPAS	Subset of the FAS, excluding patients: • With <80% relative dose intensity for at least one of the study drugs • Who violated protocol inclusion or exclusion criteria that may affect interpretation of efficacy • Who received the incorrect treatment for ≥7 days	Used for sensitivity analysis to assess for deviation bias.

Abbreviations: DCO, data cut-off; FAS, full analysis set; PPAS, per protocol analysis population; SAS, safety analysis set.

B.2.4.2 Hypothesis objective

The hypothesis of the study was that the addition of acalabrutinib to BR will result in durable remission, leading to a significant improvement in PFS.

B.2.4.3 Statistical analysis

B.2.4.3.1 PFS

A stratified log-rank test was used for the primary comparison of PFS. Additionally, a stratified Cox regression model was used to provide the estimated PFS HR and two-sided 95% confidence intervals (CIs) for ABR relative to PBR. The same analysis methods were used for the primary endpoint of IRC-assessed PFS, and investigator-assessed PFS. If the primary efficacy endpoint achieved statistical significance, the secondary efficacy endpoints were to be tested in a fixed sequential hierarchical manner for interim and final analyses.

B.2.4.3.2 OS

A stratified log-rank test was used for the comparison of OS. Additionally, a stratified Cox regression model was used to provide the estimated OS HR and two-sided 95% CI for ABR relative to PBR. Kaplan–Meier (KM) estimates and 95% CIs were calculated for event time quartiles and event-free rates at selected times.

B.2.4.3.3 ORR

The same analysis methods were used for investigator-assessed ORR and IRC-assessed ORR. ORR and the corresponding 95% two-sided CI were calculated using normal approximation to the binomial distribution. Wilson's score method with continuity correction was used to calculate a 95% CI for the difference in ORR between treatment arms (34). ORR was compared between treatment arms using the Cochran–Mantel–Haenszel test, adjusted for randomisation stratification factors.

B.2.4.4 Sample size and power calculation

In total, 635 patients were randomised; however, 37 patients (all from China) were excluded due to having less than 2 years follow-up at DCO. As a result, the full analysis set (FAS) population included 598 patients.

The study was sized to achieve approximately 90% power at final analysis to detect a HR of 0.67 in IRC-assessed PFS, which, under the model assumptions, translated into a 49% improvement in median PFS from 52.9 months in the PBR arm to 79 months in the ABR arm with a two-sided test at alpha level of 0.05. Lan-DeMets alpha-spending function (35) based on the O'Brien-Fleming boundary (36) was used to control overall type I error. The accrual period was assumed to be 43 months with 6, 20, 36, 49, 63, 81, 95, and 100% accrued by 5, 10, 15, 20, 25, 30, 35, and 43 months, respectively, and it was assumed that about 14% of the patients were likely to drop out by 30 months from the day the first patient was randomised.

The targeted number of IRC-assessed PFS events for the primary analysis was 227 events (85% information fraction, approximately 42% data maturity) for the interim analysis and 268 events (approximately 49% data maturity) for the final analysis. The interim analysis and final analysis for the primary endpoint of IRC-assessed PFS were projected to occur approximately 80 months and 101 months, respectively, after the first patient was randomised.

With consideration of potential COVID-19 death impact on the primary IRC-assessed PFS analysis, the DCO date was determined to accrue approximately 10% more IRC-assessed PFS events than protocol pre-specified 227 IRC-assessed PFS events for interim analysis. Based on the DCO of 15th February 2024, the actual number of PFS events was 247.

B.2.4.5 Data management and patient withdrawals

In general, other than for partial dates, missing data were not imputed and were treated as missing. Imputation of partial dates followed conservative rules pre-specified in the SAP Section 3.2.13, for consistency.

B.2.4.5.1 PFS

PFS was defined as the time from the date of randomisation until PD or death from any cause, whichever occurred first. Patients who exited the study or were lost to follow-up, started subsequent anti-MCL therapy, missed two or more consecutive scheduled response assessments, or were on study at the DCO date without prior documentation of PD or death were censored according to the censoring rules outlined in Table 11. These rules were applied to all patients regardless of whether the patients discontinued the treatment or not.

Table 11: PFS censoring rules

Situation	Date of event or censoring	Outcome
Death before first response assessment	Date of death	Event
PD or death	Earliest date of PD or death	Event
No PD or death at the time of data cut-off	Date of last response assessment before data cutoff	Censored
No PD or death before lost to follow-up or crossover or study exit	Date of last response assessment before lost to follow-up or crossover or study exit	Censored
No response assessment post-randomisation	Date of randomisation. Regardless of whether a subject had baseline assessment, the patients were censored at the randomisation if the post-baseline assessments were missing prior to data cut-off	Censored
Missing ≥2 consecutive response assessments	Date of last response assessment prior to the two or more consecutively missed response assessments. Regardless of whether a subject had a PD or death after two or more consecutive missing response assessments, the subject was censored at the date of last response assessment prior to or before the two or more consecutive missing assessments. A visit with assessment “unknown” was not considered a missing visit.	Censored
Start of subsequent anti-MCL therapy	Date of the last response assessment before start of subsequent anti-MCL therapy. Regardless of whether a subject had a PD or death after starting of subsequent anti-MCL therapy, the subject was censored at the date of last response assessment before start of subsequent anti-MCL therapy.	Censored

Abbreviations: MCL, mantle cell lymphoma; PD, progressed disease; PFS, progression-free survival.

B.2.4.5.2 OS

OS was defined as the time from date of randomisation to date of death due to any cause regardless of whether the subject withdrew from randomised therapy or received another anti-MCL therapy. Any subject not known to have died at the time of analysis was censored based on the last recorded date on which the subject was known to be alive. Any subject recorded as alive or to have died after the data cut-off date was censored at the date of data cut-off, as described in Table 12.

Table 12: OS censoring rules

Situation	Date of event or censoring	Outcome
Death	Date of death	Event
Lost to follow-up immediately after randomisation	Randomisation date	Censored
Not known to have died at or prior to data cut-off date	Date last known alive before data cut-off date	Censored
Not known to have died at or prior to lost to follow-up or study exit	Date last known alive before lost to follow-up or study exit	Censored

Abbreviations: OS, overall survival.

B.2.4.5.3 DOR and TTR

The same censoring rules for PFS (Table 11) were applied to DOR. For TTR, patients who did not have CR or PR prior to the DCO were censored as described in Table 13.

Table 13: TTR censoring rules

Situation	Date of event or censoring	Outcome
First documented CR	Date of first documented CR	Event
First documented PR	Date of first documented PR	Event
Lost to follow-up immediately after randomisation	Randomisation date	Censored
Not known to have CR or PR at or prior to data cut-off date	Date of last response assessment before data cut-off	Censored
Not known to have CR or PR at or prior to lost to follow-up or study exit	Date of last response assessment before lost to follow-up or study exit	Censored

Abbreviations: CR, complete response; PR, partial response; TTR, time to response.

B.2.4.5.4 Patient withdrawals

Patients had the right to withdraw from the study at any time. The date a patient withdrew from study treatment or from the study (including long-term follow-up) and the reasons for discontinuation were recorded and described on the appropriate electronic case report form. In case a patient was lost to follow-up, every possible effort was made by the study site personnel to contact the patient and determine the reason for discontinuation. Patients who withdrew consent were still encouraged to complete the safety follow-up assessments before withdrawing consent. Patients who were withdrawn or removed from study treatment were not replaced.

B.2.4.6 Participant flow in the relevant RCTs

In total, 635 patients were randomised in the study globally. In the interim analysis, 37 patients were excluded due to having less than 2 years' follow-up at the DCO, yielding 598 patients in the FAS population, enrolled at 189 sites across 26 countries. These patients were randomised in a 1:1 ratio (299 patients in the ABR arm and 299 patients in the PBR arm) (intent-to-treat [ITT]/FAS).

See Appendix D for full details of participant flow.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

ECHO was a large, randomised, multinational, double-blind, placebo-controlled, well-conducted, and methodologically robust Phase 3 study. The study protocol and amendments were approved by an independent ethics committee, and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

An Independent Data Monitoring Committee was established to monitor data on an ongoing basis to ensure the continuing safety of the study patients. Randomisation to study drugs was achieved via a central IXRS and the intervention and placebo were identical.

A summary of quality assessment results is provided in Table 14.

Table 14: Quality assessment results for ECHO

ECHO	yes/no/not clear/N/A	Justification
Was randomisation carried out appropriately?	Yes	Patients were randomised in a 1:1 ratio to receive either ABR or PBR. Randomisation was achieved via a central IXRS.
Was the concealment of treatment allocation adequate?	Yes	Treatment allocation was randomised using IXRS. Acalabrutinib and placebo were administered through the same route and schedule.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline demographics and disease characteristics were well balanced between the treatment arms.
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	The trial was conducted in a double-blind manner. The sponsor, investigator, site staff, and subject were blinded to the treatment to which the subject was randomised.
Were there any unexpected imbalances in drop-outs between groups?	No	The overall number of discontinuations was relatively similar in the two treatment arms, with the number and reasons for discontinuations from treatment not unexpected. Four patients (1.3%) in the ABR arm, and three (1.0%) in the PBR arm, were lost to follow-up during the study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The primary and key secondary outcomes listed in the protocol are consistent with those reported in the CSR.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses in the overall population were conducted on the FAS (i.e. ITT), comprising all patients randomised to treatment. Available data for patients lost to follow-up were reported.

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CRD, Centre for Reviews and Dissemination; CSR, clinical study report; FAS, full analysis set; ITT, intention-to-treat; IXRS, interactive voice/web response system; N/A, not applicable; PBR, placebo, bendamustine, rituximab.
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.6 Clinical effectiveness results of ECHO

ECHO is ongoing, with a final analysis of OS planned when approximately 268 IRC-assessed PFS events have been observed.

B.2.6.1 Primary efficacy outcome: PFS assessed by IRC

ECHO met its primary endpoint by demonstrating a statistically significant and clinically meaningful improvement in IRC-assessed PFS among patients treated with ABR versus patients treated with PBR in previously untreated MCL. With a median follow-up of 46.1 months in the ABR arm and 44.4 in the PBR arm, the median

estimated PFS was 66.4 months (95% CI: 55.1, NE) and 49.6 months (95% CI: 36.0, 64.1), respectively (Table 15). Based on the stratified analysis, ABR demonstrated a statistically significant improvement in IRC-assessed PFS compared with PBR, with a 27% reduction in risk of PD or death (HR: 0.73; 95% CI: 0.57, 0.94; p=0.0160).

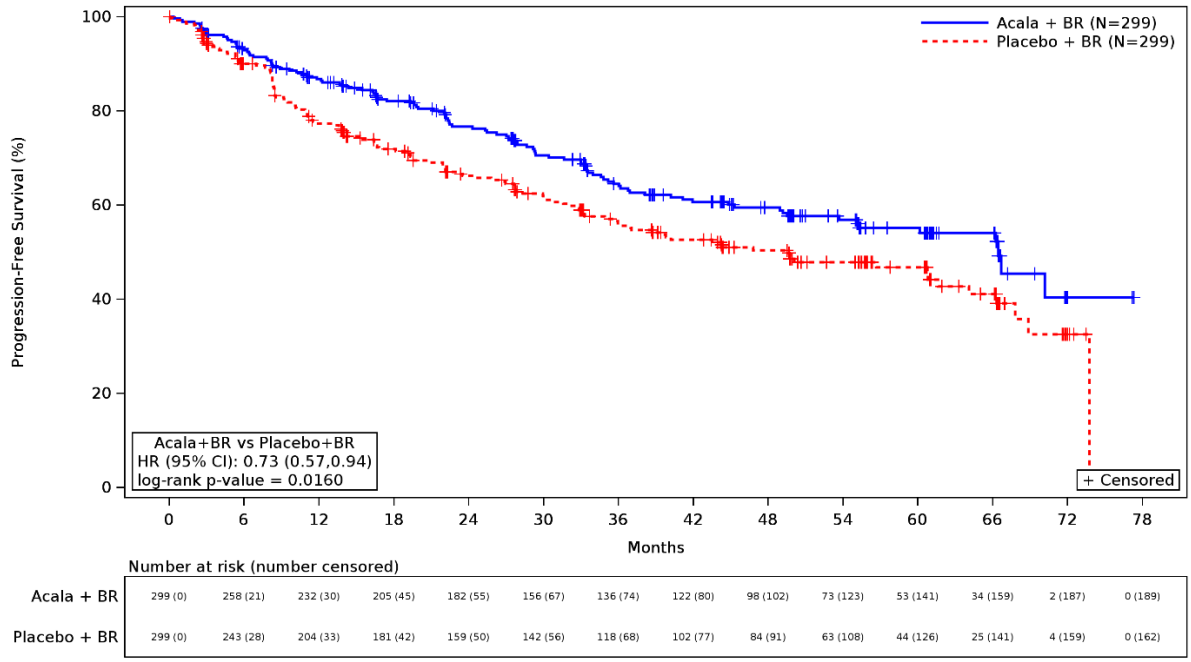
The KM plot is shown in Figure 4.

Table 15: Analysis of PFS by IRC assessment (FAS)

	ABR (N=299)	**PBR (N=299)**
Patient status		
Events, n (%)	110 (36.8)	137 (45.8)
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
PFS (months)		
Median (95% CI)	66.4 (55.1, NE)	49.6 (36.0, 64.1)
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	0.73 (0.57, 0.94)	-
p-value§	0.0160	-
Unstratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	[redacted]	-
p-value§	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.
† Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0–3], Intermediate Risk [4–5], High Risk [6–11]) as collected via IXRS.
‡ Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively.
§ Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375. Time to event (or time to censor for censored patients) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
"+" indicates a value from a censored patient.

Figure 4: KM plot for PFS by IRC assessment (FAS)



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; PFS, progression-free survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

[redacted]. With a median follow-up of 46.1 months in the ABR arm and 44.4 months in the PBR arm, the median estimated PFS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]), respectively. The overall concordance rates between the IRC-assessed PFS and investigator-assessed PFS for ABR and PBR were [redacted] and [redacted], respectively (see Appendix M for further details of investigator-assessed PFS).

B.2.6.1.1 Sensitivity analyses of PFS

The COVID-19-censored sensitivity analysis is presented in B.2.6.1.1.1. All other pre-specified sensitivity analyses were consistent with the results of the primary PFS analysis; details are provided in Appendix M.

B.2.6.1.1.1 Censoring COVID-19 deaths

Confirmed or suspected COVID-19 deaths were included as PFS events in both the IRC-assessed and investigator-assessed analysis. These included patients who did

not experience disease progression prior to death. Due to the timing of the trial, the ECHO study included a 'pre-vaccination cohort', [redacted] (see Section B.2.7.1.1). In order to understand the potential impact of COVID-19 deaths on the results, a sensitivity analysis was conducted, in which patients with death related to COVID-19 and without PD prior to death were excluded. The analysis found that after censoring for COVID-19 deaths, median PFS improved in both arms, and PFS was not reached with ABR versus 61.6 months with PBR (HR: 0.64; 95% CI: 0.48, 0.84; p=0.0017, compared with the HR of 0.73 [95% CI: 0.57, 0.94; p=0.0160] in the FAS population) (Table 16). The KM plot is shown in Figure 5.

These results highlight deaths due to COVID-19 had a relevant impact on the study outcome. Nevertheless, the clinical benefit of ABR over PBR for patients with previously untreated MCL was not compromised, and in fact improved when COVID-19 deaths were censored, confirming the robustness of the primary analysis.

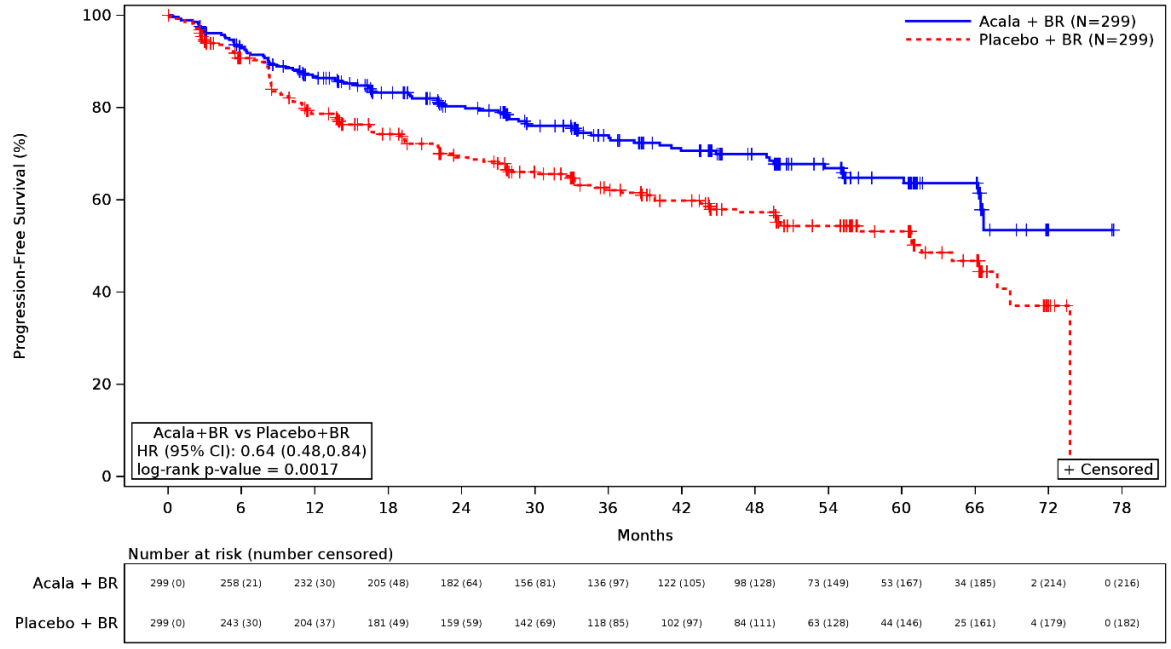
Table 16: Analysis of PFS by IRC assessment (FAS: censoring COVID-19 death)

	ABR (N=299)	PBR (N=299)
Patient status		
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Data cut-off	[redacted]	[redacted]
Missing two or more consecutive response assessments	[redacted]	[redacted]
Start of subsequent anti-MCL therapy	[redacted]	[redacted]
Lost to follow-up or study exit or crossover	[redacted]	[redacted]
No event before COVID-19 related death	[redacted]	[redacted]
No response assessment post-randomisation	[redacted]	[redacted]
Progression-free survival (months)		
Median (95% CI)	NE (66.4, NE)	61.6 (49.6, 68.9)
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	0.64 (0.48, 0.84)	-

	ABR (N=299)	PBR (N=299)
p-value§	0.0017	-
Unstratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	[redacted]	-
p-value§	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.
† Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0–3], Intermediate Risk [4–5], High Risk [6–11]) as collected via IXRS.
‡ Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively.
§ Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375. Time to event (or time to censor for censored patients) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
"+" indicates a value from a censored patient.

Figure 5: KM plot for PFS by IRC assessment (FAS: censoring confirmed/suspected COVID-19 death)



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; PFS, progression-free survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

B.2.6.2 Secondary efficacy outcome: OS

There was a positive OS trend in favour of ABR for the FAS. With an OS maturity rate of 34% (203/598 target events), the HR was 0.86 (95% CI: 0.65, 1.13; p=0.2743). The trend in OS, presented in Table 17, was observed despite 17% (n=51/299) crossover to acalabrutinib from the PBR arm following disease progression.

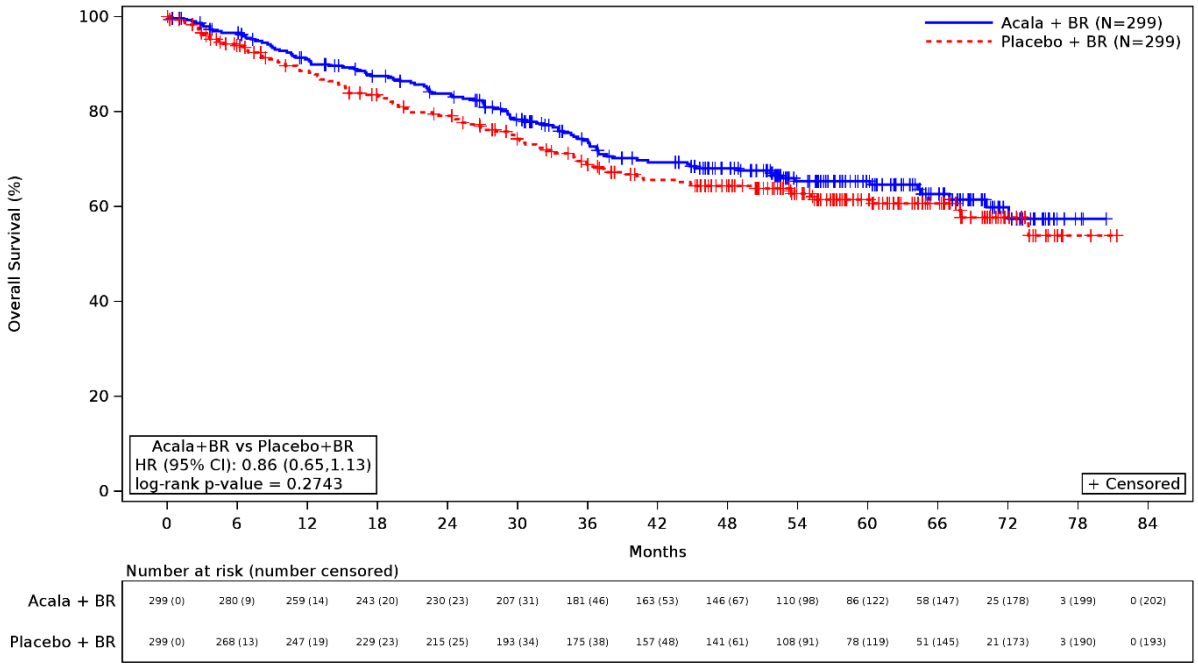
With a median follow-up of 46.1 months in the ABR arm and 44.4 months in the PBR arm, 97 (32.4%) patients in the ABR arm and 106 (35.5%) patients in the PBR arm had died. Median OS was not reached in either arm. The KM plot is provided in Figure 6.

Table 17: Analysis of OS (FAS)

	ABR (N=299)	**PBR (N=299)**
Patient status		
Total deaths, n (%)†	97 (32.4)	106 (35.5)
Censored, n (%)	202 (67.6)	193 (64.5)
Overall survival (months)		
Median (95% CI)	NE (72.1, NE)	NE (73.8, NE)
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	0.86 (0.65, 1.13)	-
p-value¶	0.2743	-
Unstratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	[redacted]	-
p-value¶	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; FAS, full analysis set; IXRS, interactive voice/web response system; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab.
† Death from any cause.
‡ Based on stratified or unstratified Cox proportional hazards model, by randomisation stratification factors as recorded in IXRS if stratified.
§ Based on stratified or unstratified log-rank test, by randomisation stratification factors as recorded in IXRS if stratified.
¶ Estimated based on stratified or unstratified log-rank test for p-value.
Months are derived as days/30.4375. Time to event (or time to censor for censored patient) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
'+' indicates a value from a censored patient.

Figure 6: KM plot for OS (FAS)



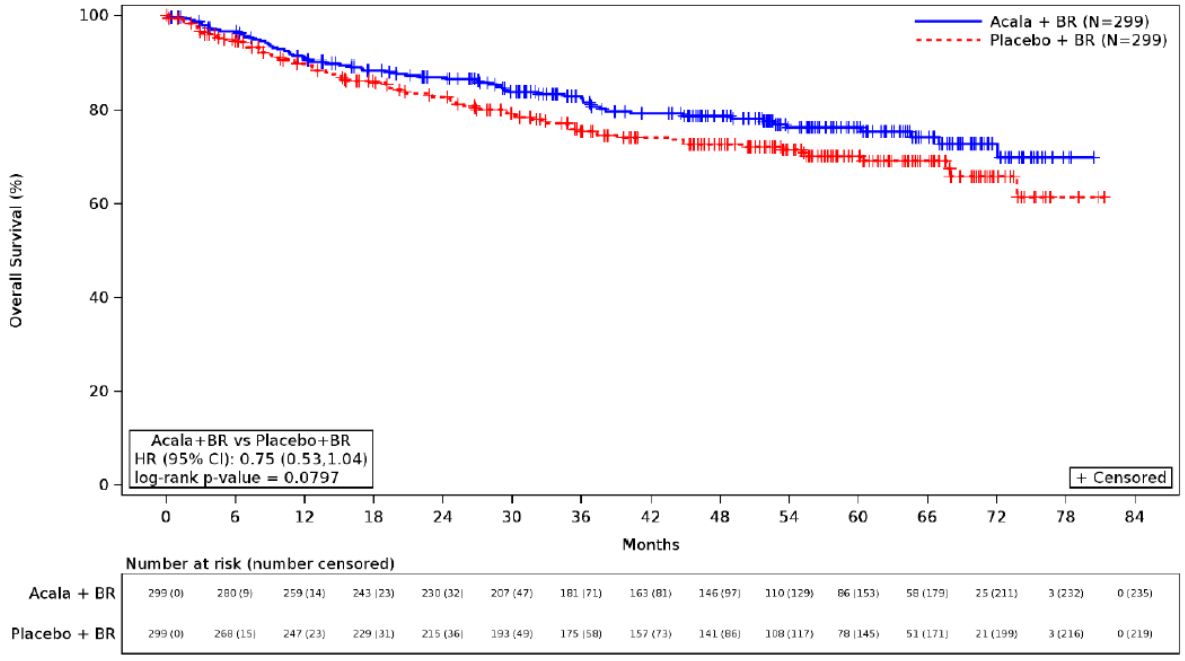
Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; KM, Kaplan–Meier; OS, overall survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

B.2.6.2.1 Sensitivity analyses of OS

B.2.6.2.1.1 Censoring COVID-19 deaths

[redacted] (see Section B.2.7.1.2). As for PFS, in order to understand the potential impact of COVID-19 deaths on OS, a sensitivity analysis was conducted, in which any patient who was known to have died of COVID-19 was censored at their COVID-19 death date. After censoring, the treatment effect of ABR on OS became more pronounced, with an HR of 0.75 (95% CI: 0.53, 1.04; p=0.0797) in favour of ABR (compared with the HR of 0.86 [95% CI: 0.65, 1.13; p=0.2743] in the FAS population) (Figure 7). COVID-19 deaths had a relevant impact on OS, but the clinical benefit of ABR over PBR for patients with previously untreated MCL was not compromised, and in fact showed a trend towards improvement when COVID-19 deaths were censored.

Figure 7: KM plot for (FAS: censoring confirmed/suspected COVID-19 death)



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; KM, Kaplan–Meier.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

B.2.6.3 Secondary efficacy outcome: ORR

The percentage of patients with an overall response (CR + PR) was similar in the ABR and PBR arms (ORR: 91.0%; 95% CI: 87.3, 93.8 and ORR: 88.0%; 95% CI; 83.9, 91.3, respectively) (Table 18). However, the CR rate was numerically higher in the ABR arm, with 13% more patients achieving a CR with ABR compared with PBR (66.6 and 53.5%, respectively).

Table 18: Best overall response by IRC assessment (FAS)

	ABR (N=299)	PBR (N=299)
Best overall response, n (%)		
CR	199 (66.6)	160 (53.5)
PR	73 (24.4)	103 (34.4)
Stable disease	[redacted]	[redacted]
PD	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
Missing†	[redacted]	[redacted]

	ABR (N=299)	PBR (N=299)
ORR (CR + PR)		
n (%)	272 (91.0)	263 (88.0)
95% CI‡	(87.3, 93.8)	(83.9, 91.3)
ORR difference (versus PBR), %	3.0	-
95% CI§	[redacted]	-
p-value¶	0.2196	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; CR, complete response; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; ORR, overall response rate; PBR, placebo, bendamustine, rituximab; PD, progressed disease; PR, partial response.
† 'Missing' category includes patients without any postbaseline response assessment.
‡ 95% CIs were based on the MID-p method.
§ 95% CI for the ORR difference was based on Miettinen-Nurminen method.
¶ Based on Cochran-Mantel-Haenzel test stratified as recorded in IXRS.

[redacted] (ORR: [redacted]; 95% CI: [redacted] and ORR: [redacted]; 95% CI: [redacted], respectively). [redacted], with [redacted] achieving a CR with ABR compared with PBR ([redacted] and [redacted], respectively). Further details are provided in Appendix M.

B.2.6.4 Secondary efficacy outcome: DOR

DOR by IRC assessment according to the Lugano classification demonstrated more durable responses among patients treated with ABR compared with PBR (Table 19). The estimated median IRC-assessed DOR for the ABR arm was 63.5 months (95% CI: 52.5, NE) and that for the PBR arm was 53.8 months (95% CI: 37.6, 66.1).

Table 19: DOR by IRC assessment (FAS: only for all responding patients [CR + PR])

	ABR (N=272)	PBR (N=263)
Duration of response (months)		
Median (95% CI)	63.5 (52.5, NE)	53.8 (37.6, 66.1)
Min, max	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; CR, complete response; DOR, duration of response; FAS, full analysis set; IRC, independent review committee; NE, not estimable; PBR, placebo, bendamustine, rituximab; PR, partial response.
Months are derived as days / 30.4375. Duration of response was calculated as date of disease progression or death (censoring date for censored patients) – (date of achieving the first CR or PR) + 1.
'+' indicates a value from a censored patient.

[redacted] The estimated median investigator-assessed DOR for the ABR arm was [redacted] (95% CI: [redacted]) and for the PBR arm was [redacted] (95% CI: [redacted]). Further details are provided in Appendix M.

B.2.6.5 Secondary efficacy outcome: TTR

Based on IRC assessment, median TTR of CR + PR was [redacted] (Table 20). Median time to CR was [redacted].

Table 20: TTR by IRC assessment (FAS: only for all responding patients [CR + PR])

	ABR (N=272)	PBR (N=263)
Time to initial CR (months)		
n	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Time to initial response of PR or better (months)		
n	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; CR, complete response; FAS, full analysis set; IRC, independent review committee; NE, not estimable; PBR, placebo, bendamustine, rituximab; PR, partial response; TTR, time to response.
Months are derived as days/30.4375. Time to initial response (CR or PR) was calculated as: (date of first documented initial response CR or PR) – (date of randomisation) + 1.

[redacted] Based on investigator-assessed response, median TTR of CR + PR was [redacted]. Median time to CR was [redacted]. Further details are provided in Appendix M.

B.2.6.6 PROs/QoL

The PRO data (FACT-Lym, EQ-5D-5L, and EORTC QLQ-C30) demonstrate that in a double-blinded manner, [redacted].

Based on previous approaches in the literature, a threshold of 5 points decrease (37) and 7 points increase (38) in mean FACT-Lym total score was deemed to be clinically meaningful. A review of the results at each timepoint found [redacted]. In the ABR arm, scores showed [redacted].

[redacted].

Focusing on the lymphoma-specific subscale (LYMS), the ABR arm showed [redacted] (38).

Results for EQ-5D-5L and EORTC QLQ-C30 were [redacted].

Mean absolute EQ-5D-5L VAS scores at baseline were [redacted]. Post-baseline, there was [redacted].

Baseline scores for the EQ-5D-5L domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) were [redacted]. Post-baseline, [redacted].

EQ-5D-5L data collected in ECHO were mapped to the EQ-5D-3L scale as outlined in Section B.3.5.1.1.

[redacted]

B.2.6.7 Efficacy conclusions

ECHO met its primary endpoint by demonstrating a statistically significant reduction in the risk of PD or death by 27% for ABR compared with PBR (PFS HR: 0.73; 95% CI: 0.57, 0.94; p=0.0160). At the DCO for the primary PFS analysis (15th

February 2024) the median estimated PFS in the ABR arm was 66.4 months (95% CI: 55.1, NE) compared with 49.6 months in the PBR arm (95% CI: 36.0, 64.1), corresponding to an approximate 17-month increase in median PFS.

With an OS maturity rate of 34% (203/598 target events), there was a positive OS trend (HR: 0.86; 95% CI: 0.65, 1.13; p=0.2743 [p-value boundary: 0.0001]) in favour of ABR treatment, which was sustained over time,

[redacted]

High response rates (≥88.0%) were observed in both treatment arms, with a numerically higher CR rate in the ABR arm, though this was not statistically significant. More durable responses were observed in those treated with ABR versus PBR, with a median duration of response of 63.5 months (95% CI: 52.5, NE) versus 53.8 months (95% CI: 37.5, 66.1), respectively.

ECHO demonstrated that acalabrutinib significantly improves PFS when added to BR, with a trend towards improved OS [redacted] in patients with untreated MCL. In the context of a disease that remains incurable, this substantial increase in median PFS represents a significant and clinically meaningful improvement over currently available SoC for the treatment of patients with previously untreated MCL, considered unsuitable for ASCT.

B.2.7 Subgroup analysis

B.2.7.1 ECHO

Pre-planned subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms. These included:

- Sex
- Age category
- Race
- Geographic region
- Baseline ECOG PS

- Tumour bulk
- Ann Arbor staging for lymphoma
- Histologically documented MCL
- MCL type (classic type versus blastoid variant and pleomorphic variant versus other)
- Ki-67
- Bone marrow involvement
- Extranodal disease
- Gastrointestinal disease
- Simplified MIPI score
- Lactate dehydrogenase (LDH) > upper limit of normal (ULN)
- COVID-19 vaccine status

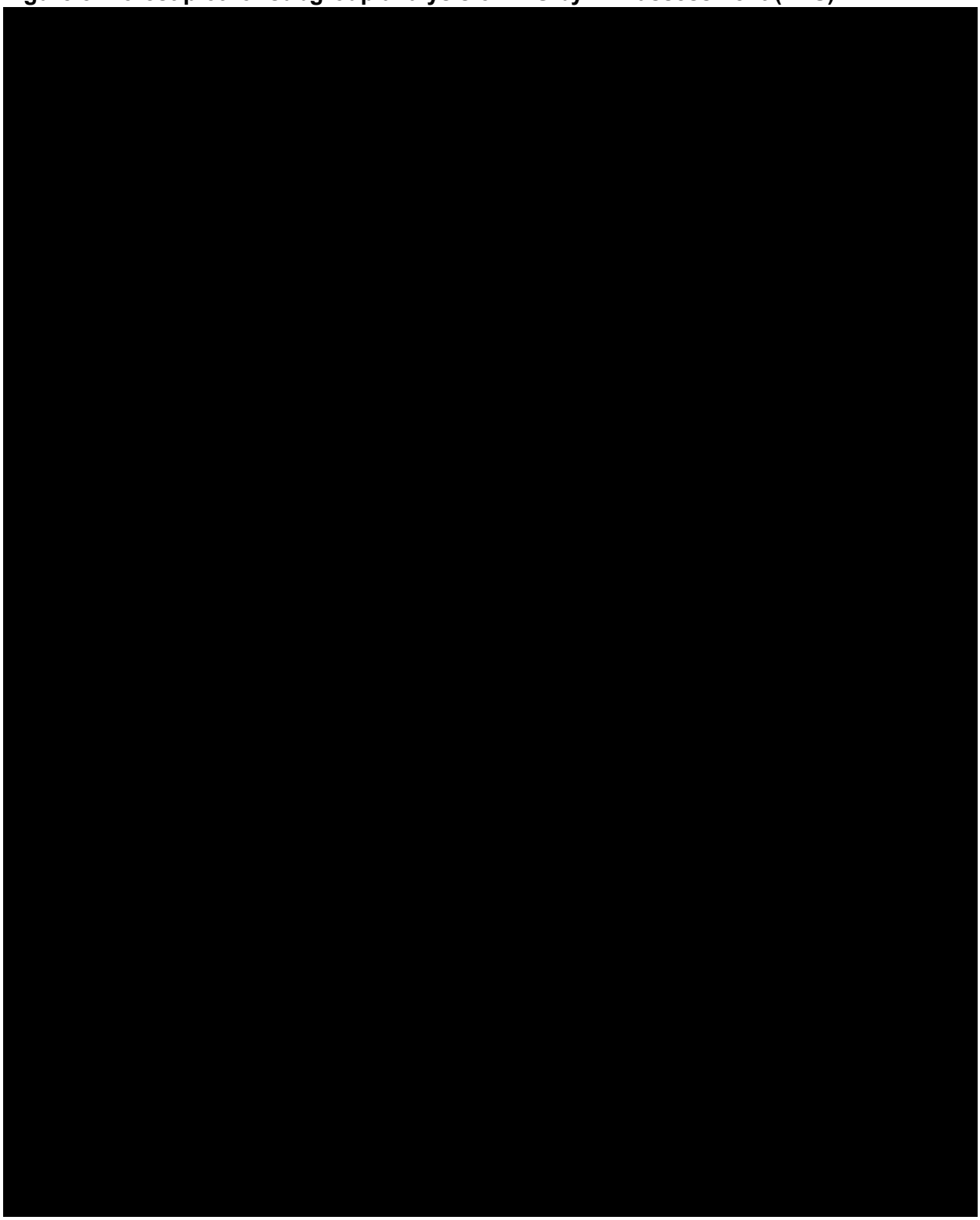
B.2.7.1.1 Subgroups for PFS

The results of the subgroup analyses of IRC-assessed PFS (FAS) [redacted] and demonstrated [redacted]. These data should be interpreted with caution due to the small number of patients in these subgroups, [redacted]. In addition, ECHO was not powered to detect treatment differences in these subgroups.

Given the relevant impact of the COVID-19 pandemic on the study, COVID-19 vaccination status was collected when feasible. Due to the timing of the study, ECHO included a 'pre-vaccination cohort', with patients included in this interim analysis randomised and receiving treatment from 8th May 2017 to 27th March 2023. [redacted]

Full results of the subgroup analysis are provided in Appendix E.

Figure 8: Forest plot for subgroup analysis of PFS by IRC assessment (FAS)



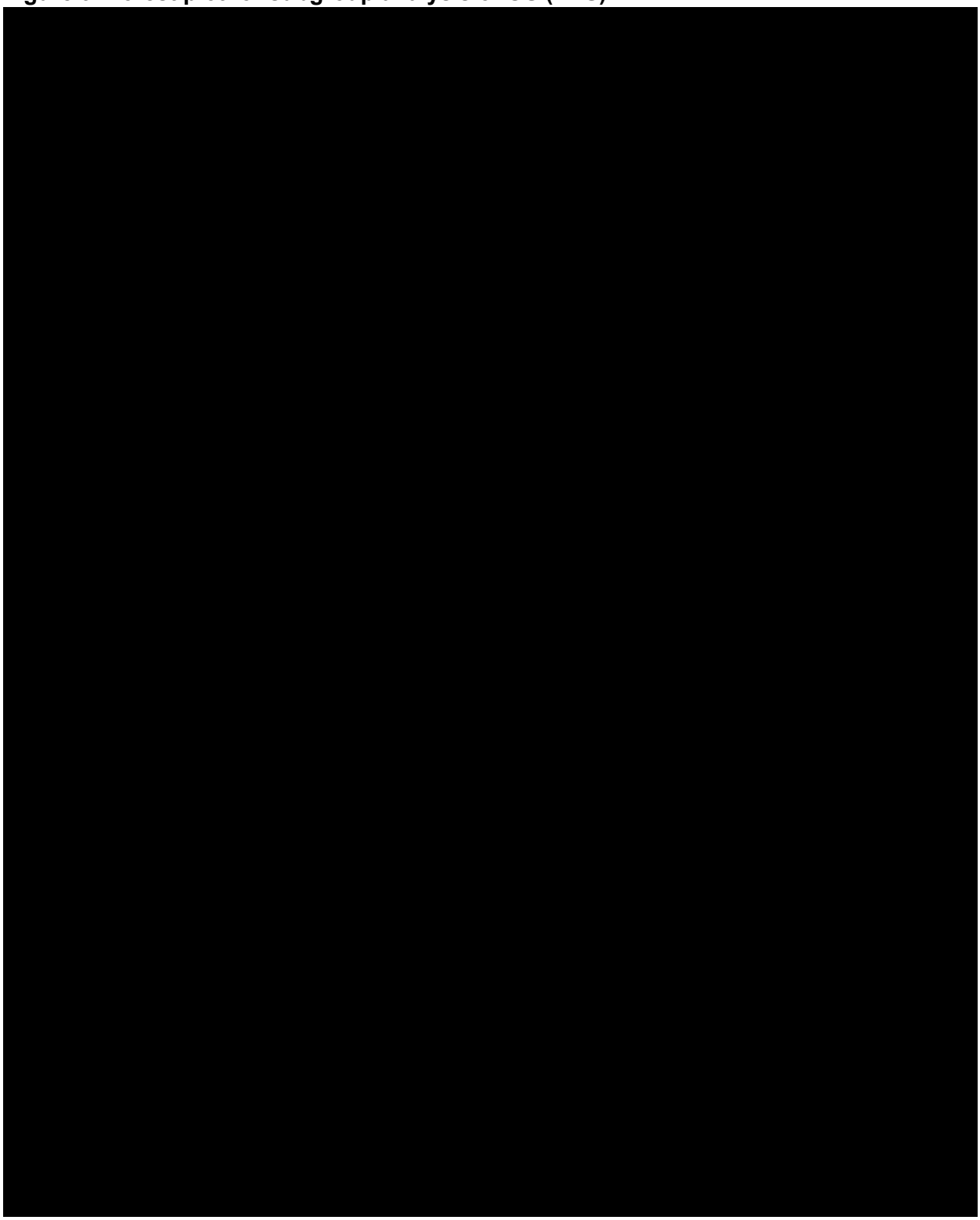
Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimated; PFS, progression-free survival.
[a] Per IXRS record.
Hazard ratios (95% CI) are based on a unstratified Cox proportional hazards model.

B.2.7.1.2 Subgroups for OS

Subgroup analyses of OS (FAS including the crossover period) demonstrated [redacted] (Figure 9).

Among patients who received the COVID-19 vaccine, [redacted]

Figure 9: Forest plot for subgroup analysis of OS (FAS)



Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IXRS, interactive voice/web response system; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimated; OS, overall survival.
[a] Per IXRS record.
Hazard ratios (95% CI) are based on a unstratified Cox proportional hazards model.

B.2.8 Meta-analysis

ECHO is the only Phase 3 RCT reporting on the efficacy and safety of ABR in patients with untreated MCL, therefore a meta-analysis was not feasible.

B.2.9 Indirect and mixed treatment comparisons

As discussed in Section B.2.1 and Appendix D, a targeted literature review (TLR) and SLR were conducted to identify all relevant clinical evidence on the efficacy and safety of ABR and potential comparators for the treatment of people with previously untreated MCL who are unsuitable for ASCT. No head-to-head RCTs between ABR and R-CHOP were identified, so an indirect treatment comparison (ITC) was performed to assess the relative efficacy of ABR, BR, and R-CHOP.

B.2.9.1 Methodology

Full details of the methodology for the ITC are provided in Appendix D.

B.2.9.1.1 Treatments of interest

The treatments of interest for the ITC were ABR, BR, and R-CHOP. Studies reporting experimental combination regimens were excluded from the ITC. To create a connected network, studies with or without rituximab maintenance therapy were considered in the ITC.

B.2.9.1.2 Outcomes of interest

The outcomes of interest for the ITC were PFS and OS. These outcomes correspond to the key endpoints in the decision problem and the primary (PFS) and key secondary (OS) endpoints of the ECHO trial.

B.2.9.1.3 Feasibility assessment

Prior to analysis, the feasibility of performing a valid ITC using the trial data identified in the SLR was assessed. The aim of the feasibility assessment was to determine whether the key assumption for the ITC, i.e. exchangeability, had been met across the included studies. To meet this assumption, the treatment effects observed in the studies informing the ITC should be the same if individuals in each trial were substituted to another trial. Full details of the feasibility assessment are provided in Appendix D.

B.2.9.1.4 Overview of ITC methodology

The ITC was performed in a Bayesian framework following the methods outlined in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 (39). The ITCs were performed on a log-hazard ratio scale, and the proportional hazards (PH) assumption was assessed in each study included. Where feasible, both fixed and random effects models were considered, using vague priors for treatment effects. For the random effects model, informative priors for between-study heterogeneity were considered due to the small network. Model fit was judged based on deviance information criterion (DIC). Further details of the methodology for the ITC are provided in Appendix D.

B.2.9.1.5 Sensitivity analysis methodology

A separate sensitivity analysis was performed using the results from the COVID-19-censored data analysis of ECHO, where patients who experienced a COVID-19 death were censored for both PFS and OS outcomes (see B.2.6.1.1.1).

B.2.9.1.6 Trials included in the ITC

From the TLR, eight unique studies, plus a further three studies from a search of conference proceedings, were identified for inclusion in the feasibility assessment alongside ECHO. A summary of these studies is provided in Appendix D. Three of these trials were included in the ITC. The remaining trials were excluded as they did not contribute to the comparisons of interest (i.e. ABR versus BR versus R-CHOP) and/or were studies that could not be connected to the network (see Appendix D). An overview of the studies included in the ITC is provided in Table 21.

Table 21: Summary of the trials used to carry out the ITC

Study	ABR	BR	R-CHOP
ECHO (11)	✓	✓	
BRIGHT (Flinn 2019) (26)†		✓	✓
StiL NHL1 (Rummel 2013) (40)		✓	✓

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ITC, indirect treatment comparison; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone.
† Assessed BR versus R-CHOP/R-CVP.

B.2.9.1.7 Feasibility assessment results

The feasibility assessment revealed heterogeneity in design, population inclusion criteria, and the treatments administered across studies. These included:

- Disease status (MCL versus a mixture of MCL and indolent lymphoma)
- Use of rituximab maintenance after induction therapy
- Choice of control arm therapy

The ECHO study enrolled patients with MCL (11), while BRIGHT and StiL NHL1 recruited a mixed cohort of patients with MCL and indolent lymphoma (26, 40). Subgroup results from the BRIGHT and StiL NHL1 studies indicated a potentially improved treatment effect in patients with MCL compared with those with indolent lymphomas (26, 40). To ensure comparability with the MCL cohort of ECHO, the ITC used the MCL subgroup results of BRIGHT and StiL NHL1. Although this approach reduced heterogeneity in the ITC, the limited reporting of baseline data for subgroups in BRIGHT and StiL NHL1 prevented a detailed assessment of between-study heterogeneity for the ITC.

While the included studies shared a common treatment arm in the form of BR, there was notable variation in the use of rituximab maintenance after induction therapy across studies, ranging from 77.4 to 82.5% in ECHO (11), 14% in BRIGHT (MCL subgroup) (26), and 0% in StiL NHL1 (40). The findings of a subgroup analysis by rituximab maintenance therapy in the overall population (MCL and indolent lymphomas) of BRIGHT, suggested that the effect of BR versus R-CHOP/rituximab, cyclophosphamide, vincristine, prednisolone (R-CVP) was not modified by the addition of rituximab maintenance therapy in both arms. To create a connected network, the three ‘BR’ arms of ECHO, BRIGHT, and StiL NHL1 were combined into a single node in the network. The relative effects of treatment versus ‘BR’ were assumed to be unaltered by rituximab maintenance use across studies.

Additionally, the BRIGHT and StiL NHL1 studies had included different control arms, with BRIGHT evaluating the efficacy and safety of BR versus treatment of physician choice of R-CHOP or R-CVP (26), and StiL NHL1 assessing BR versus R-CHOP (40). The impact of treatment choice on outcomes was assessed in a subgroup analysis of the overall population of BRIGHT, with results suggesting no meaningful

difference in the efficacy of BR versus R-CHOP and BR versus R-CVP. The study reported results for the head-to-head comparison of BR versus R-CHOP/R-CVP in patients with MCL. In the absence of data versus R-CHOP alone, the MCL subgroup results for BR versus R-CHOP/R-CVP were assumed to represent the outcomes of BR versus R-CHOP in the ITC.

In summary, the following assumptions were made:

- The label of 'placebo' was removed from the ECHO study and the 'BR' arms of ECHO, BRIGHT, and StiL NHL1 were considered as a single node in the network
- The studies in the network were not differentiated based on rituximab maintenance use, on the assumption that the treatment effect for BR versus R-CHOP is not modified by the use of rituximab maintenance, if available to both arms. This assumption was supported by subgroup results of the BRIGHT study showing no meaningful difference in efficacy between BR plus rituximab maintenance versus R-CHOP/R-CVP plus rituximab maintenance and BR versus R-CHOP/R-CVP, without rituximab maintenance
- For the BRIGHT study, the treatment effect for BR versus R-CHOP was based on the MCL subgroup results for BR versus R-CHOP/R-CVP. The treatment effect of BR versus R-CHOP was assumed to be consistent with BR versus R-CVP in patients with MCL, based on the subgroup results by treatment in the ITT group (MCL and indolent lymphoma) of the BRIGHT study

These assumptions enabled the inclusion of both StiL NHL1 and BRIGHT in the network, increasing the total sample of patients for BR versus R-CHOP from 74 (BRIGHT only) or 94 (StiL NHL1 only) to 168 (BRIGHT and StiL NHL1).

Further detail on the feasibility assessment of trials included in the ITC, including study design, baseline characteristics, and outcomes, is detailed in Appendix D.

B.2.9.2 Results

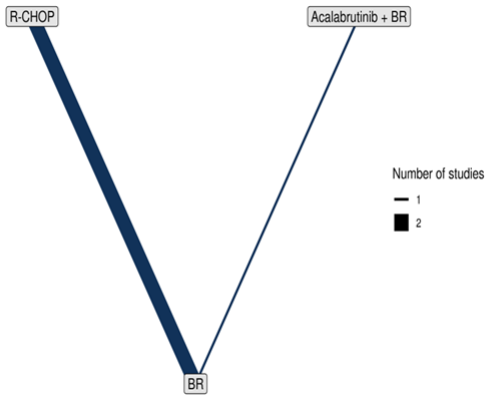
The treatment effect estimates included in the ITC are provided in Appendix D. The ITC results for PFS and OS are provided in the following sections as HRs with 95% credible intervals (CrIs). Fixed effects results are presented, as this was the

preferred model according to DIC in all cases (though the difference was less than three points so not considered meaningful); random effects results for PFS are provided in Appendix D. Overall, point estimates were similar with the random effects model, although CrIs were wider. This is to be expected, as the random effects ITC incorporates between-study differences in its efficacy estimates.

B.2.9.2.1 PFS results

The network diagram for PFS is provided in Figure 10. All three studies were included in the network for PFS, but there were no loops in the network to assess for consistency.

Figure 10: Network plot for PFS



Abbreviations: BR, bendamustine + rituximab; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

The ITC was conducted using the primary IRC-assessed PFS for ECHO, and the investigator-assessed PFS for BRIGHT and StiL NHL1. [redacted] (see Section B.2.6.1). The primary analysis was based on the ECHO FAS population, and an additional analysis was conducted based on estimates from the COVID-19-censored analysis (see Section B.2.6.1.1.1).

Table 22 presents the fixed effects ITC results for the primary PFS analysis with BR or R-CHOP as the reference treatment. The primary PFS results indicate that ABR is statistically significantly more efficacious than BR and R-CHOP as the credible interval does not cross parity. Similarly, BR is statistically significantly more efficacious than R-CHOP.

Table 22: ITC results for primary PFS analysis (fixed effects)

	HR (95% CrI)		
Reference	**ABR**	**BR**	**R-CHOP**
BR	[redacted]	-	[redacted]
R-CHOP	[redacted]	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

Results of the ITC sensitivity analysis using the COVID-19-censored PFS results from ECHO are presented in Table 23. In line with the primary analysis, the results indicate that ABR is statistically significantly more efficacious than BR and R-CHOP, and BR is statistically significantly more efficacious than R-CHOP as the credible intervals do not cross parity.

Table 23: ITC results for COVID-19-censored PFS analysis (fixed effects)

	HR (95% CrI)		
Reference	**ABR**	**BR**	**R-CHOP**
BR	[redacted]	-	[redacted]
R-CHOP	[redacted]	[redacted]	-

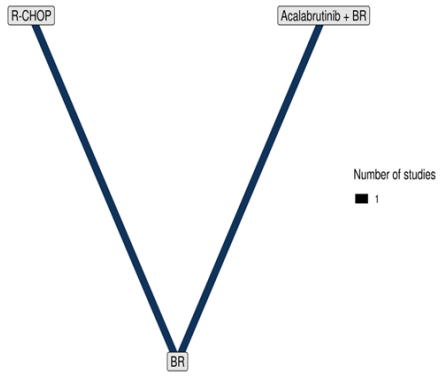
Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

Results from the PH assessment can be found in Appendix D.

B.2.9.2.2 OS results

The network diagram for OS is provided in Figure 11. Only ECHO and BRIGHT were included in the network for OS, as Stil NHL1 did not report OS data for patients with MCL. There were no loops in the network to assess for consistency.

Figure 11: Network plot for OS



Abbreviations: BR, bendamustine + rituximab; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

The ITC results for the primary OS analysis with BR or R-CHOP as the reference treatment are presented in Table 24. The results demonstrated a numerical trend for an improvement in OS for ABR when compared with BR and R-CHOP, however results were not statistically significant as the confidence intervals crossed parity.

Table 24: ITC results for primary OS analysis (fixed effects)

	HR (95% CrI)		
Reference	**ABR**	**BR**	**R-CHOP**
BR	[redacted]	-	[redacted]
R-CHOP	[redacted]	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

Table 25 presents the ITC results for the COVID-19-censored OS analysis. The results suggested a numerical trend for an improvement in OS for ABR when compared with BR and R-CHOP, however results were not statistically significant as the confidence intervals crossed parity.

Table 25: ITC results for COVID-19-censored OS analysis (fixed effects)

	HR (95% CrI)		
Reference	**ABR**	**BR**	**R-CHOP**
BR	[redacted]	-	[redacted]
R-CHOP	[redacted]	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

Results from the PH assessment can be found in Appendix D.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

Whilst a robust methodology was used to identify studies for the network, due to limitations in the available evidence for inclusion in the ITC, there are a number of uncertainties related to the inputs and assumptions used.

There was limited availability of baseline data for the MCL subgroups in the comparator trials, preventing a detailed assessment of heterogeneity. Where feasible, we attempted to reduce heterogeneity in disease status by using subgroup results for BR versus R-CHOP in patients with MCL. With the limited reporting of baseline data for subgroups in BRIGHT and StiL NHL1, it is unknown whether differences in patient characteristics may have biased the ITC. Further, due to the small sample size of these subgroups, the resulting effect estimates versus R-CHOP are uncertain.

In order to create a connected network, the treatment labels for studies had to be simplified. This included not differentiating studies based on rituximab maintenance use, which varied significantly across studies. There was also limited trial evidence for R-CHOP followed by rituximab maintenance, and an absence of data from which to create a network that differentiated studies according to rituximab maintenance treatment. Also, to facilitate network connectivity, the assumption that R-CHOP is equal to R-CVP in the BRIGHT study had to be made. This was deemed to be a reasonable assumption, given there was no meaningful difference in the efficacy of BR versus R-CHOP and BR versus R-CVP observed in the ITT group of BRIGHT.

The PFS and OS ITCs compared log-hazard ratios under the PH assumption, which may not hold for all studies in the network, though the sample sizes of the BRIGHT and StiL NHL1 studies were quite small, making the assessment more uncertain. The presence of non-PH was most noticeable for PFS, where events tended to occur around the timing of scheduled scans. For OS, there was weaker evidence of non-PH, suggesting that any associated bias may be lower than for PFS. Results of the PH assessment are provided in Appendix D.

Finally, the incidence of COVID-19 deaths in ECHO, which was the only study in the ITC conducted during the COVID-19 pandemic, had a relevant impact on study outcomes. The impact of COVID-19 on ECHO but not BRIGHT or StiL NHL1 may be a potential source of bias in the ITC. To explore this, the ITC was repeated using the prespecified analysis that censored for COVID-19 deaths. The ITC results from the COVID-19-censored analysis were comparable to the primary ITC analysis and did not alter the interpretation of results.

B.2.9.4 Conclusion

Based on a comprehensive SLR of clinical studies in MCL, the ITC analysis provided evidence of a significant improvement in the PFS outcome in patients receiving ABR compared with BR or R-CHOP. There was a numerical trend for an improvement in OS for ABR when compared with BR and R-CHOP. The validity of the assumption of exchangeability of the studies included in the ITC was assessed and key limitations identified, however there was limited scope to quantify the impact of these on the findings. The ITC results were also consistent with the results of the ECHO study, with regard to the comparison of ABR and BR.

B.2.10 Adverse reactions

B.2.10.1 ECHO

The ECHO safety analyses presented in this section were conducted based on the safety analysis set (SAS), to ensure that all patients who received any amount of acalabrutinib were included. The SAS consisted of 297 patients who received at least one dose of ABR and 297 patients who received at least one dose of PBR.

With a median follow-up of 46.1 months in the ABR arm and 44.4 months in the PBR arm, the median duration of exposure was [redacted] for patients in the ABR arm compared with the PBR arm ([redacted] versus [redacted], respectively). This supports a tolerable safety profile with the addition of acalabrutinib to BR.

B.2.10.1.1 Adverse event overview (main study period)

TEAEs were defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date

of study drug and prior to 30 days after the date of the last dose of study drug or the first date starting new anti-MCL therapy.

A summary of the TEAEs reported in the SAS is provided in Table 26. Despite the addition of acalabrutinib to BR, similar proportions of patients experienced at least one TEAE (99.7 and 99.0% of patients in the ABR and PBR arms, respectively). There were no significant differences in Grade ≥3 and Grade 5 TEAEs in the ABR and PBR arms; Grade ≥3 TEAEs were reported in 88.9 and 88.2% of patients in the ABR and PBR arms, respectively, and Grade 5 TEAEs occurred in 12.1 and 10.1% of patients. TEAEs considered by the investigator as related to any of the study drugs were reported in 94.6 and 92.3% of patients in the ABR and PBR arms, respectively, including TEAEs considered related to acalabrutinib/placebo in 68.0 and 55.6% of patients, respectively. Treatment-emergent SAEs were reported in 69.0 and 62.0% of patients in the ABR and PBR arms, respectively, and treatment-related SAEs in 38.4 and 33.3% of patients.

TEAEs leading to dose withholding of any of the study drugs were reported in 81.5 and 69.7% of patients in the ABR and PBR arms, respectively. TEAEs leading to dose reduction of acalabrutinib/placebo or bendamustine were reported in 31.6 and 25.9% of patients in the ABR and PBR arms, respectively. TEAEs leading to discontinuation of any study drug were reported in 50.5 and 35.4% of patients in the ABR and PBR arms, respectively.

Table 26: Overall summary of TEAEs (SAS)

	ABR (N=297)	**PBR (N=297)**
TEAE, n (%)		
Any grade	296 (99.7)	294 (99.0)
Grade ≥3	264 (88.9)	262 (88.2)
Grade 5 (fatal)	36 (12.1)	30 (10.1)
Treatment-emergent SAE, n (%)		
Any grade	205 (69.0)	184 (62.0)
Grade ≥3	191 (64.3)	166 (55.9)
Grade 5 (fatal)	36 (12.1)	30 (10.1)

	ABR (N=297)	PBR (N=297)
Treatment-related TEAE, n (%)		
Any study drug	281 (94.6)	274 (92.3)
Acalabrutinib/placebo only	202 (68.0)	165 (55.6)
Bendamustine only	139 (46.8)	111 (37.4)
Rituximab only	106 (35.7)	118 (39.7)
TEAE leading to dose reduction, n (%)		
Any study drug	94 (31.6)	77 (25.9)
Acalabrutinib/placebo only	30 (10.1)	25 (8.4)
Bendamustine only	77 (25.9)	60 (20.2)
TEAE leading to study drug discontinuation, n (%)		
Any study drug	150 (50.5)	105 (35.4)
Acalabrutinib/placebo only	127 (42.8)	92 (31.0)
Bendamustine only	46 (15.5)	35 (11.8)
Rituximab only	60 (20.2)	60 (20.2)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
MedDRA version 26.1.
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.

B.2.10.1.1.1 Exposure-adjusted TEAEs

Given the longer duration of exposure in the ABR arm compared with the PBR arm, exposure-adjusted incidence rates were calculated, as outlined in Table 27. When adjusting for exposure, the differences in event rates were attenuated for Grade ≥3 SAEs, and for TEAEs leading to discontinuation of acalabrutinib/placebo (Table 27).

Table 27: Exposure-adjusted event rate of overall TEAEs (SAS)

	Events per 100 patient-years of exposure	
	ABR (N=297)	PBR (N=297)
TEAE		
Any grade	753.80	719.61
Grade ≥3	141.33	138.02
Grade 5 (fatal)	4.21	3.96
Treatment-emergent SAE		
Any grade	52.65	48.64
Grade ≥3	42.59	38.62
Grade 5 (fatal)	4.21	3.96
TEAE leading to study drug discontinuation		
Any study drug	20.59	15.69
Acalabrutinib/placebo	15.09	12.13
Bendamustine	5.50	4.61
Rituximab	7.14	7.91

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
MedDRA version 26.1.
Event rate is defined as (total number of TEAEs for each category) × 100/(sum of treatment-emergent period of all patients in respective treatment in years in the main study period).

B.2.10.1.2 Treatment-emergent adverse events

As expected, with the addition of continuous acalabrutinib treatment to the BR regimen and with the longer exposure to acalabrutinib and rituximab, the incidence of some TEAEs was slightly increased in the ABR arm. However, the TEAE profile was consistent with the known safety profile of the individual treatments used in each arm.

The most frequently reported TEAEs in the ABR and PBR arms, respectively, were nausea (42.8 and 37.7%), neutropenia (40.1 and 41.4%), diarrhoea (37.4 and 27.9%), COVID-19 (30.6 and 20.9%), and headache (30.3 and 14.1%). TEAEs reported in ≥10% of patients in either arm are presented in Table 28.

The TEAEs with higher incidence (≥5% difference) in the ABR arm compared with the PBR arm were nausea (42.8 and 37.7%), diarrhoea (37.4 and 27.9%), COVID-19 (30.6 and 20.9%), headache (30.3 and 14.1%), fatigue (29.3 and 24.2%), cough

(26.9 and 20.2%), vomiting (25.6 and 13.8%), back pain (16.2 and 9.4%), rash maculopapular (15.8 and 6.4%), and contusion (11.1 and 5.4%) (Table 28). Conversely, infusion-related reactions had a lower incidence in the ABR arm (14.5 and 21.9%). It is of note that while the incidence of TEAEs was higher in the ABR arm, the exposure to acalabrutinib or the SoC chemotherapy agents was not impacted.

Table 28: TEAEs reported in ≥10% of patients in any treatment arm by preferred term, or ≥5% for Grade ≥3 AEs (SAS)

	ABR		PBR	
	Any grade (N=297) n (%)	Grade ≥3 (N=299) n (%)	Any grade (N=297) n (%)	Grade ≥3 (N=300) n (%)
Patients with at least 1 TEAE (any grade)	296 (99.7)	264 (88.9)	294 (99.0)	262 (88.2)
Nausea	127 (42.8)	4 (1.3)	112 (37.7)	4 (1.3)
Neutropenia	119 (40.1)	105 (35.4)	123 (41.4)	110 (37.0)
Diarrhoea	111 (37.4)	9 (3.0)	83 (27.9)	7 (2.4)
COVID-19	91 (30.6)	26 (8.8)	62 (20.9)	21 (7.1)
Headache	90 (30.3)	4 (1.3)	42 (14.1)	2 (0.7)
Fatigue	87 (29.3)	8 (2.7)	72 (24.2)	11 (3.7)
Pyrexia	86 (29.0)	7 (2.4)	72 (24.2)	4 (1.3)
Cough	80 (26.9)	0	60 (20.2)	1 (0.3)
Vomiting	76 (25.6)	2 (0.7)	41 (13.8)	3 (1.0)
Constipation	73 (24.6)	3 (1.0)	75 (25.3)	1 (0.3)
Anaemia	68 (22.9)	28 (9.4)	60 (20.2)	30 (10.1)
Rash	61 (20.5)	4 (1.3)	48 (16.2)	4 (1.3)
Upper respiratory tract infection	54 (18.2)	1 (0.3)	44 (14.8)	0
Neutrophil count decreased	53 (17.8)	46 (15.5)	46 (15.5)	30 (10.1)
Arthralgia	52 (17.5)	2 (0.7)	49 (16.5)	3 (1.0)
Back pain	48 (16.2)	4 (1.3)	28 (9.4)	2 (0.7)
Pneumonia	48 (16.2)	26 (8.8)	39 (13.1)	19 (6.4)
Pruritus	47 (15.8)	2 (0.7)	40 (13.5)	2 (0.7)
Rash maculo-papular	47 (15.8)	21 (7.1)	19 (6.4)	2 (0.7)
COVID-19 pneumonia	47 (15.8)	40 (13.5)	37 (12.5)	31 (10.4)
Dyspnoea	45 (15.2)	4 (1.3)	28 (9.4)	7 (2.4)
Oedema peripheral	44 (14.8)	1 (0.3)	43 (14.5)	0
Dizziness	43 (14.5)	2 (0.7)	45 (15.2)	1 (0.3)

	ABR		PBR	
	Any grade (N=297) n (%)	Grade ≥3 (N=299) n (%)	Any grade (N=297) n (%)	Grade ≥3 (N=300) n (%)
Infusion-related reaction	43 (14.5)	2 (0.7)	65 (21.9)	6 (2.0)
White blood cell count decreased	41 (13.8)	30 (10.1)	31 (10.4)	11 (3.7)
Decreased appetite	40 (13.5)	0	40 (13.5)	1 (0.3)
Myalgia	40 (13.5)	3 (1.0)	29 (9.8)	2 (0.7)
Thrombocytopenia	38 (12.8)	18 (6.1)	34 (11.4)	16 (5.4)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Contusion	33 (11.1)	0	16 (5.4)	0
Hypokalaemia	33 (11.1)	9 (3.0)	32 (10.8)	11 (3.7)
Urinary tract infection	33 (11.1)	5 (1.7)	32 (10.8)	5 (1.7)
Asthenia	31 (10.4)	3 (1.0)	29 (9.8)	2 (0.7)
Weight decreased	31 (10.4)	0	19 (6.4)	1 (0.3)
Platelet count decreased	30 (10.1)	11 (3.7)	30 (10.1)	8 (2.7)
Insomnia	30 (10.1)	1 (0.3)	20 (6.7)	0
Hyperuricaemia	29 (9.8)	9 (3.0)	40 (13.5)	4 (1.3)
Lymphocyte count decreased	22 (7.4)	19 (6.4)	29 (9.8)	29 (9.8)
Leukopenia	23 (7.7)	17 (5.7)	23 (7.7)	18 (6.1)
Febrile neutropenia	16 (5.4)	15 (5.1)	7 (2.4)	7 (2.4)
Lymphopenia	14 (4.7)	8 (2.7)	19 (6.4)	16 (5.4)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
MedDRA version 26.1.
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Preferred terms are listed in descending order of frequency for the ABR arm.
Note that this table includes Grade ≥3 TEAEs with an incidence of <5%, where the incidence of any Grade is ≥10% in either treatment arm. Likewise, any Grade TEAEs with an incidence of <10% are included if the incidence of Grade ≥3 is ≥5% in either treatment arm.

B.2.10.1.3 Treatment-related TEAEs

Treatment-related TEAEs were those considered by the investigator to be related to any study treatment (acalabrutinib/placebo, bendamustine, rituximab). Treatment-related TEAEs of any grade were reported in 94.6 and 92.3% of patients in the ABR and PBR arms, respectively, and treatment-related Grade ≥3 TEAEs in 75.1 and 74.1% of patients.

The incidences of most treatment-related TEAEs (any grade) in the ABR arm were generally similar to that in the PBR arm, with the exception (>5% difference) of headache (22.6 and 6.7%) and rash maculo-papular (11.1 and 3.0%), while infusion-related reactions were lower in the ABR arm (13.8 and 21.9%) (Table 29). The incidences of treatment-related Grade ≥3 TEAEs in the ABR arm were generally similar to those in the PBR arm with the exception (>5% difference) of neutrophil count decreased (14.8 and 9.4%), white blood cell count decreased (9.4 and 3.4%), and rash maculo-papular (5.7% and 0 patients).

Treatment-related TEAEs reported in ≥10% of patients in either arm are presented in Table 29.

Table 29: Treatment-related TEAEs reported in ≥10% of patients in any treatment arm by preferred term (SAS)

	ABR (N=297)		PBR (N=297)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Patients with at least 1 treatment-related TEAE	281 (94.6)	223 (75.1)	274 (92.3)	220 (74.1)
Neutropenia	115 (38.7)	101 (34.0)	119 (40.1)	105 (35.4)
Nausea	107 (36.0)	4 (1.3)	93 (31.3)	3 (1.0)
Headache	67 (22.6)	3 (1.0)	20 (6.7)	1 (0.3)
Fatigue	65 (21.9)	7 (2.4)	52 (17.5)	9 (3.0)
Diarrhoea	62 (20.9)	5 (1.7)	49 (16.5)	6 (2.0)
Vomiting	58 (19.5)	1 (0.3)	25 (8.4)	2 (0.7)
Neutrophil count decreased	48 (16.2)	44 (14.8)	45 (15.2)	28 (9.4)
Anaemia	48 (16.2)	16 (5.4)	43 (14.5)	17 (5.7)
Pyrexia	42 (14.1)	5 (1.7)	38 (12.8)	3 (1.0)
Infusion-related reaction	41 (13.8)	1 (0.3)	65 (21.9)	6 (2.0)
White blood cell count decreased	40 (13.5)	28 (9.4)	28 (9.4)	10 (3.4)

	ABR (N=297)		PBR (N=297)	
	Any grade n (%)	Grade ≥3 n (%)	Any grade n (%)	Grade ≥3 n (%)
Rash	38 (12.8)	3 (1.0)	25 (8.4)	3 (1.0)
Constipation	37 (12.5)	2 (0.7)	33 (11.1)	0
Thrombocytopenia	35 (11.8)	16 (5.4)	33 (11.1)	15 (5.1)
Rash maculo-papular	33 (11.1)	17 (5.7)	9 (3.0)	0
Platelet count decreased	30 (10.1)	11 (3.7)	29 (9.8)	8 (2.7)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
MedDRA version 26.1.
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.
Preferred terms are listed in descending order of frequency (any grade) for the ABR arm.

B.2.10.1.4 Treatment-emergent and treatment-related SAEs

Treatment-emergent SAEs of any grade occurred in 69.0 and 62.0% of patients in the ABR and PBR arms, respectively. Grade ≥3 SAEs occurred in 64.3 and 55.9% and Grade 5 SAEs in 12.1 and 10.1% of patients in the ABR and PBR arms, respectively. Considering the longer exposure in the ABR arm compared with the PBR arm (by 4 months), the difference in patient incidence of SAEs was attenuated when adjusted for the duration of exposure (B.2.10.1.1.1). The exposure-adjusted incidence rates of Grade ≥3 SAEs were 32.6 and 29.4 patients per 100 patient-years of exposure in the 2 arms, respectively. Further details of SAEs are provided in Appendix M.

The most frequently occurring (≥5% of patients) treatment-emergent SAEs (any grade) reported in the ABR and PBR arms, respectively, were COVID-19 pneumonia (13.8 and 11.4%), pneumonia (9.4 and 7.1%), COVID-19 (8.8 and 6.4%), and pyrexia (5.7 and 5.1%). Grade 3 to 4 SAEs reported in ≥5% of patients in either arm were COVID-19 pneumonia (8.1 and 6.7%), pneumonia (7.1 and 6.1%), and COVID-19 (5.1 and 4.0%).

SAEs with an outcome of death reported in at least one patient in either the ABR or PBR arms, respectively, were COVID-19 pneumonia (15 [5.1%] and 10 [3.4%] patients), COVID-19 (8 [2.7%] and 6 [2.0%] patients), pneumonia (3 [1.0%] and 0

patients), sepsis (1 [0.3%] and 2 [0.7%] patients), and pulmonary embolism (0 and 2 [0.7%] patients) (see Appendix M).

Treatment-related treatment-emergent SAEs (all grades) were reported in 38.4 and 33.3% of patients in the ABR and PBR arm, respectively, treatment-related Grade 3 to 4 SAEs in 31.6 and 26.3% of patients, and treatment-related Grade 5 SAEs in 3.4 and 2.0% of patients.

The most frequently reported (≥3% of patients) treatment-related SAEs in either the ABR or PBR arms, respectively, were pneumonia (4.7 and 4.4%), COVID-19 pneumonia (3.7 and 3.4%), pyrexia (3.4 and 3.7%), and infusion-related reaction (0.7 and 3.0%).

Further details are provided in Appendix M.

B.2.10.1.5 TEAEs leading to discontinuation

The incidence of all grades of TEAEs that led to discontinuation of acalabrutinib/placebo was higher in the ABR arm than in the PBR arm (42.8 vs 31.0%), primarily due to a higher incidence of TEAEs in the infections and infestations system organ class, in particular COVID-19 (4.7 and 3.0%) and COVID-19 pneumonia (4.4 and 2.7%).The difference in patient incidence of TEAEs leading to discontinuation of acalabrutinib/placebo was attenuated when adjusted for the duration of exposure (B.2.10.1.1.1).

The most frequently occurring (≥2% of patients) TEAEs that led to discontinuation of acalabrutinib/placebo in the ABR and PBR arms, respectively, were COVID-19 (4.7 and 3.0%), COVID-19 pneumonia (4.4 and 2.7%), and neutropenia (4.0 and 3.4%). Further details are provided in Appendix M.

B.2.10.2 Safety overview

The safety profile of ABR was consistent with the known safety profile of the individual treatments used in each arm. As expected, with the addition of acalabrutinib to the BR regimen and the longer exposure to acalabrutinib and rituximab in the ABR arm, the incidence of certain TEAEs were higher. However, the higher rates of SAEs and TEAEs leading to treatment discontinuation were attenuated when rates were adjusted by exposure.

B.2.11 Ongoing studies

ECHO is currently ongoing, with the final analysis planned to occur when approximately 268 IRC-assessed PFS events (~49% data maturity) have been observed.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

The efficacy and safety of ABR was demonstrated in ECHO, a global Phase 3 randomised, double-blind, multicentre, placebo-controlled trial to assess the efficacy and safety of ABR compared with PBR in patients with previously untreated MCL. At the DCO for the interim primary PFS analysis (15th February 2024), the ECHO trial demonstrated that the addition of acalabrutinib to BR statistically significantly reduced the risk of PD or death by 27% (PFS HR: 0.73; 95% CI: 0.57, 0.94; 2-sided log-rank p=0.0160). The median estimated PFS in the ABR arm was 66.4 months (95% CI: 55.1, NE) compared with 49.6 months in the PBR arm (95% CI: 36.0, 64.1), corresponding to an approximate 17-month improvement in median PFS. Subgroup analyses demonstrated [redacted]

Due to the timing of the trial, the ECHO study included by a ‘pre-vaccination cohort’, [redacted]. A sensitivity analysis found that after censoring for COVID-19 deaths, median PFS improved in both arms, and PFS was not reached with ABR versus 61.6 months with PBR (HR: 0.64; 95% CI: 0.48, 0.84; p=0.0017). This represents a 36% reduction in the risk of PD or death with ABR versus PBR, compared with a 27% reduction in the primary PFS analysis. COVID-19 had a relevant impact on the study outcome, but the clinical benefit of ABR over PBR for patients with previously untreated MCL was not compromised despite the number of COVID-19 deaths reported in the study.

After a median follow-up of 46.1 months in the ABR arm and 44.4 in the PBR arm at the DCO, the addition of acalabrutinib to BR was associated with a trend towards increased OS (HR: 0.86; 95% CI: 0.65, 1.13; p=0.2743). As for PFS, a sensitivity analysis was conducted for OS, in which any patient who was known to have died of COVID-19 was censored at their COVID-19 death date. After censoring, the treatment effect on OS improved, with an HR of 0.75 (95% CI: 0.53, 1.04; p=0.0797) in favour of ABR.

High response rates (≥88.0%) were observed in both treatment arms, with a numerically higher CR rate in the ABR arm, though this was not statistically significant. More durable responses were observed in those treated with ABR versus PBR, with median DOR of 63.5 months (95% CI: 52.5, NE) versus 53.8 months (95% CI: 37.5, 66.1), respectively.

PRO data demonstrated that in a double-blinded manner, [redacted]

The safety profile of ABR was consistent with the known safety profile of the individual treatments used in each arm. As expected, with the addition of acalabrutinib to the BR regimen and the longer exposure to acalabrutinib and rituximab in the ABR arm, the incidence of certain TEAEs was slightly higher. However, the higher rates of SAEs and TEAEs leading to treatment discontinuation were attenuated when rates were adjusted by exposure. Although the addition of acalabrutinib to BR was associated with some increased toxicity, this toxicity was generally mild and more than offset by the reduction in lymphoma-related mortality.

Given the lack of head-to-head data for ABR versus R-CHOP, an ITC was conducted to compare the relative efficacy. The ITC results for PFS suggest that ABR is significantly more efficacious than BR alone and R-CHOP, and that BR is more efficacious than R-CHOP. There was a numerical trend for an improvement in OS for ABR when compared with BR and R-CHOP. The ITC results were also consistent with the results of the ECHO study, with regard to the comparison of ABR and BR.

The availability of acalabrutinib as a 1L treatment option, offering significant improvement in outcomes over existing SoC for this patient population is of clear significance. MCL is an aggressive cancer typically with poor prognosis, and a relapsing course. Management of R/R MCL is particularly difficult, with treatments limited in number and in response durability (29). Improving the efficacy of 1L treatment, and specifically maximising the duration of first remission, remains of critical importance to obtain favourable long-term outcomes. The addition of targeted agents, such as BTKis, to chemoimmunotherapy, is a key area of advancement in the treatment of MCL. ECHO was designed to explore the use of acalabrutinib for patients with previously untreated MCL in combination with SoC, with the aim of achieving significant long-term benefit while limiting toxicity, which is also an important goal in the target population. In the context of a disease that remains incurable, the substantial increase in PFS demonstrated in ECHO represents a significant improvement in the treatment of previously untreated patients with MCL. The risk/benefit profile of acalabrutinib when given in combination with BR is therefore considered highly favourable in the proposed indication.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

Internal validity

ECHO is a Phase 3 randomised, double-blind, placebo-controlled, multi-centre study conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was conducted in a double-blind manner, with sponsor, investigator, site staff, and patients all blinded to the treatment to which the subject was randomised. Randomisation to study drugs was achieved via a central IXRS and the intervention and placebo were identical. Patient demographics and baseline disease characteristics at baseline were well-balanced between the two treatment arms.

Sensitivity analyses were conducted on the primary endpoint of PFS to evaluate the impact of any potential confounding variables and the robustness of the results. The results of the sensitivity analysis evaluating the impact of COVID-19 deaths confirmed the robustness of the primary analysis and indicated that the clinical benefit of ABR over PBR for the target population was not compromised despite the

number of COVID-19 deaths reported in the study. Similarly, in all other sensitivity analyses, the results were consistent with the primary analysis.

Pre-planned subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms. The results of the subgroup analyses of IRC-assessed PFS [redacted]. Importantly, many of the subgroup data analyses should also be interpreted with caution due to the small number of patients in these subgroups, which is reflected in the observed wide CI. ECHO was not powered to detect treatment differences in any subgroups. Similarly, subgroup analyses of OS demonstrated [redacted].

Though direct head-to-head data are not available for ABR versus R-CHOP, the ITC shows that ABR is significantly more efficacious than R-CHOP with respect to PFS, in line with clinician opinion (3). Whilst a robust methodology was used to conduct the ITC, there is some uncertainty in the results, related to the inputs and assumptions used. Of note, the sample size in the comparator trials was small, and limited baseline data were available to allow assessment of heterogeneity. In addition, the BR treatment arm was assumed to be homogeneous across the trials, despite variation in the use of rituximab maintenance therapy. Details of the uncertainties in the ITC are described in Section B.2.9.3.

External validity

ECHO enrolled patients aged ≥65 years, as this is the population most likely to be unsuitable for ASCT. The ECHO population is therefore largely reflective of the population for ABR addressed in the decision problem (although this is narrower than the anticipated regulatory label). ECHO patient demographics and disease characteristics at baseline were considered by clinical experts to be representative of the targeted patient population of patients with untreated MCL who are considered to be unsuitable for ASCT (3). The trial covered a number of countries in Western

Europe, where demographics are likely to be similar to those in England, as validated by clinical experts (3). In the ECHO subgroup analysis of patients enrolled in Western Europe, [redacted]. Whilst ECHO only enrolled patients aged ≥65 years, clinical experts expected the outcomes from ECHO to be similar in the small number of patients who are <65 years and unsuitable for ASCT (3).

Whilst a number of different treatment options are recommended in guidelines from NICE (4) and BSH (2), clinicians highlighted that the key treatments used in the 1L setting are BR and R-CHOP, with a combined use in ~90% of patients (3). ECHO provides direct head-to-head data versus BR, the most commonly used treatment in the 1L setting, demonstrating a clinically meaningful improvement in PFS.

PFS was the primary endpoint for ECHO, and is a well-established clinical outcome, relevant to the oncology setting. Progression was defined according to the Lugano Classification for NHL, which is the well-recognised standard for measurement of progression in MCL (17). In conjunction with OS, which typically requires a long follow-up period in order to collect mature data, PFS can measure outcomes in studies with shorter follow-ups and is not affected by crossover or confounding later lines of therapy; it therefore represents a direct effect of ABR. In addition, PFS is a patient-relevant endpoint and can act as a surrogate for OS in cases where access to treatments is urgent, such as advanced MCL where patients have poor prognosis and are thus in need of rapid access to more effective treatments. Regulatory agencies allow PFS to be used as a primary endpoint to evaluate drug efficacy in cancers; the European Medicines Agency (EMA) allows PFS to be selected as the primary endpoint for cancers, normally requiring OS to be reported as a secondary endpoint (41). The OS data showed a positive trend favouring the ABR arm, however the median OS was not reached at the DCO.

B.3 Cost effectiveness

B.3.1 Summary cost effectiveness

Overview

- ABR is an efficacious, well-tolerated treatment studied in the ECHO study, which is a Phase 3, randomised, double-blind, multi-centre trial
- A cost-effectiveness analysis from the National Health Service (NHS) perspective was performed comparing ABR with BR alone (referred to as PBR in the ECHO trial, i.e. placebo plus BR) and R-CHOP, which represent established clinical management and SoC for the treatment of adult patients with previously untreated MCL who are considered unsuitable candidates for ASCT
- The cost-effectiveness model was based on a conventional three-health state partitioned survival analysis, guided by consideration of key modelling criteria, including disease setting and the primary endpoints assessed in the ECHO trial. The disease course, treatment pathway, and previously published model structures were also considered
- The long-term survival estimates for the ABR and PBR arms are derived from parametric survival models fitted to the patient data from the ECHO trial. Survival estimates for R-CHOP are derived using HRs from an ITC
- The deterministic base case analysis indicates that ABR is more costly and more efficacious against both comparators, with an incremental cost-effectiveness ratio (ICER) of £10,153 and £2,486 for BR and R-CHOP, respectively
- The probabilistic sensitivity analysis demonstrated very similar outcomes for the comparison of ABR versus BR. For the comparison against R-CHOP, however, ABR is found to be less costly and more efficacious. This is primarily due to the wide confidence intervals around the relative efficacy estimates (HRs) used to model R-CHOP OS and PFS; therefore, alternative HRs were explored in the scenario analysis.
- Deterministic sensitivity analyses indicated that the most influential parameters are the duration of subsequent treatment with ibrutinib, and the proportion of non-fatal PFS in both the BR and the ABR arm. In all scenario

analyses, the ICER was below £30,000 per quality-adjusted life year (QALY) gained and remained relatively stable in all explored scenarios. These parameters were derived from the ECHO trial and are therefore directly reflective of the modelled population.

Further to the important clinical benefits to patients, ABR has been demonstrated to be a cost-effective treatment option for adult patients with previously untreated MCL who are considered unsuitable candidates for ASCT, when compared with established clinical management

B.3.2 Published cost-effectiveness studies

B.3.2.1 Identification of studies

A systematic review of the non-clinical literature was conducted on 27th June 2024 to identify economic evidence (economic burden, economic evaluations or models, and health state utility values [HSUVs]) relevant to the decision problem. Searches were made on electronic databases, including Embase®, MEDLINE®, and the Cochrane library, and also captured conference proceedings. Supplementary searches of the grey literature were conducted, including searches of previous relevant health technology assessments (HTAs) and public registries and databases, to identify evidence not captured in the database searches. Full search strategies, inclusion and exclusion criteria, and the PRISMA flow diagram are provided in Appendix G.

B.3.2.2 Description of identified studies

The searches identified one publication (42) and two HTA submissions (one to NICE (23) and one to the Scottish Medicines Consortium [SMC] (43)) that reported outcomes of cost effectiveness and met the prespecified inclusion criteria relating to population, intervention/comparator, and study design. As shown in Table 30, all three economic evaluations reported VR-CAP as cost effective when compared with R-CHOP in the prespecified population. The lack of published economic models in this setting reflects the lack of new treatment options available to these patients.

Given the paucity of modelling precedent in the previously untreated MCL setting, an additional targeted review was conducted on 19th January 2024 to include NICE appraisals in R/R MCL and 1L CLL as a proxy disease area (full details of the

supplementary targeted review are reported in Appendix G). 1L CLL was chosen as a proxy, as both CLL and MCL are lymphoid neoplasms characterised by the multiplication of CD5+ B cells that may involve bone marrow, blood, and lymphoid tissues (44). The two disease areas also have similar epidemiological, biological, and clinical features. The targeted review identified two NICE appraisals in R/R MCL (45, 46) and five NICE appraisals in 1L CLL (47-51).

For brevity, Table 30 summarises the published cost-effectiveness studies for previously untreated and R/R MCL. A summary of the 1L CLL modelling studies is provided in Appendix G.

Table 30: Summary of published cost-effectiveness studies

Source	Year	Summary of model	Intervention and comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator), £	ICER (per QALY gained)
van Keep et al: VR-CAP for patients with previously untreated mantle cell lymphoma (42)	2018	Markov model with 5 health states, modelling PFS 1L, PD 1L, PFS 2L, PD 2L, and death (average age of 65.82 years)	Intervention: VR-CAP Comparator: R-CHOP	Adults with newly diagnosed mantle cell lymphoma for whom HSCT is unsuitable	Total QALYs of VR-CAP: 4.10 Total QALYs of R-CHOP: 3.29 Incremental QALYs versus R-CHOP: 0.81	Total costs of VR-CAP: 45,842 Total costs of R-CHOP: 29,630 Incremental costs: £16,212	£19,880
TA370: Bortezomib for previously untreated mantle cell lymphoma (23)	2015	Markov model with 5 health states, modelling PFS 1L, PD 1L, PFS 2L, and death	Intervention: VR-CAP Comparator: R-CHOP	Adults with newly diagnosed MCL who were ineligible or not considered for stem cell transplant	Total QALYs of VR-CAP: 4.15 Total QALYs of R-CHOP: 3.35 Incremental QALYs versus R-CHOP: 0.80	Total costs of VR-CAP: 45,838 Total costs of R-CHOP: 29,625 Incremental costs: 16,213	£20,362
SMC No. (1075/15) (43)	2015	Markov model with 5 health states, modelling PFS 1L, PD 1L, PFS 2L, and death	Intervention: VR-CAP Comparator: R-CHOP	Adults with previously untreated MCL who are not suitable for HSCT	Incremental QALYs versus R-CHOP: 0.75 Total QALYs per arm redacted	Incremental costs versus R-CHOP: 17,162 Total costs per arm redacted	£23,020
TA502: Ibrutinib in R/R MCL (45)	2016	Markov model with 3 health states, modelling PFS, PD, and death	Intervention: ibrutinib Comparator: R-CHOP	Patients with R/R MCL who had either only one previous line or more than one previous line of therapy	Incremental QALYs for ibrutinib versus R-CHOP ranging from 0.82 to 1.87 depending on the scenario Total QALYs per arm redacted	Incremental costs (ibrutinib with PAS versus R--CHOP): 93,196 Total costs per arm redacted	£62,650 (base-case versus R-CHOP) Scenario (incremental QALY of 1.87): £49,849

Source	Year	Summary of model	Intervention and comparator	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator), £	ICER (per QALY gained)
TA677: Brexucabragene autoleucel in 3L MCL (46)	2021	Partitioned state model with 3 health states, modelling PFS, PD, and death	Intervention: KTE-X19 Comparator: SoC	Patients with R/R MCL who have previously received a BTKi	Total and incremental QALYs redacted	Total and incremental costs redacted	£46,898 per QALY (base case compared with SoC) Range between £46,898 and £72,920

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BTKi, Bruton's tyrosine kinase inhibitor; HSCT, haematopoietic stem cell transplant; ICER, incremental cost-effectiveness ratio; MCL, mantle cell lymphoma; PAS, patient access scheme; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R/R, relapsed/refractory; SoC, standard of care; SMC, Scottish Medicines Consortium; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisolone.

B.3.3 Economic analysis

As summarised in Table 30, none of the economic evaluations identified in the systematic review compared ABR with the current SoC (BR and R-CHOP) in patients with previously untreated MCL, unsuitable for ASCT. Therefore, for the purpose of this submission, a *de novo* economic model was developed. The cost-effectiveness analysis was undertaken from the perspective of the NHS, comparing ABR with established clinical management and SoC (BR and R-CHOP) for the treatment of previously untreated MCL, unsuitable for ASCT. A partitioned survival model (PSM) was developed with a lifetime time horizon and a discount rate of 3.5% for cost and health outcomes.

The economic evaluation conducted adheres to the methodological requirements set out in the updated NICE health technology evaluations manual published in January 2022 (52).

B.3.3.1 Patient population

The anticipated marketing authorisation indication is for the treatment of adult patients with previously untreated MCL. The population considered in this analysis focuses on adult patients with previously untreated MCL who are considered unsuitable candidates for ASCT. This is reflective of the patient population in the ECHO trial. The base case population is modelled using key clinical characteristics from ECHO, as detailed in Section B.2.3.7.

Further justification of the chosen modelled population is detailed in Section B.1.

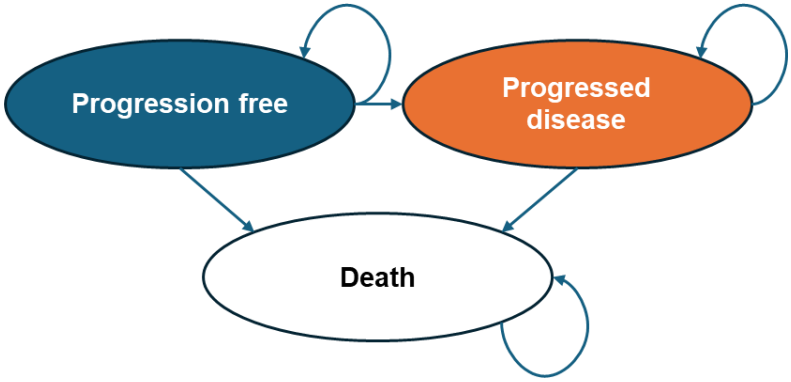
In clinician interviews held in October 2024 (see Appendix N), patient demographics and disease characteristics from the ECHO trial at baseline (see Table 8 in B.2.3.7) were considered by clinical experts to be representative of patients with untreated MCL who are unsuitable for ASCT in England (3) and where use of ABR would be expected in clinical practice.

B.3.3.2 Model structure

B.3.3.2.1 Description of model structure and patient flow

A *de novo* cost-effectiveness model was developed in Excel®. The chosen model structure was a PSM, consisting of three mutually exclusive health states: progression free, progressed disease, and death (Figure 12).

Figure 12: Three-state structure

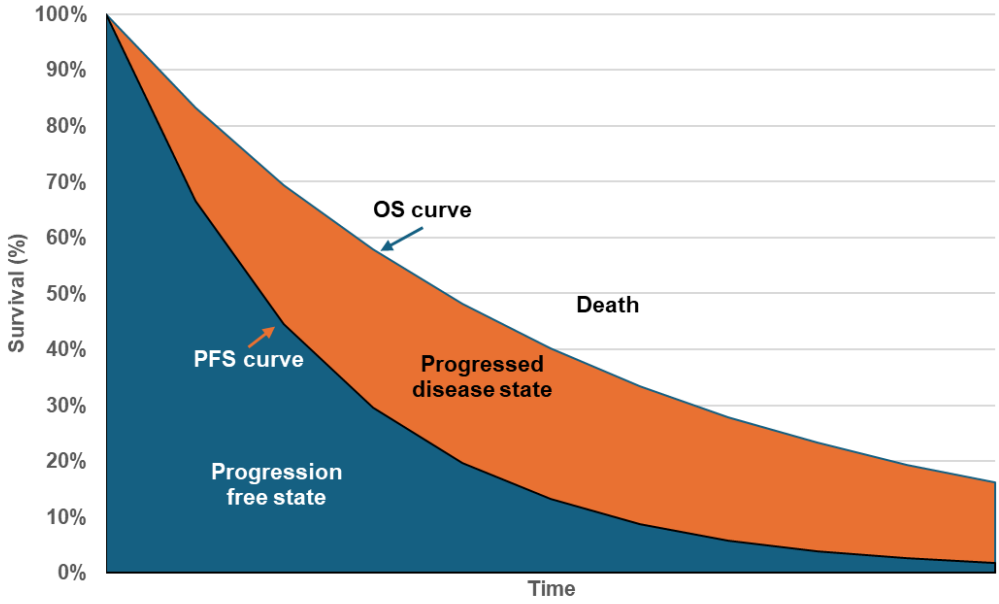


All patients begin in the progression-free health state and are assumed to initiate 1L treatment for MCL. Whilst in the progression-free health state, patients can either remain or progress to the progressed disease or death health states at the end of each cycle. As depicted in Figure 13, the proportion of patients who are progression free is calculated directly from the cumulative survival probabilities for PFS from the ECHO trial (ABR and BR alone) and the ITC (R-CHOP). Following progression, patients may remain in the progressed disease health state or transition to the absorbing death health state. Consistent with the natural history of MCL, it was assumed that disease progression is irreversible, meaning patients cannot return to the progression-free health state.

In each model cycle, the proportion of patients with progressed disease was calculated as the difference between the cumulative survival probabilities of OS and PFS (i.e. patients who are alive but not progression free). The death state is an absorbing state: patients who enter the death state remain in that state until the end of the time horizon. The state occupancy for death was calculated as one minus OS (i.e. all patients who are not alive). Extrapolated OS curves were adjusted for general population mortality

informed by life tables for England and Wales (53) to ensure that the disease-specific probability of death never falls below that of the general population.

Figure 13: PSM structure



Abbreviations: OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model.

B.3.3.2.2 Rationale for selected model structure

Based on the identified modelling precedents in MCL, there was no clear consensus on the preferred modelling approach, as both PSMs and state transition models (STMs) were used (23, 45-51). As shown in Table 30, in previously untreated MCL, an STM was used for the evaluation of VR-CAP, while one evaluation in R/R MCL adopted a PSM structure and one adopted a STM structure.

As per the NICE DSU TSD 19 (54), partitioned survival modelling is well-understood, intuitive, and easy to communicate, therefore, on balance, this was deemed the most appropriate modelling approach. PSMs are widely accepted and commonly used in oncology, as they are able to simply reflect the progressive nature of the disease. A key strength of the PSM is that it allows for both PFS and OS, key endpoints collected in the ECHO trial, to be utilised directly to determine the proportion of patients occupying each health state at each model cycle. The PSM reflects the disease progression from the trial and the observed survival profile of patients

treated. The three-state structure with a four-weekly cycle reflects the natural disease course and the primary objectives of treatment for patients with MCL in the form of delaying progression, with its associated impact on QoL and extending survival. PFS and OS are also readily available from the published evidence for R-CHOP, which is critical to generate comparator survival outcomes, given R-CHOP is not a direct comparator in the ECHO trial.

At an advisory board conducted in July 2024 (33) (see Appendix N), clinical and health economic experts indicated that a PSM was sufficient to capture costs and health outcomes in previously untreated MCL. It was noted that additional health states within an STM, and the requirement to independently model post-progression survival, may increase discrepancies in long-term OS projections. Therefore, the structural simplicity of a PSM may be advantageous.

Overall, the PSM approach offered optimal alignment with the available data and was considered appropriate to model the outcomes collected in the ECHO trial in this submission.

B.3.3.2.3 General model settings

The model used a cycle length of 28 days (4 weeks), providing a long enough time to capture costs and utilities associated with events in MCL. This cycle length also aligns with the administration frequency of ABR and BR.

A half-cycle correction (via a lifetable approach) was included in the model to account for the fact that events and transitions may occur at any point during each cycle, as opposed to the start or end of a cycle. This correction was applied to the costs assigned to the progression-free and progressed disease states and to the generation of QALYs and life years (LYs). The half-cycle correction was not applied to the acquisition and administration costs for 1L therapy (ABR, BR, and R-CHOP), as these costs are expected to accrue at the start of each cycle. This is justified by the administration schedules of 1L therapies. For both BR and R-CHOP, the initiation of treatment starts at Day 1 of each cycle. For acalabrutinib, treatment is administered in a 30-day tablet pack. The costs of a full 30-day pack of medication would be accrued regardless of when discontinuation occurs, as any unused tablets

from an open pack would be discarded. In addition, half-cycle correction was not applied to one-off adverse event (AE) costs and disutilities, which are included in the first cycle.

The model employs a lifetime time horizon. This is considered long enough to capture all potential differences in costs and health outcomes between the considered treatments. As the starting age in the model is 71.6 years, a time horizon of 28 years is assumed to model a lifetime time horizon (i.e. lifetime, aged 100 years).

A discount rate of 3.5% per year is applied to costs and QALYs, as specified in the NICE reference case (52).

The general model settings are summarised and compared with previous submissions in MCL in Table 31. The previous submissions were identified via a targeted review of prior NICE submissions (see Appendix G).

Table 31: Features of the economic analysis – Comparison to prior submissions in MCL

	Previous evaluations			Current evaluation	
Factor	**TA370 – Bortezomib for previously untreated MCL (23)**	**TA502 – Ibrutinib for treating R/R MCL (45)**	**TA677 – Autologous anti-CD19-transduced CD3+ cells for treating R/R MCL (46)**	**Chosen values**	**Justification**
Time horizon	Lifetime (20 years)	Lifetime (15 years)	Lifetime (15 years)	Lifetime time horizon (28 years)	Lifetime is considered a long enough time to allow for all relevant downstream costs and health benefits accrued over a patient's lifetime to be captured
Cycle length	Treatment cycle (21 days)	Treatment cycle (28 days)	1 month (30.44 days)	28 days (4 weeks)	This aligns with the administration frequency of ABR, and BR
Treatment waning effect	Not applied	Not applied	Not applied	Not applied	Not appropriate given patients receive treatment until progression. This also aligns with the previous NICE appraisals in MCL

	Previous evaluations			Current evaluation	
Factor	**TA370 – Bortezomib for previously untreated MCL (23)**	**TA502 – Ibrutinib for treating R/R MCL (45)**	**TA677 – Autologous anti-CD19-transduced CD3+ cells for treating R/R MCL (46)**	**Chosen values**	**Justification**
Source of utilities	Data were sourced from EQ-5D-5L data collected from the LYM-3002 study and a literature review of health utilities for NHL, stated as the most similar condition to MCL in terms of expected impact on health status. This was done to account for the lack of EQ-5D data in MCL to support the model approach	Data were sourced from the EQ-5D data collected from the RAY (MCL3001) trial	Data were sourced from EQ-5D-5L data collected from the ZUMA-2 study and mapped to EQ-5D-3L (pre-progression only) and post-progression utility estimated using the data for committee decision-making and in ERG exploratory analyses	EQ-5D-5L data collected from the ECHO trial and mapped to EQ-5D-3L via the Hernendez–Alava algorithm were used for progression-free estimates; for post-progression, utility values were estimated by calculating the difference between the utility values for the progression-free and progressed disease health states in TA502 and applying this difference to the ECHO trial-derived progression-free utility value	Utilised the ECHO trial data where possible, and adjusted based on accepted values in the most recent NICE submission in MCL
Source of costs	NHS reference costs, eMIT, MIMS online, Unit Costs of Health and Social Care (PSSRU), published literature, and UK clinical expert opinion	NHS reference costs, eMIT, BNF, Unit Costs of Health and Social Care (PSSRU), MIMS, CMU, published literature, previous HTAs	NHS reference costs, eMIT, Unit Costs of Health and Social Care (PSSRU), MIMS, CMU, published literature, previous HTAs	NHS reference costs, BNF, eMIT, Unit Costs of Health and Social Care (PSSRU)	In line with NICE guidance

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BNF, British National Formulary; BR, bendamustine + rituximab; CMU, Commercial Medicines Unit; eMIT, drugs and pharmaceutical electronic market information tool; ERG, Evidence Review Group; HTA, health technology assessment; MCL, mantle cell lymphoma; MIMS, Monthly Index of Medical Specialties; NHL, non-Hodgkin lymphoma; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; R/R, relapsed/refractory.

B.3.3.3 Intervention technology and comparators

B.3.3.3.1 Intervention

The intervention, ABR, was implemented as a 1L treatment in the model, as per the anticipated marketing authorisation, and is reflective of the decision problem described in Section B.1.1.

As described in Section B.1.2, acalabrutinib is a selective second-generation BTKi. BTKis bind covalently to a cysteine residue in the Bruton's tyrosine kinase (BTK) active site and, through irreversible inactivation of BTK, inhibit the multiplication of cancerous B cells. Acalabrutinib is currently indicated as monotherapy or in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL, and as monotherapy for the treatment of adult patients with CLL who have received at least one prior therapy (5).

Acalabrutinib is an orally administered tablet that is given in combination with BR, according to a dosing schedule of:

- Acalabrutinib 100 mg, given orally, twice daily until progression
- Bendamustine 90 mg/m^2, given IV on Days 1 and 2 of each 28-day cycle for a maximum of 6 cycles
- Rituximab 375 mg/m^2, given IV on Day 1 of each 28-day cycle for a maximum of 6 cycles

To reflect the ECHO clinical trial design, and to be consistent with treatment practices in England, the model includes rituximab maintenance following 1L immunochemotherapy. This is given intravenously (IV) at a dose of 375 mg/m^2 every 2 months for a maximum of 12 additional doses up to Cycle 30 (55).

B.3.3.3.2 Comparators

Patients who are unsuitable for aggressive induction therapy, such as intensive chemotherapy induction and ASCT, are restricted to immunochemotherapy options that have limited efficacy in preventing relapses, in turn leading to high mortality. ABR is compared against established clinical management and SoC for the 1L treatment of MCL, which consists of primarily BR, and to a lesser extent, R-CHOP.

Bendamustine, a type of chemotherapy, is an antineoplastic agent and alkylating drug, which works by interfering with the DNA in cancer cells, preventing them from multiplying. It is typically administered in combination with rituximab, a monoclonal antibody that targets the CD20 proteins on the surface of white blood cells. BR is recommended as a treatment for previously untreated patients with MCL who are ineligible for ASCT according to the BSH guidelines (2). The dosing regimen is as per the BR component of ABR.

R-CHOP consists of rituximab, doxorubicin, vincristine, cyclophosphamide, and prednisolone. Doxorubicin, vincristine, and cyclophosphamide are chemotherapies, whilst prednisolone is a corticosteroid. R-CHOP is recommended for the treatment of patients with previously untreated MCL unsuitable for ASCT. Dosing schedules were informed by the South West Strategic Clinic Network Cancer Alliance (55) and the relative dose intensity from the BRIGHT study (2, 56):

- Rituximab 375 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of 8 cycles
- Cyclophosphamide 750 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of 8 cycles
- Doxorubicin 50 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of 8 cycles
- Vincristine 1.4 mg/m^2 IV on Day 1 of each 21-day cycle for a maximum of 8 cycles
- Prednisolone 100 mg given orally on Days 1–5 of each 21-day cycle for a maximum of 8 cycles

As described in Section B.1.3.2, BR and R-CHOP are recommended in treatment guidelines for patients with previously untreated MCL who are unsuitable for ASCT. Input from clinicians further highlighted that BR and R-CHOP are the predominant treatment options for 1L used in the UK (3). Clinical experts estimated that over 90% of patients on active 1L treatment are receiving these therapies; specifically, it was estimated that 60–75% of patients receive BR and 20–30% of patients receive R-CHOP (3). This is largely due to toxicity concerns relating to VR-CAP and R-BAC (2, 3).

As noted in Section B.3.3.3.1, the model includes rituximab maintenance following 1L immunochemotherapy. This is given at a dose of 375 mg/m^2 IV every 2 months for a maximum of 12 additional doses up to Cycle 30 (55).

B.3.3.3.3 Subsequent therapies

The model considers up to two lines of subsequent therapies following initial treatment with ABR, BR, or R-CHOP. A percentage of patients in each treatment arm are given 2L and 3L subsequent treatments from a range of treatments. These are further detailed in Section B.3.6.1.3.

B.3.4 Clinical parameters and variables

B.3.4.1 Overview of clinical effectiveness data

The clinical parameters used to inform the ABR and comparator treatments in the economic model are summarised in Table 32 and detailed further throughout this section.

Table 32: Overview of clinical data used to inform the model

Component	Application in model	Source for ABR	Source for PBR	Source for R-CHOP
OS (Section B.3.4.2)	Used to fit parametric survival curves to capture lifetime OS estimates • Curve selections: ○ ABR: gamma ○ PBR: gamma	• ECHO trial, censoring COVID-19 deaths, February 2024 data cut (11) • UK lifetables (53)		• Hazard ratios from a network meta-analysis, applied against BR values (Section B.3.4.5) • UK lifetables (53)
PFS (Section B.3.4.3.4)	Used to fit parametric survival curves to capture lifetime PFS estimates • Curve selections: ○ ABR: gamma ○ PBR: gamma			
TTD (Section B.3.4.4)	Used to fit parametric survival curves to capture time on first-line treatment • Curve selections: ○ ABR: Weibull ○ PBR: NA	• ECHO trial, censoring COVID-19 deaths, February 2024 data cut (11)		• Hazard ratios from a network meta-analysis, applied against BR values (Section B.3.4.5)

Component	Application in model	Source for ABR	Source for PBR	Source for R-CHOP
AE incidence (Section B.3.5.3)	Informed the proportion of patients who incur costs and disutilities associated with each AE			• LYM-3002 (27)
Utility values (Section B.3.5.4)	Used to inform the utility of progression-free and progressed disease patients	• Progression-free: ECHO trial, FAS population (11) • Progressed disease: ECHO trial (11), TA502 decrease (45) • Age-matched general population utility values		

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; BR, bendamustine + rituximab; FAS, full analysis set; NA, not applicable; OS, overall survival; PBR, placebo, bendamustine + rituximab; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; TTD, time to discontinuation.

B.3.4.1.1 Censoring COVID-19 deaths

The ECHO trial was conducted during the COVID-19 pandemic, and COVID-19-related deaths had a relevant impact on study outcomes (see Section B.2.6). In the ECHO trial, [redacted] of overall deaths in the ABR arm were due to COVID-19, compared with [redacted] of deaths in the PBR arm.

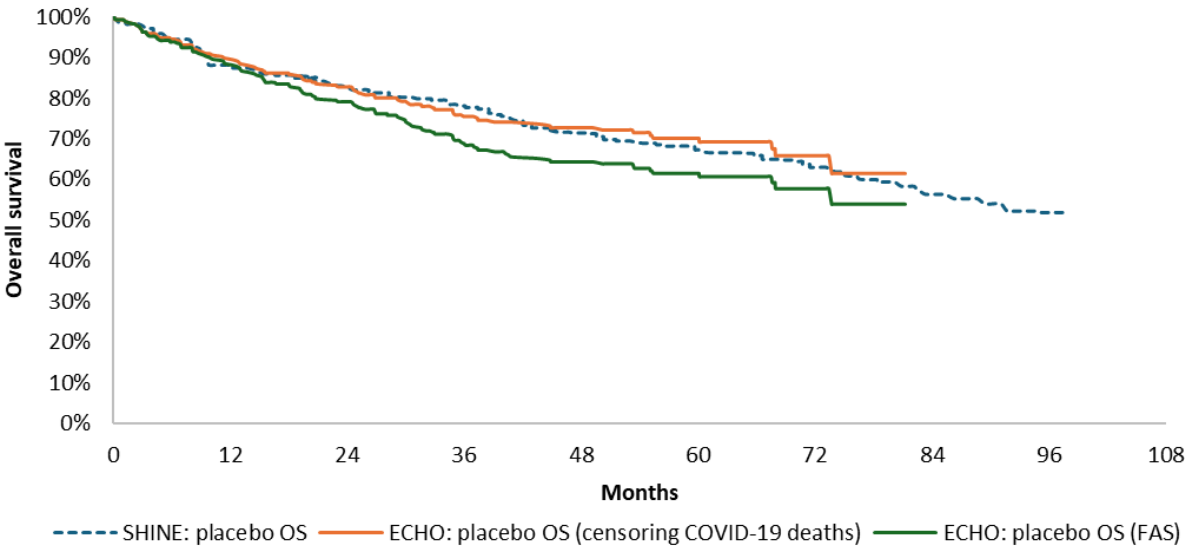
The increased deaths from COVID-19 in the ECHO trial reflect the specific time period during the pandemic in which the trial took place. The current post-pandemic health landscape has significantly changed. To account for this shift and more accurately represent the present-day situation, the ECHO data were censored to adjust for excess COVID-19-related deaths.

The COVID-19 pandemic has now ended, therefore the data censored for COVID-19-related deaths are considered more appropriate to be included as a base case in the cost-effectiveness model, as it removes the effect of the pandemic on the trial results. This can be observed in Figure 14, where the ECHO OS data for the PBR arm has been compared with the placebo arm from the recent international, randomised, double-blind, Phase 3 SHINE trial. SHINE, which compared the combination of ibrutinib and BR versus BR alone, is a similar study to ECHO that was otherwise conducted pre-pandemic (37) and therefore provides a benchmark for clinical outcomes without the impact of the COVID-19 pandemic. Both studies have a similar study design, identical trial comparator arms (PBR with the same dosing and

treatment regimens), and study population of interest (i.e. transplant unsuitable patients).

Both SHINE and ECHO also included a population of patients with broadly similar baseline characteristics, including prognostic clinical characteristics such as age, sex, ECOG PS, disease stage, tumour bulk, and presence of extranodal disease. The placebo (PBR) arms across the SHINE and ECHO studies would therefore be expected to demonstrate consistent survival outcomes. However, when the placebo OS from the FAS and COVID-19-censored KMs from the ECHO study were compared with OS KM from the SHINE study, it demonstrated that the ECHO COVID-19-censored OS KM (orange line) was more closely aligned with the SHINE OS KM (dashed line). Given the study designs, comparator arms and patient populations across both trials were generally well matched, this illustrates that the outcomes from the ECHO study were impacted by the COVID-19 pandemic.

Figure 14: Comparison of ECHO OS and SHINE OS for the placebo arms



Abbreviations: FAS, full analysis set; OS, overall survival.

B.3.4.2 Modelling of PFS for ABR and PBR

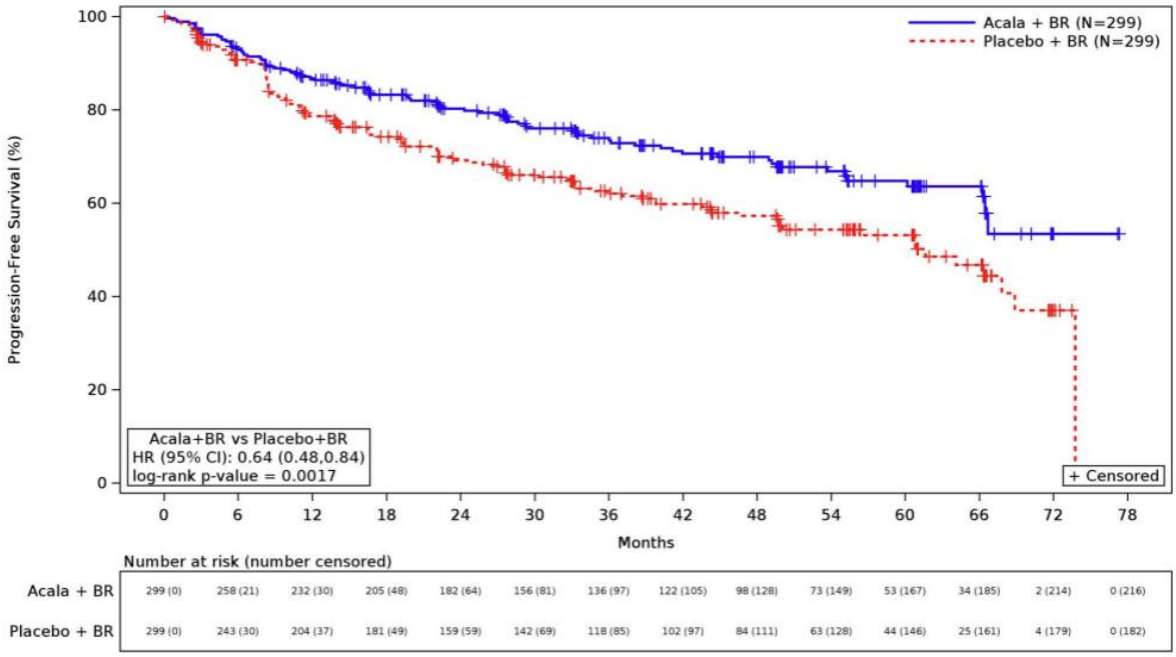
PFS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for OS from the ECHO trial (censoring COVID-19 deaths) (data cut-off: February 2024). A summary of the observed trial data and corresponding KM curves can be found below (see Table 33 and Figure 15).

Table 33: Analysis of IRC PFS from the censoring COVID-19 deaths analysis of ECHO

	ABR (N=299)	PBR (N=299)
Total events, n (%)	83 (27.8)	117 (39.1)
Censored, n (%)	216 (72.2)	182 (60.9)
Median PFS (95% CI) (months)	NE (66.4, NE)	61.6 (49.6, 68.9)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; CSR, clinical study report; IRC, independent review committee; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.
Reference: ECHO Interim CSR (11).

Figure 15: KM plot for IRC PFS (FAS: censoring COVID-19 death)



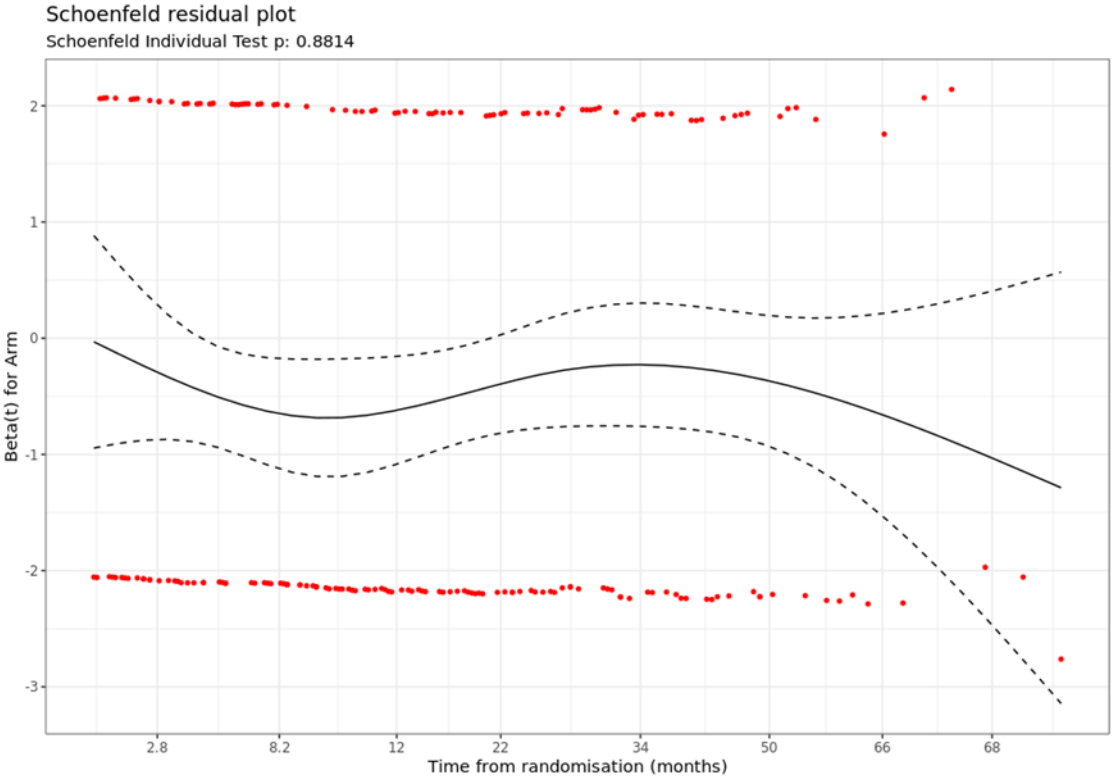
Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; KM, Kaplan–Meier; PFS, progression-free survival.

B.3.4.2.1 Diagnostic assessment

To determine the appropriate method of extrapolation of the PFS data over the lifetime time horizon, the methods outlined in NICE DSU TSD 14 were followed (57). First, assessment of PH between the two arms was undertaken using Schoenfeld residuals (Figure 16) and log-cumulative hazards plots (Figure 17). The Schoenfeld residual test, presented in Figure 16, reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. Likewise, the visual inspection of the log-cumulative hazard curves appear to be generally parallel over time. However, the Schoenfeld residuals plot shows a non-linear and non-zero

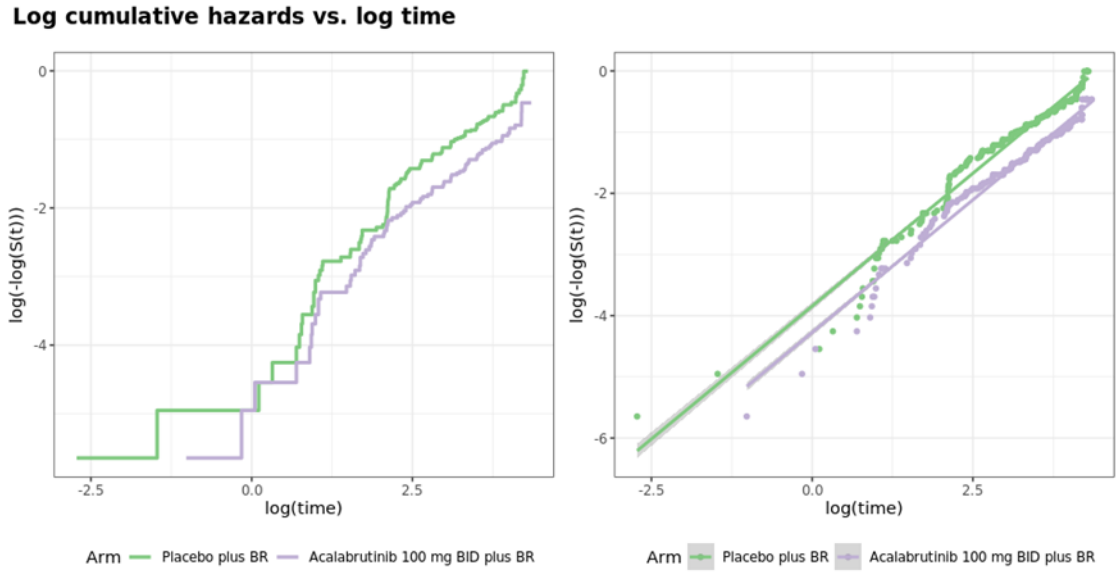
gradient for residuals over the follow-up period, therefore indicating that proportionality may not be reasonable to assume (Figure 16). Given the totality of the diagnostic assessment indicating a possibility for PH to be violated, independent parametric models were fitted to the patient-level PFS data from the ECHO trial in alignment with the NICE DSU TSD 14 (57).

Figure 16: Schoenfeld residual plots for PFS data



Abbreviations: PFS, progression-free survival.

Figure 17: Log-cumulative hazard plots for PFS data

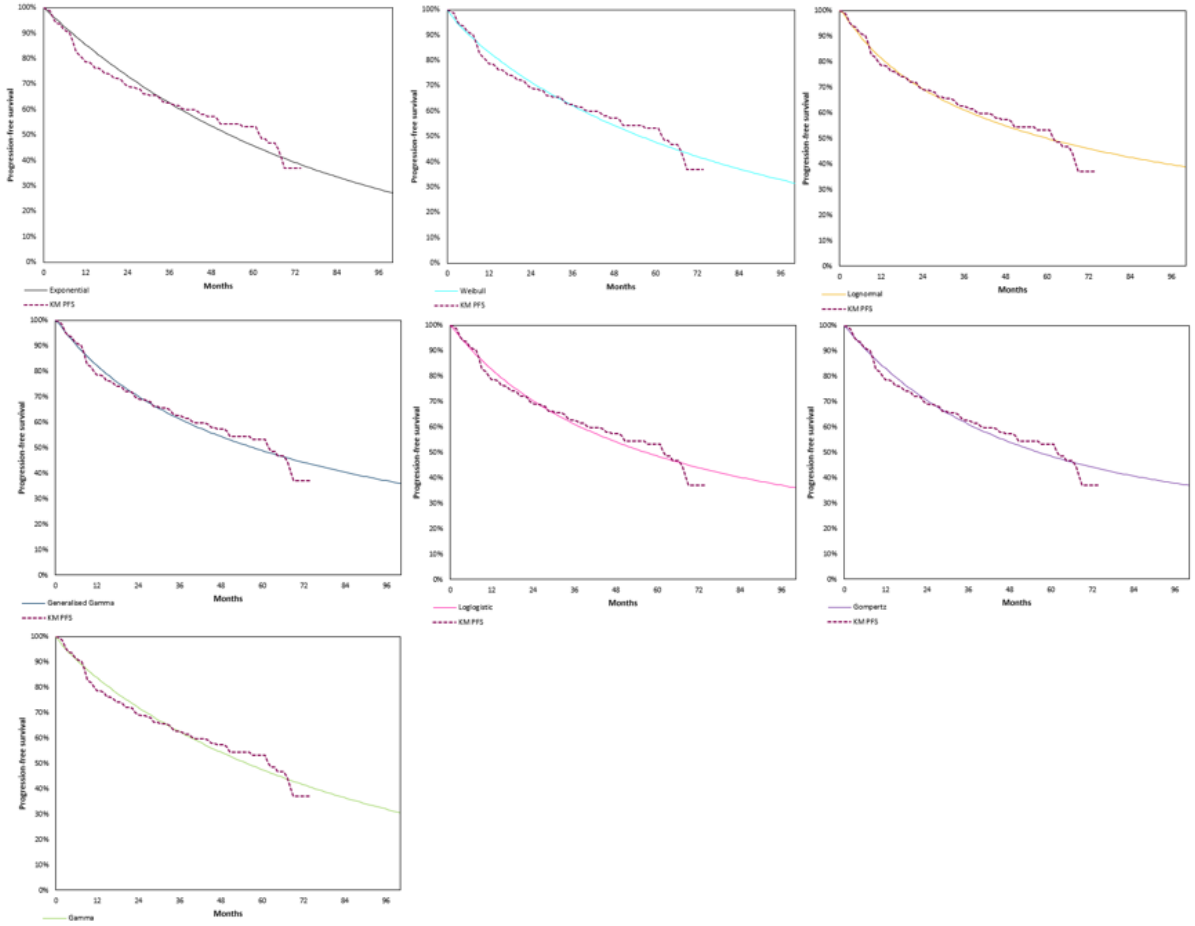


Abbreviations: BID, twice daily; BR, bendamustine + rituximab; PFS, progression-free survival.

B.3.4.2.2 Visual and statistical fit

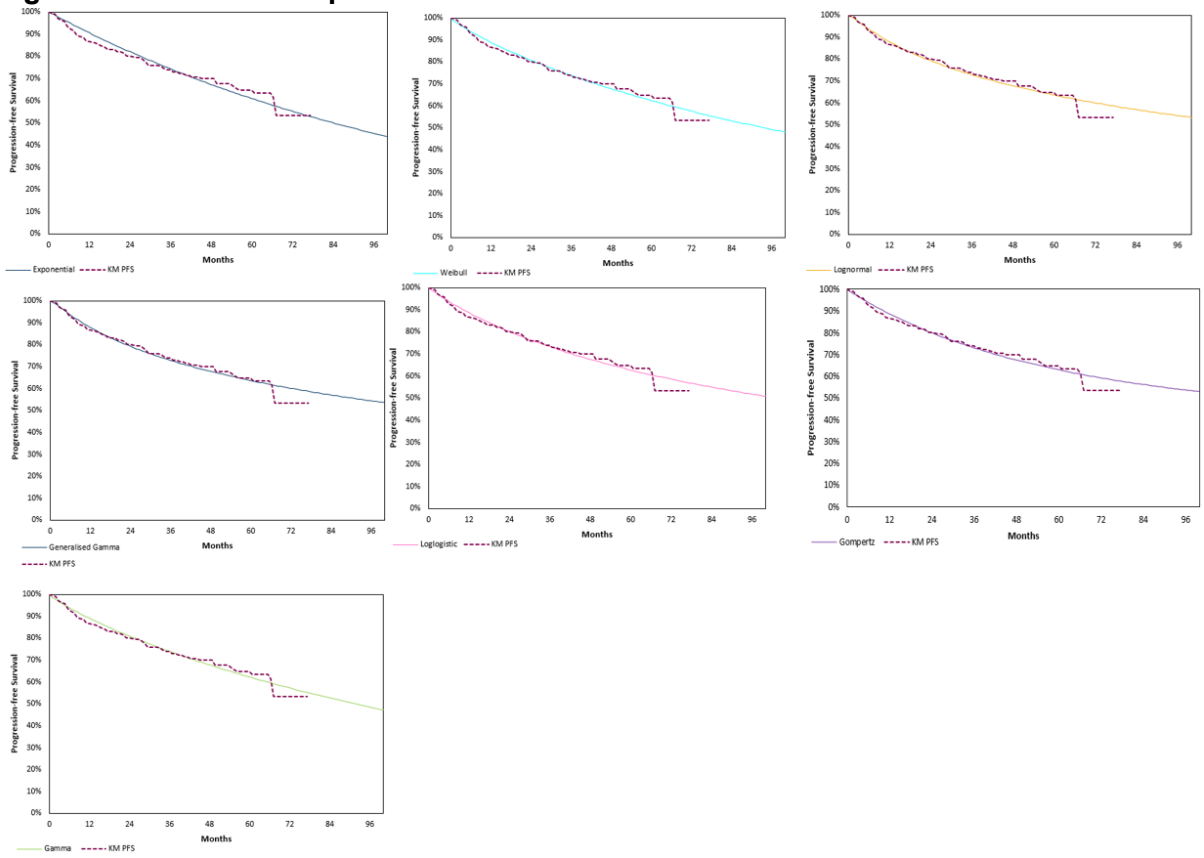
Next, parametric survival models were fitted to patient-level PFS data for each arm of the ECHO study and assessed for goodness of fit. In line with NICE DSU TSD 14 (57), the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma and Gompertz) were considered. Based on visual inspection of the extrapolations fitted in Figure 18 and Figure 19, the log-normal, generalised gamma, and log-logistic curves provided relatively better visual fits to both the ABR and PBR arms. The exponential, Weibull and Gompertz curves, to a varying degree, showed a slight underestimation in the first 24 months, with tendency to overestimate PFS towards the tail end of the KM period.

Figure 18: KM data and parametric curves for PFS data: PBR



Abbreviations: KM, Kaplan–Meier; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Figure 19: KM data and parametric curves for PFS data: ABR



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; KM, Kaplan–Meier; PFS, progression-free survival.

The statistical fit of each distribution was assessed using both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics, with the results summarised in Table 34. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. For all models used for ABR and PBR, the AIC and BIC statistics were similar, which suggests that the parametric models fit relatively well to the observed portion of the PFS data. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 34: AIC and BIC scores for parametric curves for PFS data

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	964.4	6	968.1	1	1251.9	7	1255.6	1
Weibull	964.0	5	971.4	5	1250.5	5	1257.9	5

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Log-normal	961.1	1	968.5	2	1249.1	2	1256.5	3
Log-logistic	963.2	3	970.6	3	1248.7	1	1256.1	2
Gompertz	963.5	4	970.9	4	1249.7	3	1257.1	4
Generalised gamma	963.1	2	974.2	7	1249.7	3	1260.8	7
Gamma	964.4	6	971.8	6	1251.1	6	1258.5	6

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

B.3.4.2.3 Landmark and external validation

To externally validate the PFS extrapolations, landmark from ECHO and digitised data from SHINE trial were assessed. The full set of extrapolations for PFS from both treatment arms were considered in the landmark analyses given that they all provided reasonable statistical fits.

PFS extrapolations at different landmarks are displayed in Table 36 for ABR and Table 35 for PBR. Based on the latest available landmark at approximately 6 years from ECHO and SHINE (available for PBR only) studies, the exponential, Weibull, and gamma distributions provided the most closely aligned predictions within the observed data range, with the remaining curves across both arms tending to slightly overestimate PFS.

Table 35: Landmark PFS proportions for parametric curves – PBR

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	78.6	69.2	37.0	-
SHINE	80.0	68.2	43.5	-
Exponential	85.6	73.2	39.3	21.1
Weibull	83.2	71.6	42.1	26.1
Log-normal	81.3	69.4	46.0	35.1
Log-logistic	82.5	70.3	44.0	32.0
Gompertz	83.0	70.5	44.2	33.7
Generalised Gamma	82.2	70.2	44.3	31.7

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
Gamma	83.6	72.0	41.6	24.8

Abbreviations: PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Table 36: Landmark PFS proportions for parametric curves – ABR

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	86.7	80.3	53.4	-
Exponential	90.6	82.1	55.3	37.3
Weibull	88.9	80.8	57.6	42.5
Log-normal	87.9	79.3	60.1	49.0
Log-logistic	88.6	80.1	58.7	46.5
Gompertz	88.8	80.0	59.3	48.5
Generalised Gamma	87.9	79.3	60.2	49.1
Gamma	89.1	81.0	57.3	41.4

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; PFS, progression-free survival.

B.3.4.2.4 Clinical validation

Four UK clinical experts with experience of treating MCL were consulted to clinically validate the appropriate choice of extrapolation. The method of eliciting clinical expert viewpoint is summarised in Appendix N. The majority of the experts excluded the log-normal, Gompertz, generalised gamma, and log-logistic models in the first instance, as they predicted that >30% of patients treated with BR would be alive and progression free by the 10-year timepoint. The experts explained that this was an optimistic projection of PFS for BR in patients with an average age of 71 years at diagnosis of MCL. The experts highlight that they would instead expect PFS at 10 years to be between 20–25% in the cohort of patients with previously untreated MCL treated with BR (3). As presented in Table 35, PFS extrapolations using the exponential and gamma distributions resulted in long-term projections that best aligned with expert viewpoint at Year 10.

For the long-term PFS estimates of ABR, there was no clear consensus among the clinical experts on a reasonable long-term estimation for PFS. They did, however, highlight that in alignment with the observed PFS benefit in the ECHO trial for the

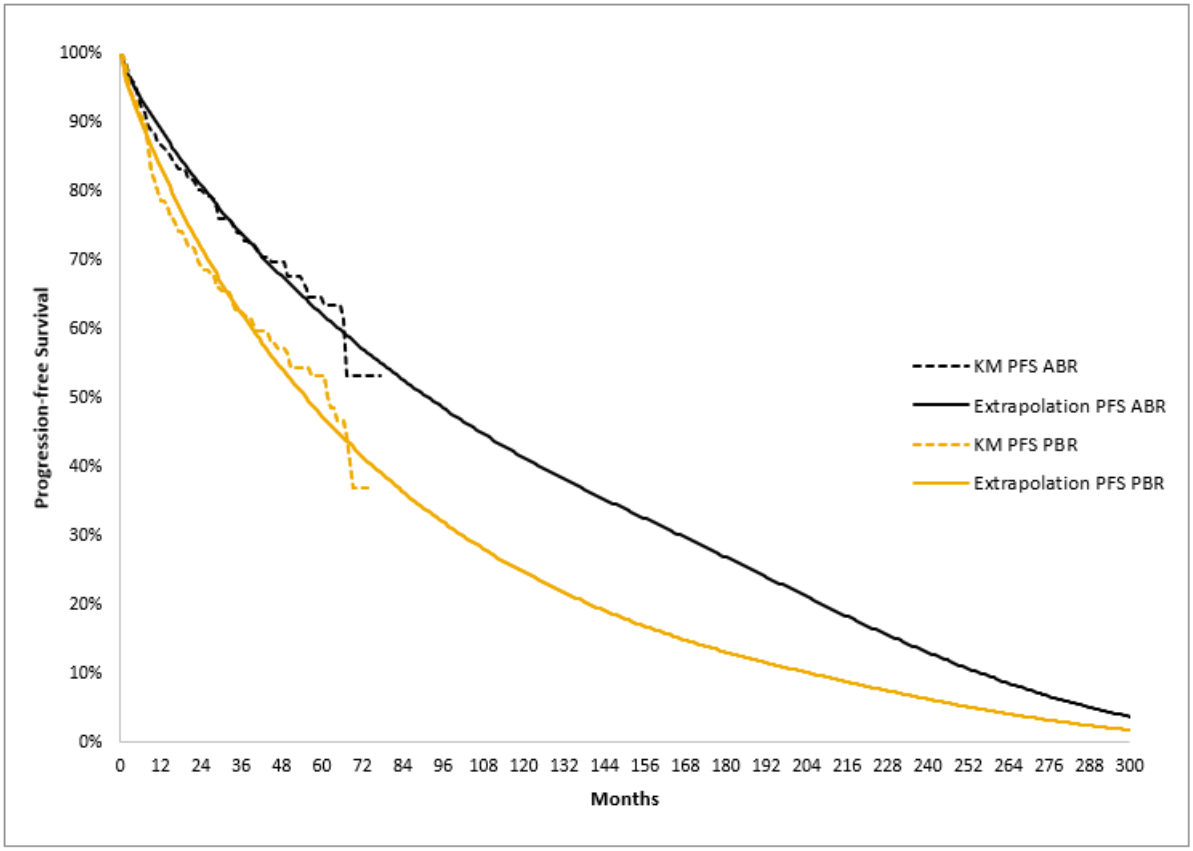
ABR arm, a clinical benefit in favour of ABR compared with BR would be expected in first-line MCL (3).

B.3.4.2.5 PFS curve selection conclusion

The selection of an appropriate parametric distribution to PFS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness of fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14 (57), the same distribution was preferred across both treatment arms; therefore, the final selection considered models that were appropriate to select for both treatment arms.

Based on the goodness-of-fit assessment, none of the distributions had a substantially improved fit relative to others. However, when expert feedback was considered, the log-normal, Gompertz, generalised gamma, and log-logistic were deemed to overestimate long-term PFS and could therefore be excluded. Among the remaining exponential and gamma distributions, most clinical experts preferred the relatively more conservative long-term estimate of PFS based on the exponential distribution (~21% vs ~25% for the gamma distribution at Year 10). However, the expert preference for an exponential curve for both treatment arms is at odds with the visual and diagnostic assessments (see Sections B.3.4.2.1 and B.3.4.2.2) – the former showed the exponential as the relatively worse fitting curve, and the latter suggested the possibility for the PH assumption to be violated for PFS. On this basis, the gamma distribution was selected for the base case extrapolation of PFS, with the more conservative exponential curve explored in a scenario analysis.

Figure 20: Base case selection (gamma) for extrapolation of PFS



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; KM, Kaplan-Meier; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

B.3.4.3 Modelling of OS for ABR and PBR

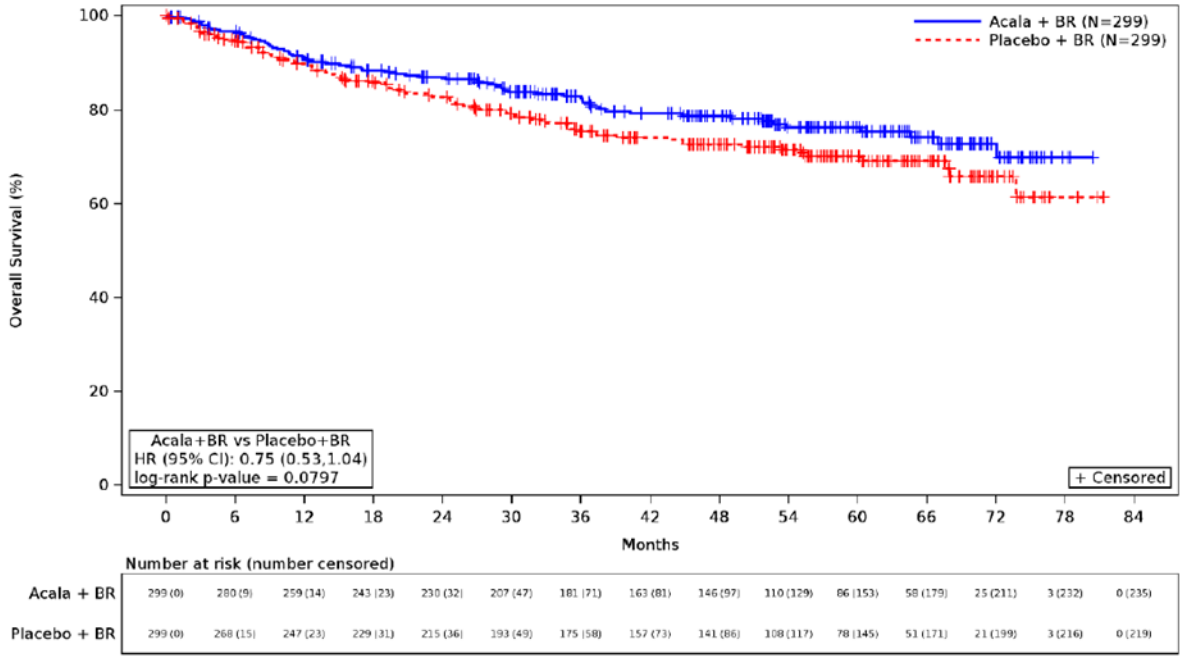
OS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for OS from the ECHO trial (censoring COVID-19 deaths) (data cut-off: February 2024). A summary of the observed trial data and corresponding KM curves can be found below (see Table 37 and Figure 21).

Table 37: Analysis of OS from the censoring COVID-19 deaths analysis of ECHO

	ABR (N=299)	PBR (N=299)
Total deaths, n (%)	64 (21.4)	80 (26.8)
Censored, n (%)	235 (78.6)	219 (73.2)
Median OS (95% CI) (months)	NE (NE, NE)	NE (73.8, NE)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; CSR, clinical study report; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab.
Reference: ECHO Interim CSR (11).

Figure 21: KM plot for OS (FAS: censoring COVID-19 death)

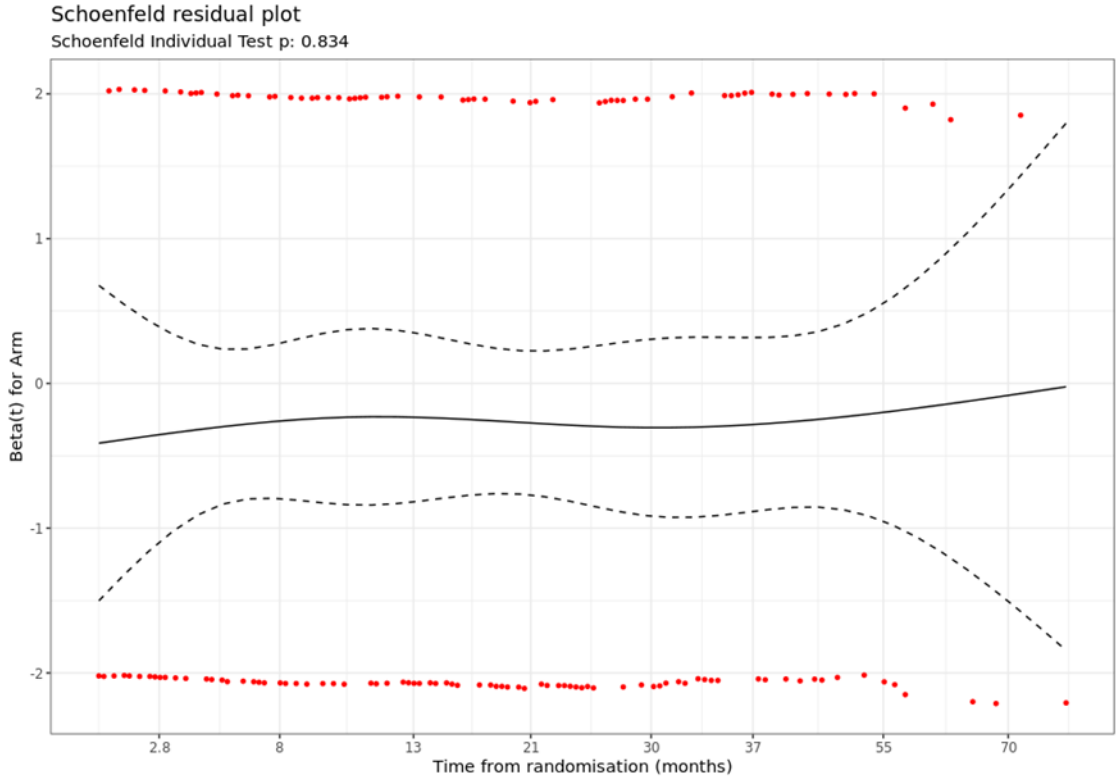


Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; KM, Kaplan–Meier; OS, overall survival.

B.3.4.3.1 Diagnostic assessment

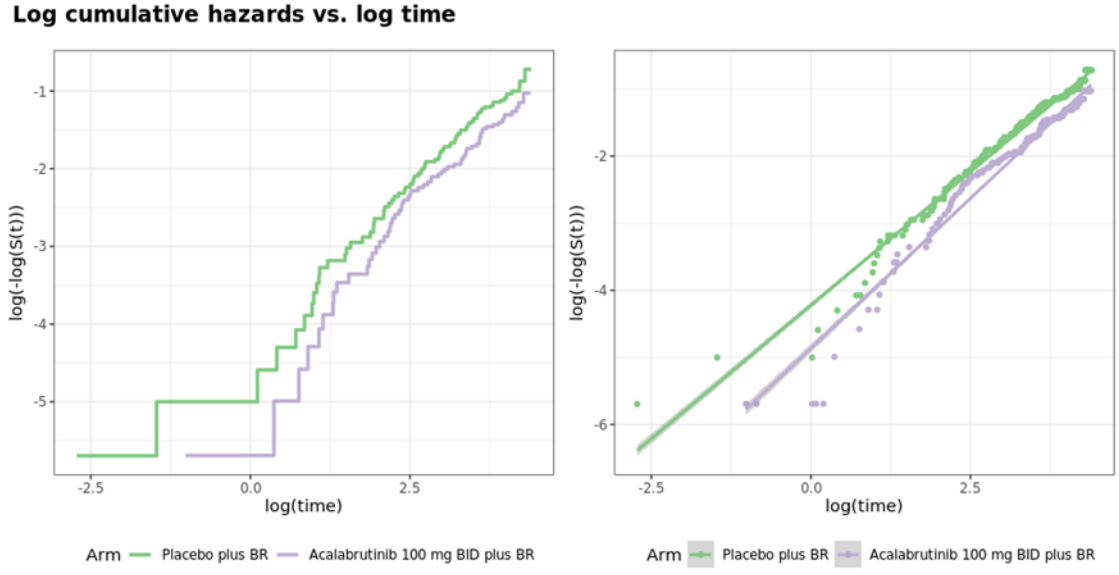
Following the same approach used for PFS modelling, and in line with NICE DSU TSD 14 (57), assessment of PH for OS in the ECHO trial was undertaken, followed by consideration of the best fitting parametric models for long-term extrapolation. First, assessment of PH between the two arms was undertaken using Schoenfeld residuals and log-cumulative hazards plots. The Schoenfeld residual test, presented in Figure 22 reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. Likewise, the visual inspection of the log-cumulative hazard curves appear to be generally parallel over time. However, the Schoenfeld residuals plot shows that a non-linear and non-zero gradient for residuals emerges at the tail of the plot, therefore indicating that proportionality may not be reasonable to assume (Figure 23). On balance, the diagnostic assessment implies a possibility for PH to be violated, and for consistency with the approach taken for PFS, independent parametric models were fitted to the patient-level OS data from the ECHO trial.

Figure 22: Schoenfeld residual plots for OS data



Abbreviations: OS, overall survival.

Figure 23: Log-cumulative hazard plots for OS data



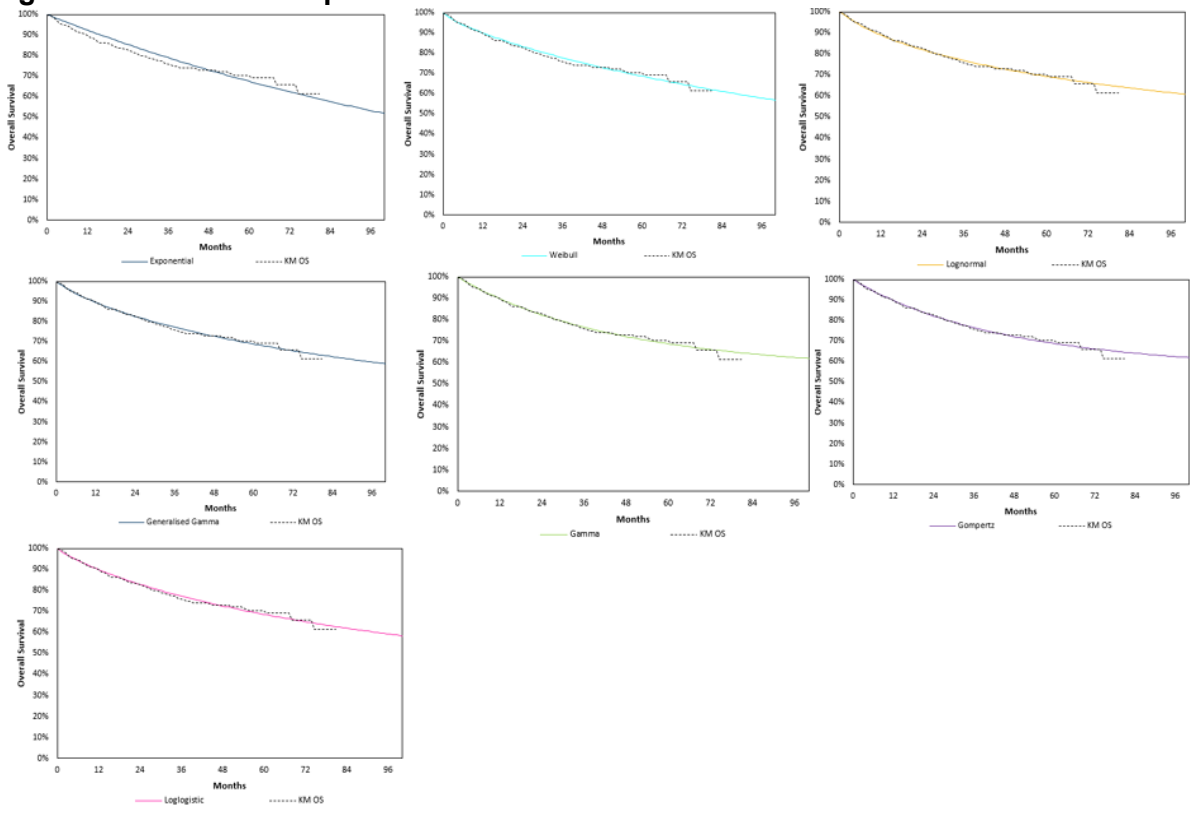
Abbreviations: BID, twice daily; BR, bendamustine + rituximab; OS, overall survival.

B.3.4.3.2 Visual and statistical fit

Similarly, parametric survival models were also fitted to patient-level OS data for each arm of the ECHO study and assessed for visual and goodness of fit. In line with NICE DSU TSD 14 (57), the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma, and Gompertz) were considered.

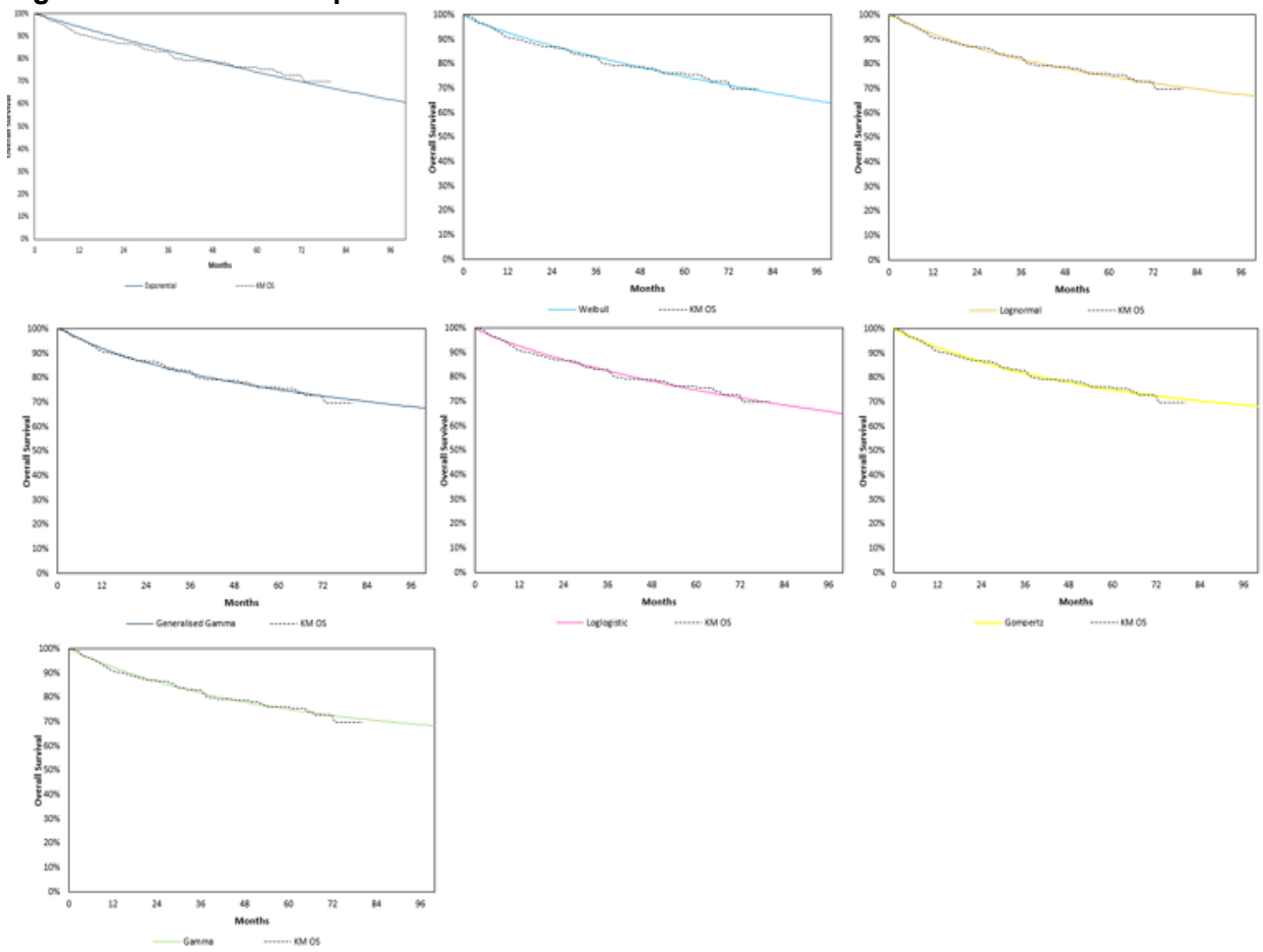
Based on visual inspection of the extrapolations fitted in Figure 24 and Figure 25, the log-normal, generalised gamma, loglogistic, and Gompertz curves provided relatively better visual fits to both the PBR and ABR arms. The exponential and to a lesser extent, the Weibull curves, appeared to slightly overestimate survival during the initial part of the observed period, with slight underestimation towards the tail end of the KM period, particularly in the PBR arm.

Figure 24: KM data and parametric curves for OS data: PBR



Abbreviations: KM, Kaplan–Meier; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Figure 25: KM data and parametric curves for OS data: ABR



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; KM, Kaplan–Meier; OS, overall survival.

The statistical fit of each distribution was assessed using both the AIC and BIC goodness-of-fit statistics, with the results summarised in Table 38. The best statistical fits are distributions with the lowest values, indicating the most parsimonious fit to the data. For all models used for ABR and PBR, the AIC and BIC statistics were similar, which suggests that the parametric models provided a relatively similar fit to the observed portion of the PFS data. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 38: AIC and BIC scores for parametric curves for OS data

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	808.4	6	812.1	1	966.3	7	970.0	3
Weibull	808.1	5	815.5	5	962.7	4	970.1	5
Log-normal	805.1	1	812.5	2	962.6	3	970.0	3
Log-logistic	807.2	4	814.6	4	961.7	2	969.1	2
Gompertz	806.4	2	813.8	3	961.4	1	968.8	1
Generalised gamma	806.9	3	818.0	7	963.6	6	974.7	7
Gamma	808.4	6	815.8	6	963.2	5	970.6	6

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PBR, placebo, bendamustine, rituximab.

B.3.4.3.3 Landmark and external validation

To externally validate the OS extrapolations, landmark from ECHO (censoring COVID-19 deaths) and digitised data from the SHINE trial were assessed. The full set of extrapolations for OS considered in the visual and diagnostic assessment from both treatment arms were included in the landmark analysis.

OS extrapolations at different landmarks are displayed in Table 39 for PBR and Table 40 for ABR. Based on the latest available landmark at approximately 6 years from ECHO and SHINE studies, the gamma, Weibull, generalised gamma, and log-logistic distributions provided predictions within the range of observed datasets for the PBR arm. For the ABR arm, with the exception of the exponential, most of the curves provided a close approximation to the observed 6-year OS from ECHO.

Table 39: Landmark OS proportions for parametric curves – PBR

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	89.9	82.8	65.9	-
SHINE	87.5	83.0	63.1	-
Exponential	92.5	85.5	62.5	45.6
Weibull	90.1	83.4	64.8	52.0
Log-normal	89.0	82.0	66.5	55.1
Log-logistic	89.9	82.9	65.1	53.4
Gompertz	89.9	82.3	66.2	55.0

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
Generalised Gamma	89.6	82.7	65.5	53.9
Gamma	90.2	83.6	64.6	51.2

Abbreviations: OS, overall survival; PBR, placebo, bendamustine, rituximab.

Table 40: Landmark OS proportions for parametric curves – ABR

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	91.0	87.0	72.8	-
Exponential	94.2	88.7	69.9	55.1
Weibull	92.8	87.5	71.3	58.6
Log-normal	92.3	86.5	72.3	60.0
Log-logistic	92.7	87.1	71.5	59.2
Gompertz	92.5	86.6	72.4	60.2
Generalised Gamma	92.1	86.3	72.5	60.2
Gamma	92.9	87.6	71.2	58.2

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; OS, overall survival.

B.3.4.3.4 Clinical validation

UK clinical experts with experience of treating MCL were consulted to clinically validate the appropriate choice of extrapolation for OS. The majority of the experts excluded the log-normal, Gompertz, generalised gamma, and log-logistic models, as these predicted that >50% of patients treated with BR would be alive by the 10-year timepoint. Some experts highlighted that this was an optimistic projection of OS, and instead would expect survival at 10 years for those treated with BR to be between 45–50%. Based on this feedback, the exponential and gamma curves provided the most clinically plausible estimates, with the remaining distributions overestimating OS for PBR.

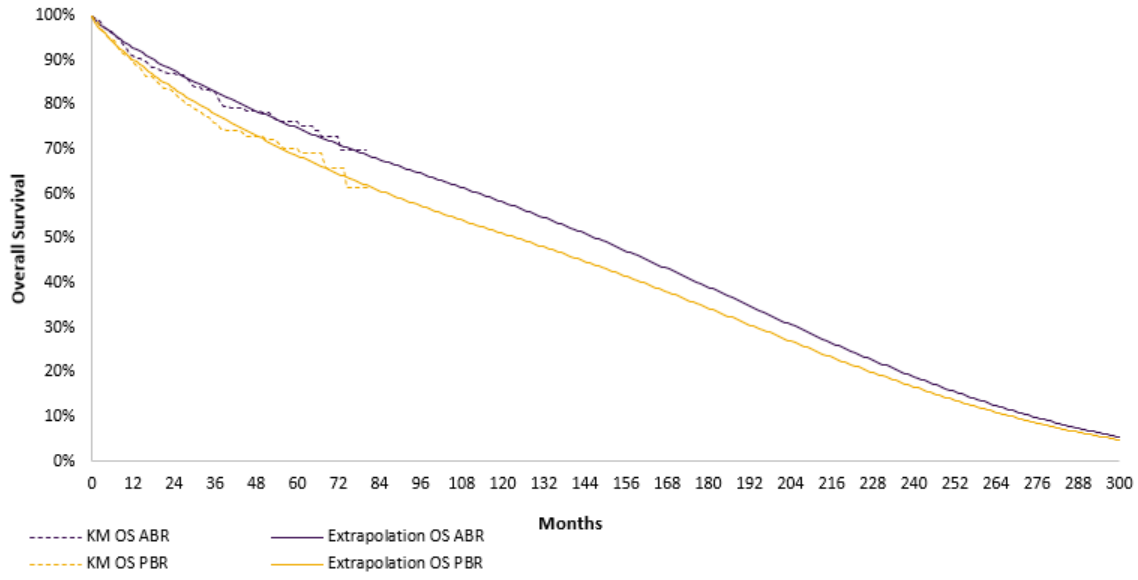
Similar to the feedback for PFS, experts shared that an OS benefit in favour of ABR was clinically plausible but that there was no single consensus on the long-term expectations of OS for ABR based on the ECHO study. On this basis, the majority of clinicians advised on the use of the more conservative OS model predictions for ABR (i.e. exponential and gamma).

B.3.4.3.5 OS curve selection conclusion

The selection of an appropriate parametric distribution of OS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness of fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14 (57), the same distribution was preferred across both treatment arms, therefore the final selection considered models that were appropriate to select for both treatment arms.

Based on visual assessment, the exponential and Weibull curves provided relatively worse fits to the observed OS data. The goodness-of-fit assessment, however, suggested that none of the distributions had a substantially improved fit relative to others. When expert feedback is considered, the log-normal, Gompertz, generalised gamma, and log-logistic models were deemed to overestimate long-term OS and could therefore be excluded. Among the remaining distributions, the exponential and gamma distributions provided the most conservative long-term estimate of OS. Given that the diagnostic assessment for OS (see Section B.3.4.3.1) was suggestive of PH violation, the gamma distribution was selected for the base case extrapolation of OS, with the more conservative exponential curve explored in a scenario analysis.

Figure 26: Base case selection (gamma) for OS extrapolation



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; KM, Kaplan–Meier; OS, overall survival; PBR, placebo, bendamustine, rituximab.

B.3.4.4 TTD for ABR and PBR

In both the ABR and PBR regimens, the BR component was administered for a fixed duration (i.e. for a maximum of 6 cycles). Therefore, costing for BR in the model was applied according to this specified treatment duration. For acalabrutinib, however, treatment could be given until progression or unacceptable toxicity and the extrapolation of TTD was used, therefore it was required to inform the acalabrutinib costing over the lifetime horizon. The use of TTD results to estimate drug cost reflect the impact of delayed disease progression and tolerability on treatment duration.

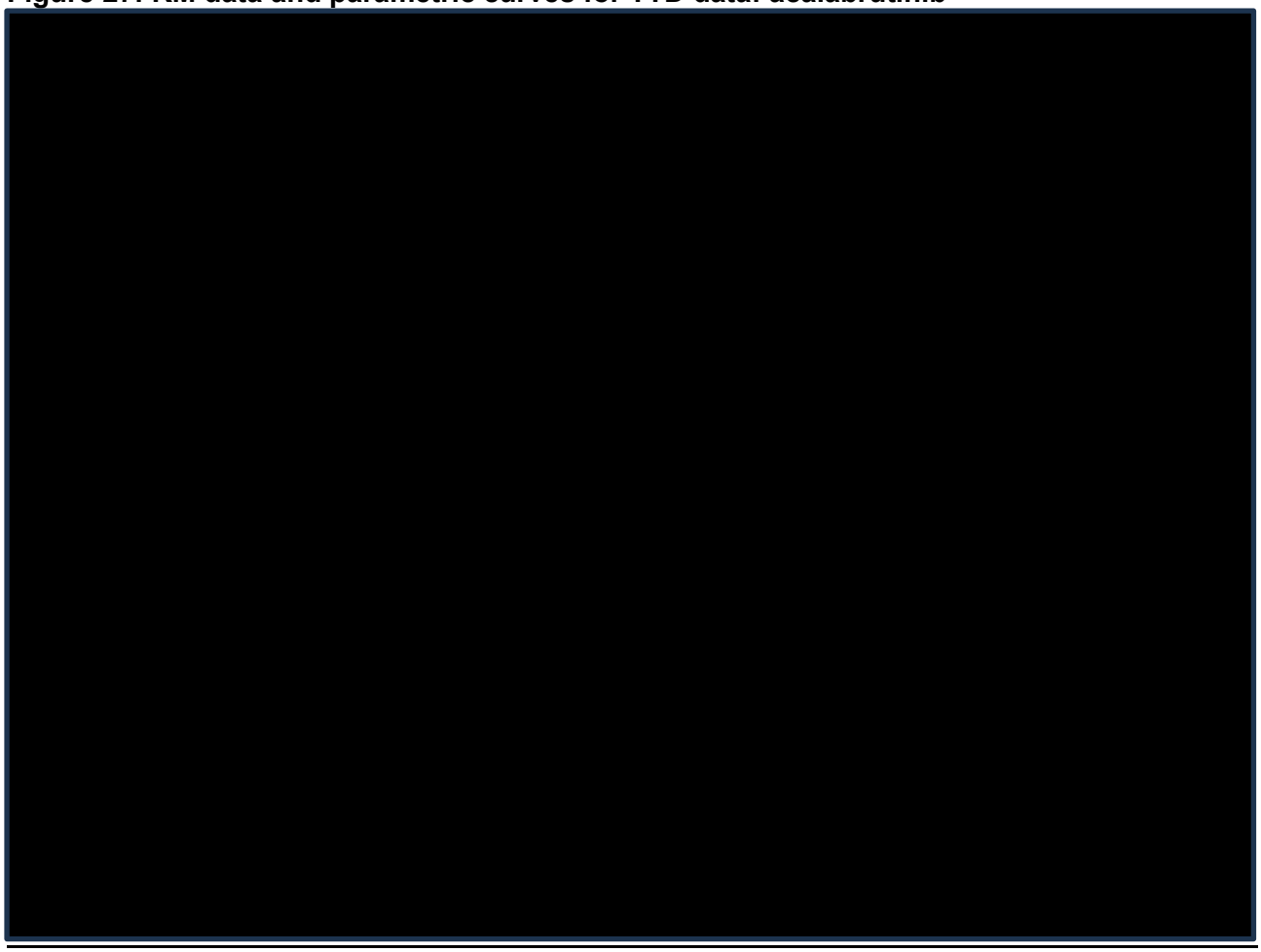
Following ABR or PBR, patients with complete or partial response in the ECHO trial received maintenance rituximab. The TTD KM curves for rituximab (which capture the time during which rituximab was given as part of ABR and PBR, i.e. in the induction phase, in addition to the maintenance phase) showed that almost all patients had discontinued by the end of the trial follow-up. Given the duration of the rituximab TTD data, the KM estimates were directly used in the model, and no extrapolations were needed. The rituximab TTD data were used to cap patients' time on treatment when receiving BR.

In order to model TTD for the acalabrutinib component of ABR over the time horizon in the model, parametric curves were fitted to patient-level data from the ECHO trial (censoring COVID-19 deaths), consistent with the OS and PFS endpoints. Sections B.3.4.4.1.1 and B.3.4.4.1.2 detail the curve selection process for the acalabrutinib TTD.

B.3.4.4.1.1 Visual and statistical fit

The visual and goodness of fit of the fitted patient-level data from the ECHO trial for the censoring COVID-19 deaths analysis was assessed for TTD. With the exception of the exponential curve, all the extrapolations (Figure 27) provided relatively reasonable visual fit to the ABR arm. The exponential showed an overestimation in the first 24 months, with tendency to underestimate TTD towards the tail end of the KM period.

Figure 27: KM data and parametric curves for TTD data: acalabrutinib



Abbreviations: KM, Kaplan–Meier; TTD, time to discontinuation.

The statistical fit of each distribution was assessed based on AIC and BIC goodness-of-fit statistics, with the results summarised in Table 41. Similar to the visual assessment, the exponential based on its AIC and BIC scores was the worst-fitting curve to the observed TTD data for ABR. All other curves provided a reasonable fit.

Table 41: AIC and BIC scores for parametric curves for TTD data

Distribution	Acalabrutinib			
	AIC		BIC	
	Result	Rank	Result	Rank
Exponential	1723.3	7	1727.0	7
Weibull	1707.3	4	1714.7	3
Log-normal	1705.2	1	1712.7	1
Log-logistic	1706.3	3	1713.7	2
Gompertz	1710.7	6	1718.1	6

Distribution	Acalabrutinib			
	AIC		BIC	
	Result	Rank	Result	Rank
Generalised gamma	1706.0	2	1717.1	5
Gamma	1709.0	5	1716.4	4

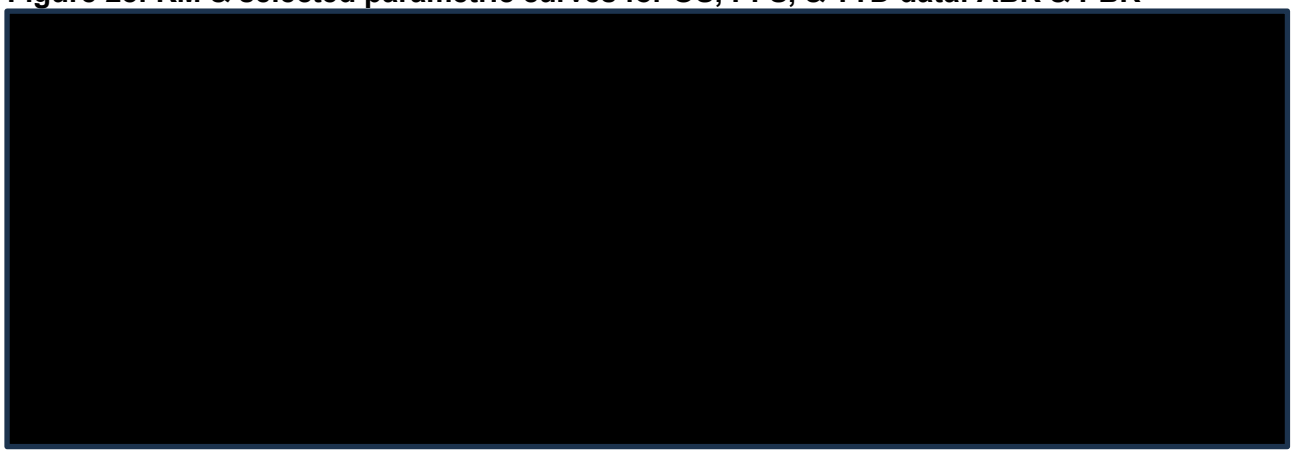
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to discontinuation.

B.3.4.4.1.2 TTD curve selection conclusion

The selection of an appropriate parametric distribution to TTD data for acalabrutinib was based on a combination of visual inspection of the fitted curves and comparison of statistical goodness of fit. Based on the AIC and BIC scores, the log-normal, generalised gamma distribution resulted in the lowest scores, indicating best statistical fit. However, the log-normal hazard function assumed a decreasing hazard over time, generating a long tail in the extrapolated curve for ABR. This assumption was not considered plausible and would result in the TTD curve crossing PFS in the long term, which lacks face validity and is not supported by clinical practice.

Given the known trend for TTD in the ECHO study and the summary of product characteristics for ABR, it is recommended that treatment is continued until either disease progression or toxicity is observed. The Weibull distribution for treatment discontinuation, which does not exceed PFS extrapolation over the time horizon, was deemed appropriate for the base case. A cap was also applied to all treatment discontinuation curves in the model, such that time on treatment does not exceed PFS over the time horizon. The selected OS, PFS, and TTD curves for the ABR and the selected OS and PFS curves for the PBR arm are plotted together in Figure 28.

Figure 28: KM & selected parametric curves for OS, PFS, & TTD data: ABR & PBR



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.
Note: Selected parametric curves presented here have been corrected for background mortality.

The log-normal model for TTD is explored in scenario analyses.

B.3.4.5 PFS, OS, and TTD for R-CHOP

As the ECHO trial only compared ABR with PBR, efficacy estimates for R-CHOP were derived from the results of the ITC involving the ECHO, BRIGHT (BR versus R-CHOP (26)), and StiL NHL1 (BR versus R-CHOP (40)) trials, as R-CHOP is considered another relevant comparator in clinical practice in the UK. Further details on the ITC are provided in Section B.2.9 and Appendix D.

The relative efficacy for R-CHOP is expressed as the HR versus BR. When the HR is >1, R-CHOP is associated with worse efficacy outcomes in comparison with BR. The HRs for R-CHOP versus BR derived from the ITC, using the COVID-19-censored analysis of ECHO, are reported in Table 42. For TTD, a pragmatic assumption was made that TTD for R-CHOP can be estimated by applying the same HR as that used for PFS versus BR.

Table 42: Hazard ratios of clinical outcomes for R-CHOP versus BR (fixed effects)

Efficacy estimate	Hazard ratio (R-CHOP versus BR)	Lower bound	Upper bound
OS	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]

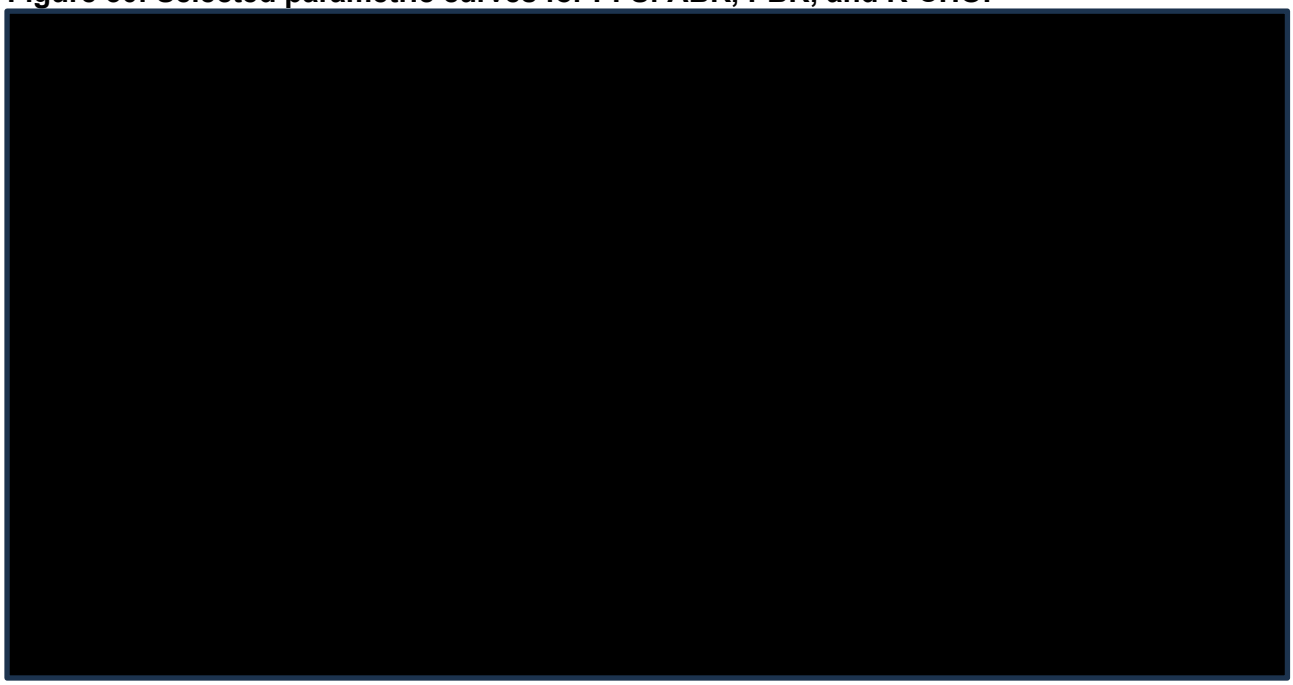
Abbreviations: BR, bendamustine + rituximab; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

OS, PFS and TTD outcomes were generated for R-CHOP based on the HR from the ITC applied to the parametric curves for BR, (see Figure 29 and Figure 30), which demonstrate extrapolations for R-CHOP sitting below BR in line with the results from the ITC and expectations from clinicians (Section B.3.4.3.4).

Figure 29: Selected parametric curves for OS: ABR, PBR, and R-CHOP

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; OS, overall survival; PBR, placebo, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
Note: Selected parametric curves presented here have been corrected for background mortality.

Figure 30: Selected parametric curves for PFS: ABR, PBR, and R-CHOP



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
Note: Selected parametric curves presented here have been corrected for background mortality.

A scenario analysis was also explored, setting the HRs for R-CHOP to their lower bounds to test the robustness of the cost-effectiveness results to conservative estimates for the relative efficacy of R-CHOP.

B.3.4.6 General population mortality

General population survival was based on the most recent life tables published annually by the UK's Office for National Statistics (53). These tables provide survival estimates for transition probabilities by age and gender. The dataset that was used is based on data for England & Wales from 2020 to 2022, adjusting for the proportion of males and females in the ECHO trial.

The OS, PFS, and TTD curves in the model were adjusted for background mortality to ensure that for every cycle, event risks were always greater than or equal to the risk of death in the age- and gender-matched general population. Additionally, to avoid negative state occupancy in the PSM, PFS, and TTD curves, these were assumed to be equal to or less than OS.

B.3.4.7 Summary

Given that the COVID-19 pandemic has now ended, the data censored for COVID-19-related deaths from ECHO is considered the most appropriate for the base case analysis in the cost-effectiveness model.

The selection of an appropriate parametric distribution to model OS and PFS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness of fit (using AIC/BIC statistics), and external validity checks, and through validation from clinicians and expected survival from other data sources.

Based on this, the gamma model was selected for use within the base case for PFS and OS of both ABR and PBR, whilst R-CHOP was estimated via an HR derived from the network meta-analysis (NMA) (see Figure 29 and Figure 30). A conservative approach to selecting the survival distributions used in the base case analysis was deemed most appropriate to align with clinical expectations. On balance, the gamma model for both PFS and OS were more aligned with clinician expectations but also considered the visual fit to the observed ECHO trial data and statistical fit with the exponential curves also being explored as scenario analyses.

For acalabrutinib TTD, the Weibull model was selected for the base case analysis based on it being a good visual fit to the observed ECHO trial data and generating long-term estimates not exceeding PFS. Alternative survival distributions for PFS, OS, and TTD were explored as scenario analyses.

B.3.5 Measurement and valuation of health effects

B.3.5.1 HRQoL data from clinical trials

EQ-5D-5L data were collected in the ECHO trial at the following timepoints for the FAS population:

- During patient screening, within 30 days before the first administration of the study drug
- At Cycles 3, 5, and 8 of the treatment phase
- Every 4 cycles of the treatment phase thereafter

- During post-treatment disease follow-up, after 12 weeks from the last visit until disease progression, study withdrawal, loss to follow-up, or study termination by the sponsor

B.3.5.1.1 Mapping

A mixed model for repeated measures (MMRM) analysis was used to estimate HSUVs for the progression-free and progressed disease health states from the collected EQ-5D-5L data, using the EQ-5D-5L UK value set and cross-walked to EQ-5D-3L using the methodology in Hernandez-Alava et al. (2023) (58). This is in accordance with the NICE DSU TSD 22 (59), which notes that if data are collected using the EQ-5D-5L, they should be mapped to the EQ-5D-3L value set using this mapping function.

An MMRM method was used to model HSUVs, to account for repeated measurements in the study. This was performed on a dataset excluding observations recorded after the time of censoring for progression, as observations during censoring have an unknown health status.

In total, four MMRMs were fitted to the patient-level data. These included models with adjustment for health state only, treatment arm only, and health state and treatment arm with and without interaction terms. For input to the economic model, the mean utility (and its associated variance) by treatment arm and/or health state were estimated via least squares or marginal means from the best fitting models.

According to AIC, the best fitting MMRM was the model that contained a covariate for progression status only. [redacted]. The MMRM analysis was performed using the restricted maximum likelihood method, with progression status included as a covariate for fixed effects.

The final HSUVs derived from ECHO trial data are reported in the marginal (least square) means and 95% CIs for the FAS population, in Table 43. As discussed in Section B.3.5.4, there are limitations with these data that are adjusted for in the model base case.

Table 43: HSUVs from ECHO trial data

	Progression free	Lower bound, upper bound	Progressed disease	Lower bound, upper bound
EQ-5D-3L (modelled using MMRM)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HSUV, health state utility value; MMRM, mixed model for repeated measures.
Reference: ECHO EQ-5D MMRM analysis (data on file) (60).

B.3.5.2 HRQoL studies

The SLR identified one source reporting alternative HSUVs in MCL (see Appendix H). Six additional sources were identified during a targeted search of NICE technology appraisals (TAs). Three of these were in 1L and four were in R/R MCL. Of these, only two appraisals reported utilities from a UK perspective: LYM-3002, utilised in TA370 (23), and RAY/MCL-3001 and SPARK/MCL-2001, utilised in TA502 (45). Both submissions estimated HSUVs from trial data using a mixed model. The HSUVs are reported in Table 44.

Table 44: HSUVs from literature sources

	Progression free	Lower bound, upper bound	Progressed disease	Lower bound, upper bound
TA370 (23)	0.764	0.746, 0.781	0.693	0.639, 0.744
TA502 (45)	0.780	0.762, 0.799	0.680	-0.691, 0.770

Abbreviations: HSUV, health state utility value.

B.3.5.3 Adverse reactions

TEAEs are included in the model for 1L treatments and are associated with a utility decrement to patients' QoL. Incidence rates for ABR and PBR are sourced from the ECHO trial (11), and TEAE rates for R-CHOP are sourced from LYM-3002 (27).

Specifically, TEAEs with a severity of Grade ≥3 that occurred in more than 5% of patients in either the ABR or BR arms of the ECHO trial are included in the model. To align with the cut-off criteria used for ABR and BR, TEAEs for R-CHOP were included if they occurred in more than 5% of patients in the R-CHOP arm of LYM-3002, or in the ABR and BR arms of the ECHO trial.

TEAEs included in the model are presented in Table 45.

Table 45: TEAE incidence rate (Grade ≥3) inputs in the cost-effectiveness model

AE	ABR, %	PBR, %	R-CHOP, %
Anaemia	9.4	10.1	13.6
Febrile neutropenia	5.1	2.4	13.6
Leukopenia	5.7	6.1	29.3
Lymphopenia	2.7	5.4	8.7
Neutropenia	35.4	37.0	66.9
Pneumonia	8.8	6.4	4.5
Thrombocytopenia	6.1	5.4	5.8
COVID-19 pneumonia	15.5	10.1	0.0
COVID-19	13.5	10.4	0.0
Rash maculo-papular	10.1	3.7	0.0
Neutrophil count decreased	15.5	10.1	0.0
White blood cell count decreased	10.1	3.7	0.0
Lymphocyte count decreased	6.4	9.8	0.0
Hypertension	5.4	8.4	0.0
Source	ECHO trial (11)	ECHO trial (11)	LYM-3002 (27)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; CSR, clinical study report; PBR, placebo, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; TEAE, treatment-emergent adverse event.

B.3.5.3.1 Adverse event utility decrements

TEAE utility decrements are sourced from previous submissions in previously untreated MCL and 1L CLL. They are adjusted by the duration of the event and applied in the first cycle of the model. AE disutilities and durations are presented in Table 46, with the total AE utility decrements by treatment arm provided in Table 47.

NICE TA370 was chosen as the source for utility decrements, as these were collected directly via the pivotal trial, which measured utility using EQ-5D at each cycle of treatment (42). For hypertension and infections, these were not reported in TA370, therefore, desk research to identify disutility values for these events in recent NICE appraisals was conducted, and values from TA931 and TA891 were used, respectively. For the COVID-19 events and rash maculo-papular, disutility values could not be sourced; therefore, these were assumed to be equal to the average of the other Grade 3+ disutility values. For lab-based AEs (based on results from blood tests, e.g. decreased neutrophile count), the model assumes the same utility

decrement and cost as for the associated condition (e.g. neutropenia); these are set to incur a disutility of 0 in a scenario analysis.

Table 46: AE utility decrements and duration inputs in the cost-effectiveness model

AE	Disutility	Duration (days)	Source
Neutropenia	-0.032	9.1	TA370
Thrombocytopenia	-0.038	10.08	TA370
Anaemia	-0.007	9.73	TA370
Leukopenia	-0.042	9.45	TA370
Lymphopenia	-0.065	16.73	TA370
Febrile neutropenia	-0.014	8.33	TA370
Pneumonia	-0.058	16.03	TA370
COVID-19 pneumonia	-0.032	23.78	Assumed to equal an average of other disutilities
COVID-19	-0.032	23.78	
Rash maculo-papular	-0.032	23.78	
Neutrophil count decreased	-0.032	9.10	TA370
White blood cell count decreased	-0.042	9.45	TA370
Lymphocyte count decreased	-0.065	16.73	TA370
Hypertension	-0.163	15.09	TA931

Abbreviations: AE, adverse event.

Table 47: Total AE QALY decrements by treatment arm

	ABR	PBR	R-CHOP
Total AE QALY decrements	-0.002354	-0.002254	-0.001355

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; PBR, placebo, bendamustine, rituximab; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

B.3.5.4 HRQoL data used in the cost-effectiveness analysis

The review of the published literature provided utility estimates from a UK perspective that were relevant to different health states in the model. However, to align with the modelled population, the EQ-5D-5L measured in the ECHO trial was considered the most appropriate source to include in the model.

The data collection schedule for EQ-5D-5L in ECHO included the routine measurement of data up to progression only. [redacted]

[redacted]

[redacted]

[redacted]. As a result, the estimates of utility for progressed disease in ECHO were limited and likely underestimate the true impact of progression in this population. Therefore, alternative HSUVs were explored in the model to parameterise the HSUV for progressed disease patients.

The difference between the HSUVs for the progression-free and progressed disease health states in the most recent MCL NICE technology appraisal, TA502 (45), was estimated and applied to the progression-free utility value estimated in the ECHO trial. The decrement calculated and the resulting utility value for the progressed disease health state are presented in Table 48.

Table 48: Calculated HSUVs for progressed disease using TA502

	Absolute difference between progression-free and progressed disease HSUV	Progression-free HSUV from ECHO	Resulting HSUV for progressed disease
Utility	0.100	[redacted]	[redacted]

Abbreviations: HSUV, health state utility value.

To ensure the HSUVs do not exceed those of the age-matched general population, in the model base case, the progression free utility has been capped. Considering the mean age of 71 years used in the model, the age-equivalent general population utility is 0.787; therefore, the progression free utility is capped at this. The progressed disease utility value was also adjusted to ensure the same relative difference between the progression free utility and the progressed disease utility holds (i.e. the relative difference is calculated as [redacted]). This relative difference is then applied to the progression free utility value (i.e. [redacted]). The confidence intervals used to vary health states utility in the probabilistic analysis are based on the pre-capped utility values, as per Table 48.

Table 49 summarises the utility values used in the base case cost-effectiveness analysis. Alternative HSUVs are explored in the scenario analyses, where the progression-free and progressed disease utility values from TA502 are used, or the utility values directly derived from the ECHO trial are used.

Table 49: Summary of utility values for cost-effectiveness analysis

	Utility value	95% CI	Reference in submission (section and page number)	Justification
Health state				
Progression free	[redacted]	[redacted] (pre-capped values varied, per Table 48)	Section B.3.5.1, Section B.3.5.2	Data sourced directly from the ECHO trial, capped by age-matched general population utility
Progressed disease	[redacted]	[redacted] (pre-capped values varied, per Table 48)	Section B.3.5.1, Section B.3.5.2	Data sourced from the ECHO trial and adjusted by the difference between "progression free" and "progressed disease" in TA502
Grade ≥3 AEs				
Anaemia	-0.01	-0.0057, -0.0084	Section B.3.5.3.1	Data are sourced from previous submission (TA370; TA891) (23, 51)
Febrile neutropenia	-0.01	-0.0114, -0.0169		
Leukopenia	-0.04	-0.0342, -0.0506		
Lymphopenia	-0.07	-0.0528, -0.0783		
Neutropenia	-0.03	-0.0260, -0.0386		
Pneumonia	-0.06	-0.0472, -0.0699		
Thrombocytopenia	-0.04	-0.0309, -0.0458		
COVID-19 pneumonia	-0.03	-0.0262, -0.0388		TA370, ECHO trial, TA931, model calculations
COVID-19	-0.03	-0.02620, -0.0388		
Rash maculo-papular	-0.03	-0.02620, -0.0388		
Neutrophil count decreased	-0.03	-0.02620, -0.0388		
White blood cell count decreased	-0.04	-0.0342, -0.0506		
Lymphocyte count decreased	-0.07	-0.0528, -0.0783		
Hypertension	-0.16	-0.1323, -0.1962		

Abbreviations: AE, adverse event; CI, confidence interval.

B.3.6 Cost and healthcare resource use identification, measurement, and valuation

The SLR identified a total of five publications to inform the healthcare resource use (HCRU) costs for patients with previously untreated MCL (see Appendix I). One publication reported HCRU in untreated patients (61) and the remaining in patients treated with BR, R-CHOP, ibrutinib, and rituximab (42, 62-64). Only one publication (42) reported HCRU in the UK, with the remaining reporting data from Canada, US, and Japan.

The supplementary grey literature review identified two UK submissions: one to NICE (TA370 (23)), and one to the SMC (Bortezomib SMC 1075;15 (43)). Both included cost-utility analyses that provided resource use and costs for patients with previously untreated MCL.

Total costs incurred for ABR and each comparator arm in the model are summarised in Table 50.

Table 50: Summary of total costs per cycle

	ABR (incl. confidential patient access scheme for acalabrutinib)	PBR	R-CHOP
1L model cycle costs, £			
Drug acquisition	[redacted]	698	925
Administration	804	804	549
Rituximab maintenance	937	937	937
Total 1L (per cycle)	[redacted]	**2,438**	**2,411**
HCRU costs, £ (per cycle)			
Progression-free state	468		
Progressed disease	883		
Subsequent treatment costs (2L),† £			
Drug acquisition	3,379	105,630	105,630
Administration	6,763	0	0
Total 2L (one off)	**10,143‡**	**105,630**	**105,630**
Subsequent treatment costs (3L),† £			
Drug acquisition	27,925	45,517	43,249
Administration	6,086	25,202	9,035

	ABR (incl. confidential patient access scheme for acalabrutinib)	PBR	R-CHOP
Total 3L (one off)	**34,010**	**70,719**	**52,284**
Safety costs, £			
Adverse events	3,406	2,978	3,424
End of life, £			
End-of-life care	7,441		

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; HCRU, healthcare resource use; PBR, placebo, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Applied as a one-off cost to the incident progressed disease patients per cycle.
‡ Totals have been rounded up to the nearest integer.

B.3.6.1 Intervention and comparators' costs and resource use

The per cycle costs of ABR and BR were calculated by applying acquisition costs to the dosing regimen stipulated by the ECHO trial protocol (7). The per cycle cost of R-CHOP was calculated similarly, using the dosing regimen specified by the South West Strategic Clinic Network Cancer Alliance (55). The cost per cycle was determined by combining the unit cost per mg and dose per administration or day.

All costs are presented in 2024 GBP. Where costs identified from the literature are not current, these were inflated to 2024 values using the Consumer Price Index (CPI) for health from the Office of National Statistics (65). Costs from the latest version of the NHS national schedule of costs (66) are assumed to be the presently used costs, regardless of the year of publication.

Costs were calculated for 1L treatment regimens, as summarised in Table 51 below.

Table 51: Summary of 1L treatment costs

Treatment regimen	Drug acquisition, £	Administration, £	Rituximab maintenance, £	TOTAL, £
ABR	[redacted]†	804	937	[redacted]
PBR	698	804	937	**2,438**
R-CHOP	925	549	937	**2,411**

Abbreviations: 1L, first-line; ABR, acalabrutinib, bendamustine, rituximab; PBR, placebo, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes existing confidential patient access scheme for acalabrutinib.
All numbers have been rounded to the nearest integer.

B.3.6.1.1 Drug acquisition costs

Drug acquisition costs were sourced from the drugs and pharmaceuticals electronic market information tool (eMIT) (9) in the first instance, and supplemented by British National Formulary (BNF) costs from 2024 (67). When more than one formulation was available, the model used the optimal vial combination with the lowest cost per mg (Table 53).

A price of [redacted] per pack for acalabrutinib, reflecting the existing patient access scheme discount of [redacted], has been incorporated into the drug costing calculations herein.

The total acquisition costs for 1L treatments account for fixed and continuous administration regimens. The fixed component treatment costs are calculated accounting for the total duration of each corresponding treatment, applied on a cycle basis during the period of interest. The continuous treatment costs are applied on a cycle basis until discontinuation. TTD was estimated using time on treatment data from the ECHO trial for various interventions:

- Rituximab induction and maintenance time on treatment in ABR, PBR, and R-CHOP: rituximab TTD KM data, as described in Section B.3.4.4, was used to inform rituximab use and discontinuation in ABR and PBR. For R-CHOP, rituximab maintenance discontinuation was assumed equal to BR data
- Acalabrutinib time on treatment in ABR: acalabrutinib TTD models as described in Section B.3.4.4
- Bendamustine induction time on treatment in ABR and PBR: bendamustine time on treatment was informed using the mean cycles registered for ABR and PBR in the ECHO trial (Table 52)

Table 52: Bendamustine treatment exposure in the ECHO trial

Mean (SD)	ABR (N=297)	PBR (N=297)
Cycles administered	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; PBR, placebo, bendamustine, rituximab; SD, standard deviation.

2L and 3L treatment acquisition and administration costs were applied as a one-off cost and are described in more detail in Section B.3.6.1.3.

The drug dosing schedules are displayed in Table 53. The cost per mg calculated for 1L treatment (Table 54) was applied to the total amount of drug administered per cycle (accounting for the number of administrations) to calculate the drug acquisition cost per cycle for each treatment in the model. Table 55 shows the costs for subsequent treatments.

Table 53: Drug acquisition costs

Cost component	Drugs	Strength (mg per vial/tablet)	Pack size	Mode of admin	Cost per pack, £	Cost/mg, £	Minimum cost/mg, £	Source
Intervention: ABR	Acalabrutinib	100 mg (per capsule)	60	Oral	[redacted]†	[redacted]	[redacted]	BNF 2024
	Bendamustine	25 mg (powder for infusion)	5	IV	40.86	0.33	0.25	eMIT 2024
		100 mg (powder for infusion)	1		91.99	0.92		
		100 mg (powder for infusion)	5		127.14	0.25		
	Rituximab	100 mg/10 mL (concentrate for solution for infusion vial)	2	IV	314.33	1.57	0.96	BNF 2024
		500 mg/50 mL (concentrate for solution for infusion vial)	1		785.84	1.57		
		1,400 mg/11.7 mL (solution for injection vial)	1		1,344.65	0.96		
Comparator: BR	Bendamustine	See above						
	Rituximab	See above						
Comparator: R-CHOP	Rituximab	See above						
	Cyclophosphamide	1,000 mg	1	IV	13.11	0.01	0.01	eMIT 2024

Cost component	Drugs	Strength (mg per vial/tablet)	Pack size	Mode of admin	Cost per pack, £	Cost/mg, £	Minimum cost/mg, £	Source
		(powder for solution for injection vial)						
		2,000 mg (powder for solution for injection vial)	1		27.50	0.01		
		500 mg (powder for solution for injection vial)	1		11.18	0.02		
	Doxorubicin	10 mg (10 mg/5 mL vial)	1	IV	4.20	0.42	0.09	eMIT 2024
		200 mg (200 mg/100 mL vial)	1		17.67	0.09		
		50 mg (50 mg/25 mL vial)	1		10.06	0.20		
	Vincristine	1 mg/mL (vial)	5	IV	30.08	6.02	3.84	eMIT 2024
		2 mg/2 mL (vial)	5		38.42	3.84		
	Prednisolone	25 mg (per tablet)	56	Oral	12.78	0.01	0.01	eMIT 2024
Subsequent treatment	Ibrutinib	140 mg	28	Oral	1,430.80	0.37	0.37	BNF 2024
		280 mg	28		2,861.60	0.37		

Cost component	Drugs	Strength (mg per vial/tablet)	Pack size	Mode of admin	Cost per pack, £	Cost/mg, £	Minimum cost/mg, £	Source
		420 mg	28		4,292.40	0.37		
		560 mg	28		5,723.20	0.37		
Subsequent treatment	Brexucabtagene autoleucel	1 infusion	1	IV	316,118			TA677 (46)
Subsequent treatment: R-BAC	Rituximab	See above						
	Bendamustine	See above						
	Cytarabine	100 mg/mL	5	IV	13.85	0.03	0.01	eMIT 2024
		100 mg/5 mL	5	IV	20.70	0.04		
		100 mg/10 mL	1	IV	7.76	0.08		
		200 mg/200 mL	1	IV	14.81	0.07		
		500 mg/5 mL	5	IV	30.79	0.01		
Subsequent treatment: VR-CAP	Bortezomib	2.5 mg	1	IV	97.54	39.02	13.71	eMIT 2024
		3.5 mg	1	IV	55.87	22.35		
		3.5 mg/1.4 mL	1	IV	48.00	13.71		
	Rituximab	See above						
	Cyclophosphamide	See above						
	Doxorubicin	See above						
	Prednisolone	See above						

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BNF, British National Formulary; BR, bendamustine + rituximab; eMIT, drugs and pharmaceutical electronic market information tool; IV, intravenous; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
† Includes existing confidential patient access scheme for acalabrutinib.

Table 54: Dosing regimens and per-cycle acquisition costs: 1L

Treatment regimen	Drug	Dosing	Treatment cycle length, days	Admin per cycle	Maximum duration of treatment	Relative dose intensity, %	Dose per cycle-induction, mg	Cost per mg, £	Cost per cycle† (induction & continuous), £	Source
ABR	Acalabrutinib	100 mg	28	56	Until progression	89	4,988	[redacted]	[redacted]‡	ECHO CSR Section 9.1.1 (11)
	Bendamustine	90 mg/m^2	28	2	6 cycles	86	295	0.25		
	Rituximab	375 mg/m^2	28	1		93	661	0.96		
BR	Bendamustine	90 mg/m^2	28	2	6 cycles	87	296	0.25	697.53	ECHO CSR Section 9.1.1 (11)
	Rituximab	375 mg/m^2	28	1		91	648	0.96		
R-CHOP	Rituximab	375 mg/m^2	21	1	6 cycles	96	683	0.96	924.77	SWAG Cancer Alliance NHS (55), dose based on relative dose intensity from BRIGHT study
	Doxorubicin	50 mg/m^2	21	1		96	91	0.09		
	Vincristine	1.4 mg/m^2	21	1		72	2	3.84		
	Cyclophosphamide	750 mg/m^2	21	1		96	1,367	0.01		
	Prednisolone	50 mg/m^2	21	5		94	444	0.01		
R-maintenance	Rituximab	375 mg/m^2	56	1	30 cycles	77	546	0.96	524.69	BSH guidelines (2), RDI pooled average across arms in ECHO

Treatment regimen	Drug	Dosing	Treatment cycle length, days	Admin per cycle	Maximum duration of treatment	Relative dose intensity, %	Dose per cycle-induction, mg	Cost per mg, £	Cost per cycle† (induction & continuous), £	Source
										=(78.51%*245+74.88%*230)/(245+230)

Abbreviations: 1L, first-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CSR, clinical study report; SWAG Cancer Alliance, Somerset, Wiltshire, Avon and Gloucester Cancer Alliance ;BSH, British Society for Haematology ;NHS, National Health Service; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDI, Relative dose intensity.
† Accounting for vial sharing.
‡ Includes existing confidential patient access scheme for acalabrutinib.

Table 55: Dosing regimens and per-cycle acquisition costs: subsequent treatments

Treatment regimen	Drug	Dosing	Treatment cycle length, days	Admin per cycle	Maximum duration of treatment	Relative dose intensity, %	Dose per cycle	Cost per mg, £	Cost per cycle† (fixed & continuous), £	Source
Ibrutinib	Ibrutinib	560 mg	28	28	Until progression	94	14,799 mg	0.37	5,401.56	SmPC Ibrutinib (68), UHS NHS - MCL Ibrutinib protocol; RDI based on crossover data from ECHO
R-CHOP	Rituximab	375 mg/m^2	21	1	6 cycles	100	712 mg	0.96	963.56	SWAG Cancer

Treatment regimen	Drug	Dosing	Treatment cycle length, days	Admin per cycle	Maximum duration of treatment	Relative dose intensity, %	Dose per cycle	Cost per mg, £	Cost per cycle† (fixed & continuous), £	Source
	Doxorubicin	50 mg/m^2	21	1		100	95 mg	0.09		Alliance NHS (55),
	Vincristine	1.4 mg/m^2	21	1		100	3 mg	3.84		
	Cyclophosphamide	750 mg/m^2	21	1		100	1,424 mg	0.01		
	Prednisolone	50 mg/m^2	21	5		100	475 mg	0.01		
CAR-T and bridging therapy (one cycle of R-BAC)	Brexucabtagene autoleucel	1 infusion	28	1	1 cycle	100	1 infusion	316,118.00	316,118.00	TA677
	Rituximab	375 mg/m^2	28	1	1 cycle	37	139 mg	0.96	157.37	CEM
	Bendamustine	70 mg/m^2	28	2			52 mg	0.25		
	Cytarabine	800 mg/m^2	28	3			888 mg	0.01		
R-BAC	Rituximab	375 mg/m^2	28	1	1 cycle	100	375	0.96	425.33	CEM
	Bendamustine	70 mg/m^2	28	2			140	0.25		
	Cytarabine	800 mg/m^2	28	3			2,400	0.01		
VR-CAP	Bortezomib	1.3 mg/m^2	28	4	6 cycles	100	5.2 mg	13.71	450.30	CEM
	Rituximab	375 mg/m^2	28	1			375 mg	0.96		

Treatment regimen	Drug	Dosing	Treatment cycle length, days	Admin per cycle	Maximum duration of treatment	Relative dose intensity, %	Dose per cycle	Cost per mg, £	Cost per cycle† (fixed & continuous), £	Source
	Cyclophosphamide	750 mg/m^2	28	1			750 mg	0.01		
	Doxorubicin	50 mg/m^2	28	1			50 mg	0.09		
	Prednisolone	100 mg/m^2	28	5			500 mg	0.01		

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CEM, cost-effectiveness model; MCL, mantle cell lymphoma; NHS, National Health Service; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SmPC, summary of product characteristics; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone; RDI, Relative dose intensity; SWAG Cancer Alliance, Somerset, Wiltshire, Avon and Gloucester Cancer Alliance; UHS, University Hospital Southampton..
† Accounting for vial sharing.

B.3.6.1.2 Dosing and administration costs

Drug administration unit costs are presented in Table 56. Unit costs were taken from the NHS National Schedule of Costs 2022/23 and align with previous submissions in MCL and CLL. The codes for the administration of chemotherapy are based on the healthcare resource group (HRG) codes identified in TA677 (46). The model assumes that chemotherapy administration takes place in an outpatient setting, and if a patient receives more than one IV chemotherapy a day, only a single administration cost is applied. Oral drugs do not incur administration costs.

The administration costs for running a CAR-T service in the NHS are uncertain. This model is based on the evaluation conducted for NICE TA895 (69), during which consensus was reached by both the submitting company and NHS England to apply a cost per administration of £41,101.00 (excluding costs for bridging therapy, consolidation SCT, and hypogammaglobulinemia management). This figure was also accepted by the NICE committee for TA872 (axicabtagene ciloleucel as 3L treatment) (70).

Table 56: Drug administration unit costs

Administration type	HRG Code	Unit cost, £	Source
Intravenous administration	SB12Z: Simple parenteral chemotherapy at first attendance	412.00	NHS National Schedule of Costs 2022/23 (66)
	SB15Z: Subsequent elements of a chemotherapy cycle	392.00	
Oral administration	NA	0.00	Assumed no administration costs
CAR-T administration	NA	41,101.00	TA895 (69)

Abbreviations: CAR-T, chimeric antigen receptor T-cell; HRG, healthcare resource group; NA, not applicable; NHS, National Health Service.

The drug dosing schedules are summarised in Table 57.

Table 57: Drug dosing schedules

Treatment Regimen	Drug	Administration	Dosing schedule	Source
ABR	Acalabrutinib	Oral	Twice daily on Days 1–28 in a 28-day cycle	ECHO CSR – Section 9.1.1. (11)

Treatment Regimen	Drug	Administration	Dosing schedule	Source
	Bendamustine	IV	Day 1 and 2 of each 28-day cycle	
	Rituximab	IV	Day 1 of each 28-day cycle	
BR	Bendamustine	See above		
	Rituximab	See above		
R-CHOP	Rituximab	IV infusion	Day 0 or 1 of each 21-day cycle	SWAG Cancer Alliance NHS (55); dose based on relative dose intensity from BRIGHT study
	Doxorubicin	IV bolus	Day 1 of each 21-day cycle	
	Vincristine	IV infusion	Day 1 of each 21-day cycle	
	Cyclophosphamide	IV bolus	Day 1 of each 21-day cycle	
	Prednisolone	Oral	Day 1–5 of each 21-day cycle	
R-maintenance	Rituximab	IV infusion	Every cycle (i.e. every 56 days)	ECHO CSR (11)
Ibrutinib	Ibrutinib	Oral	Once a day on a 28-day cycle	SmPC Ibrutinib (68)
CAR-T	Brexucabtagene autoleucel	IV infusion	Once in a 28-day cycle	Tecartus SmPC
	Rituximab	IV infusion	Once in a 28-day cycle	NICE TA677, Table 56 (46)
	Bendamustine	IV infusion	Twice in a 28-day cycle	
	Cytarabine	IV	Three administrations in a 28-day cycle	
R-BAC	Rituximab	IV infusion	Once in a 28-day cycle	NICE TA677, Table 56 (46)
	Bendamustine	IV infusion	Twice in a 28-day cycle	
	Cytarabine	IV	Three administrations in a 28-day cycle	
VR-CAP	Bortezomib	IV	Four administrations in a 28-day cycle	NICE TA370 , Table 51 (23)

Treatment Regimen	Drug	Administration	Dosing schedule	Source
	Rituximab	IV infusion	Once in a 28-day cycle	
	Cyclophosphamide	IV infusion	Once in a 28-day cycle	
	Doxorubicin	IV	Once in a 28-day cycle	
	Prednisolone	Oral	Five administrations in a 28-day cycle	

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor T-cell; CSR, clinical study report; IV, intravenous; R, rituximab; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SmPC, summary of product characteristics; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

Drug administration costs were calculated for each treatment based on their respective dosing schedules and treatment durations (Table 59). The baseline characteristics of patients are summarised in Table 58 below.

Table 58: Baseline patient characteristics

Variable	Value
Age, years	71.6
Proportion male, %	70.74
Weight, kg	77.04
Height, cm	168.68
BSA, m^2	1.90

Abbreviations: BSA, body surface area; CSR, clinical study report.
Reference: ECHO Interim CSR (11).

The model base case applied vial sharing for all treatments dosed according to body surface area (BSA). A scenario analysis was conducted in which no sharing of vials was assumed.

Table 59: Administration costs

		Administration				
Treatment regimen	**Drug**	**Mode**	**# first administration**	**# subsequent admin**	**Cost per cycle, £**	**Source**
ABR	Acalabrutinib	Oral-BID	Assumed no cost			ECHO CSR Section 9.1.1. (11)
	Bendamustine	IV	No cost	1	392.00	
	Rituximab	IV	1	One per cycle	412.00	
BR	Bendamustine	IV	No cost	One per cycle	392.00	ECHO CSR Section 9.1.1. (11)
	Rituximab	IV	1	One per cycle	412.00	
R-CHOP	Rituximab	IV infusion	1	One per cycle	412.00	SWAG Cancer Alliance NHS (55)
	Doxorubicin	IV bolus	No cost	One per cycle	0.00	
	Vincristine	IV infusion				
	Cyclophosphamide	IV bolus				
	Prednisolone	Oral	Assumed no cost		0.00	
R-maintenance	Rituximab	IV infusion	Not applicable	0.5 per cycle	412.00	BSH guidelines (2)
Ibrutinib	Ibrutinib	Oral	Assumed no cost			SmPC Ibrutinib (68)
R-lenalidomide	Lenalidomide	Oral	Assumed no cost			Wang et al. 2012 (71)
	Rituximab	IV infusion	1	One per cycle	412.00	BSH guidelines (2)
CAR-T	Brexucabtagene autoleucel	IV infusion	1	One per cycle	41,101.00	Tecartus SmPC, TA 895 (69)
	Rituximab	IV infusion	1	One per cycle	412.00	TA677, Table 56 (46)
	Bendamustine	IV infusion	No cost	1	392.00	
	Cytarabine	IV	No cost	2	784.00	
R-BAC	Rituximab	IV infusion	1	One per cycle	412.00	TA677, Table 56 (46)
	Bendamustine	IV infusion	No cost	1	392.00	

		Administration				
Treatment regimen	**Drug**	**Mode**	**# first administration**	**# subsequent admin**	**Cost per cycle, £**	**Source**
	Cytarabine	IV	No cost	2	784.00	
VR-CAP	Bortezomib	IV	1	3	1,588.00	TA370, Table 51 (23)
	Rituximab	IV infusion	1	One per cycle	412.00	
	Cyclophosphamide	IV infusion	No cost	One per cycle	0.00	
	Doxorubicin	IV				
	Prednisolone	Oral	Assumed no cost			

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BID, twice daily; BR, bendamustine + rituximab; BSH, British Society of Haematology; CAR-T, chimeric antigen receptor T-cell; CSR, clinical study report; IV, intravenous; NHS, National Health Service; R, rituximab; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; SmPC, summary of product characteristics; TA, technology appraisal; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone; SWAG Cancer Alliance, Somerset, Wiltshire, Avon and Gloucester Cancer Alliance.

B.3.6.1.3 Subsequent treatment costs

In addition to the modelling of the main intervention and comparators of interest, the costs of subsequent lines of therapy were included in the model.

According to the BSH guidelines, for patients relapsing after 1L immunochemotherapy, the use of a BTKi, such as ibrutinib, an approved and reimbursed SoC option in the UK, is well-established in clinical practice (2). In England, ibrutinib is currently the only reimbursed option (3).

Consultation with UK clinical experts revealed that additional treatments prescribed in 2L in the future – if a BTKi, such as acalabrutinib, were to be used in the 1L setting – would include R-CHOP (3). Less common alternatives would include VR-CAP and R-BAC, although these are not typically given due to toxicity concerns.

It is noted that patients given a BTKi as a 1L treatment for MCL would not then be treated with another BTKi (2). Patients who progress following treatment with a BTKi may develop resistance to this mechanism of action, meaning that subsequent treatment with the same mechanism of action would be ineffective. Therefore, patients initiated on ABR would not then receive ibrutinib in clinical practice.

As ECHO is a multinational trial, the subsequent treatment data reflected available 2L SoC in different geographies, including immunochemotherapy, rituximab monotherapy, and other therapies such as lenalidomide. Therefore, UK clinical expert opinion was sought to ensure the subsequent treatment model inputs are generalisable to clinical practice in England and Wales. Based on input from UK clinical experts consulted as part of this submission (3), the subsequent treatment options in 2L used in the model are:

- Ibrutinib
- R-CHOP
- R-BAC
- VR-CAP

Furthermore, the model incorporates treatments received in 3L. Again, these were informed by consultations with clinical experts in the UK, who said that they would

expect to use CAR-T therapy if the patient is eligible, or participation in a clinical trial (3). The model includes the following treatments in 3L:

- R-CHOP
- CAR-T
- R-BAC
- VR-CAP

A summary of the included subsequent treatments, mechanisms of action, and dosing regimens is provided in Table 60.

Table 60: Subsequent treatments

Treatment	Mechanism	Dosing regimen
Ibrutinib	A small molecule that acts as an irreversible BTKi	560 mg/m^2 once a day in a 21-day cycle
BR	As in 1L treatment	As in 1L treatment
R-CHOP	As in 1L treatment	As in 1L treatment
CAR-T	Advanced immunotherapy directed against CD19, a B cell-specific cell surface antigen expressed in MCL	Single infusion, for autologous or intravenous use, for a target dose of 2x 10^6 CAR-T cells/kg bodyweight, with a maximum of 2x 10^8 CAR-T cells
R-BAC	Combination immunotherapy	Rituximab (375 mg/m^2) on Day 1; bendamustine (70 mg/m^2) on Day 2 and 3; cytarabine (500 mg/m^2) on Day 2 to 4 administered every 4 weeks by IV for up to 6 cycles
VR-CAP	Combination immunotherapy	Bortezomib (1.3 mg/m^2) on Day 1, 4, 8, 11 followed by 21-day rest; rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (500 mg/m^2) on Day 1 by IV; oral prednisolone (100 mg/m^2) on Day 1, 3, 4, 5

Abbreviations: 1L, first-line; BR, bendamustine + rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell; IV, intravenous; MCL, mantle cell lymphoma; R, rituximab; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

Table 61 and Table 62 below summarise subsequent treatment costs for 2L and 3L respectively. These are applied as a one-off cost to the incident progressed disease patients per cycle and were calculated from the number of PFS events at each cycle, multiplied by the proportion of PFS events that were non-fatal, and the proportion of

progressed patients that had subsequent treatment. The one-off costs applied were based on the distribution of subsequent treatment options as well as the time on treatment.

In line with clinical practice, subsequent therapy costs are assumed to apply upon progression (72), and so the cost of subsequent treatment was applied to the percentage of patients progressing, based on the PFS curve (see Table 64 and Table 66 in Section B.3.6.1.3.1).

Table 61: Summary of subsequent treatment costs – 2L

Treatment regimen	Drug acquisition, £	Administration, £	TOTAL, £
ABR	3,379	6,763	10,143
BR	105,630	0	105,630
R-CHOP	105,630	0	105,630

Abbreviations: 2L, second-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
All numbers have been rounded to the nearest integer.

Table 62: Summary of subsequent treatment costs – 3L

Treatment regimen	Drug acquisition, £	Administration, £	TOTAL, £
ABR	27,925	6,086	34,010
BR	45,517	25,202	70,720
R-CHOP	43,249	9,035	52,284

Abbreviations: 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
All numbers have been rounded to the nearest integer.

B.3.6.1.3.1 Subsequent treatment distribution

As noted previously, the subsequent treatment costs are modelled as a one-time cost applied to patients who experience a non-fatal progression event (Table 63).

Table 63: Proportion of non-fatal progression events eligible for further treatment (COVID-19-censored analysis)

	ABR	PBR	R-CHOP (assumed equal to BR)
% non-fatal progression events eligible for further treatment	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CSR, clinical study report; PBR, placebo, bendamustine, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
Reference: ECHO Interim CSR (11).

The proportion of progressed disease patients receiving 2L treatment was obtained from ECHO trial data for ABR and PBR. This was estimated as the total number of patients who received one line of subsequent treatment in the ECHO trial, out of the total number of progressed patients. In the absence of data to inform the R-CHOP arm, the model assumed the same proportion as PBR. These proportions are shown in Table 64.

Table 64: Patients receiving subsequent treatment (2L) in the ECHO trial

	ABR	PBR	R-CHOP
% progressed disease patients receiving 2L treatment	[redacted]	[redacted]	[redacted]

Abbreviations: 2L, second-line; ABR, acalabrutinib, bendamustine, rituximab; CSR, clinical study report; PBR, placebo, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
Source: ECHO Interim CSR (11).

The distribution of treatments for those patients receiving subsequent 2L treatment is shown in Table 65, as determined by clinical experts in the UK (3), in order to best represent UK clinical practice. The model uses this over the proportions from the multinational ECHO trial, as these were not considered representative of UK clinical practice and guidance from UK clinicians. Patients in the ECHO trial received a BTKi as a subsequent treatment following disease progression in both treatment arms. This is clinically plausible in the PBR arm, as ibrutinib is approved for patients with R/R MCL, and UK clinical experts noted that patients would be expected to receive ibrutinib as the only targeted regimen in the R/R stage. However, patients initiated on ABR would not receive a BTKi following disease progression, according to clinical guidelines (2). Thus, it was considered more representative of clinical reality to use

the subsequent treatment distributions informed by UK clinical experts in order to be aligned with treatment guidelines in MCL (Table 65).

Table 65: Distribution of subsequent treatments (2L) for patients who received a subsequent treatment

Subsequent treatment (2L)	1L treatment, %		
	ABR	BR	R-CHOP
R-CHOP	74.4	0.0	0.0
Ibrutinib	0.0	100.0	100.0
R-BAC	11.1	0.0	0.0
VR-CAP	14.4	0.0	0.0

Abbreviations: 1L, first-line; 2L, second-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.
Reference: AstraZeneca Data on File REF-251322, 2024 (3).

The proportion of patients who would receive 3L treatments was calculated from the ECHO trial for the ABR and PBR treatment arms. Specifically, this was calculated as the percentage of patients who progressed and received two, three, or more than four subsequent treatments. Again, in the absence of data to inform the R-CHOP arm, the model assumed the same proportion as BR.

Table 66: Patients receiving subsequent treatment (3L) in the ECHO trial

	ABR	PBR	R-CHOP
% progressed disease patients receiving 3L treatment	[redacted]	[redacted]	[redacted]

Abbreviations: 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; CSR, clinical study report; PBR, placebo, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
Reference: ECHO Interim CSR (11).

The distribution of treatments for those patients receiving subsequent 3L treatment is shown in Table 67, as determined by clinical experts in the UK (3). The model uses this as the base case, as the proportions from the ECHO trial were not considered to represent the treatments available in the UK, nor the clinical decisions taken by UK clinicians.

Table 67: Distribution of subsequent treatments (3L) for patients who received a subsequent treatment

Subsequent treatment (3L)	1L treatment, %		
	ABR	BR	R-CHOP
R-CHOP	16.7	15.6	16.3
Ibrutinib	0.0	15.6	16.3
CAR-T	50.0	37.5	35.0
R-BAC	16.7	15.6	16.3
VR-CAP	16.7	15.6	16.3

Abbreviations: 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor T-cell; R-BAC, rituximab, bendamustine, cytarabine, R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.
Reference: AstraZeneca Data on File REF-251322, 2024 (3).

B.3.6.1.3.2 Subsequent treatment duration

The cost for subsequent lines of treatment after 1L progression was accounted for in the model by calculating cycle costs for subsequent therapies in the same way as the intervention and comparator treatments.

The number and type of subsequent treatments affect costs only, as the potential effects of subsequent treatments on survival were assumed to be captured in the extrapolated OS curves of the comparators. The duration of subsequent treatments was modelled by considering the time on treatment, as detailed in Table 68.

The per cycle costs of subsequent treatments alongside the time on treatment were used to estimate the one-off cost of subsequent treatments. These were then applied to the incident progressed disease patients.

Table 68: Duration of subsequent treatment

	Time on treatment, months	Source
Ibrutinib	22.00	Restricted mean survival time cross over (acalabrutinib), ECHO trial (11)
R-CHOP	5.52	Maximum treatment duration, LYM3002 (27)
CAR-T: Brexucabtagene autoleucel	1	Patients receive a single infusion of CAR-T therapy (73)
R-BAC	10.10	Median PFS, R-BAC in R/R MCL (74)
VR-CAP	30.50	Median PFS, VR-CAP in 1L MCL (75)

Abbreviations: 1L, first-line; CAR-T, chimeric antigen receptor T-cell; MCL, mantle cell lymphoma; PFS, progression-free survival; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP; rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

B.3.6.2 Health-state unit costs and resource use

Costs related to clinical disease management and treatment monitoring were modelled using a health state approach, in alignment with previous submissions to NICE, such as TA370, TA502, and TA677 (23, 45, 46). Per cycle HCRU costs, by health state, are summarised in Table 69.

Table 69: Total HCRU cost per cycle

Treatment	Progression-free state, £	Progressed disease, £
ABR, BR, and R-CHOP	468.38	883.39

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; HCRU, healthcare resource use; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

HCRU inputs were identified through a review of previous MCL publications and NICE appraisals (i.e. van Keep et al 2016, TA370, TA502, and TA677 (23, 42, 45, 46), see Appendix I). From these, TA502 was deemed the most robust for informing HCRU inputs, as it was based on a survey with 52 participants (15 oncologists, 19 haematologists and 18 haematologist oncologists), and subsequently validated by key opinion leaders (45). Given that TA502 assessed treatment in R/R MCL patients, the model assumed that resource use items and frequencies are representative of the current population of interest (i.e. patients with untreated MCL), an approach ratified by the advisory board (33).

TA502 reported resource use according to stable disease, PR, CR, and post progression survivors (45). This model assumes that resource use for patients with stable disease applies to patients on treatment, and post-progression resource use applies to patients off treatment. This assumption was made to reflect that patients who are not able to receive treatment (off treatment) have a worse prognosis and faster decline in QoL than those on treatment. Table 70 shows the frequency and cost of clinical disease management and treatment monitoring resource items as well as their unit cost.

Table 70: Clinical disease management and treatment monitoring cost and healthcare resource unit frequencies

Resource type	HRG code	Unit cost, £	Source	Progression-free state		Progressed disease		Source
				Frequency	Time interval	Frequency	Time interval	
Full blood count	Haematology / DAPS05 / Directly accessed pathology services (DAPS)	2.75	NHS National schedule of costs 2022/23 (66)	0.50	Every 2 months	0.75	Every 1.5 months	TA502 (45)
X-ray	DAPFI - Direct access plain film	41.00	NHS National schedule of costs 2022/23 (66)	0.80	Once per year	0.80	Once per year	
Blood glucose	Clinical Biochemistry / DAPS04 / Directly accessed pathology services (DAPS)	1.61	NHS National schedule of costs 2022/23 (66)	0.00	NA	0.00	NA	
Lactate dehydrogenase		1.61		0.33	Every 3 months	0.42	Five times a year	
Lymphocyte count	Haematology / DAPS05 / Directly accessed pathology services (DAPS) – weighted average of all service codes with number of tests used as weight	2.75	NHS National schedule of costs 2022/23 (66)	0.5	Every 2 months	0.75	Every 1.5 months	
Bone marrow exam	Diagnostic Bone Marrow Extraction / SA33Z / Outpatient procedures, clinical haematology	487.00	NHS National schedule of costs 2022/23 (66)	0.80	Once per year	0.00	NA	
Haematologist visit	Non-Admitted Face-to-Face Attendance, Follow-up / WF01A (Service code 303) / Outpatient procedures, clinical haematology – Consultant-led	201.43	NHS National schedule of costs 2022/23 (66)	0.50	Every 2 months	0.75	Every 1.5 months	

Resource type	HRG code	Unit cost, £	Source	Progression-free state		Progressed disease		Source
				Frequency	Time interval	Frequency	Time interval	
Inpatient visit (medical)	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's codes SA31F / elective inpatient	3,447.80	NHS National schedule of costs 2022/23 (66)	0.00	Once a year	0.00	Every 6 months	
Biopsy	Core Needle Biopsy of Axillary Lymph Nodes / YJ04Z (Service code 100) / Outpatient procedures, general surgery	492.00	NHS National schedule of costs 2022/23 (66)	0.08	Once a year	0.00	NA	
Blood transfusion	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over / SA44A (Service code 303) / Outpatient	453.00	NHS National schedule of costs 2022/23 (66)	0.08	Once a year	0.33	Every 3 months	
Platelet transfusion		453.00	NHS National schedule of costs 2022/23 (66)	0.00	NA	0.17	Every 6 months	

Abbreviations: DAPS, directly accessed pathology services; DAPFI, Direct access plain film ;HRG, healthcare resource group; NA, not applicable; NHS, National Health Service.

B.3.6.3 Adverse reaction unit costs and resource use

Table 71 provides a summary of the Grade 3 to 4 AE costs per treatment arm, which were applied as one-off costs in the first year of each incident cohort.

Table 71: Summary of AE costs

Treatment	Total one-off costs of AEs, £
ABR	3,406.29
BR	2,978.20
R-CHOP	3,424.19

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse events; BR, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

Table 72 presents AE unit costs, which were informed by the corresponding HRG codes for the management of the identified AEs; applicable HRG codes were sourced through previous 1L and R/R MCL NICE appraisals (TA370, TA502, and TA677 (23, 45, 46)). The costs used in the model were informed by extracting the costs associated with the respective HRG codes from the NHS National schedule of costs 2022/23 workbook (66). Where a HRG code related to a specific AE was not available, the cost was identified through NICE appraisals in other indications, such as 1L CLL.

Table 72: AE unit costs

AE	HRG code	Unit cost, £	Source
Anaemia	SA01G-K: Weighted average of non-elective spells for acquired pure red cell aplasia or other aplastic anaemia with CC score from 0-8+. Activity used as weight and taken from NHS Cost Collection 2022/2023 total HRG data.	2,914.41	NHS National Schedule of Costs 2022/23
Febrile neutropenia	SA35A-E: Weighted average of non-elective spells for agranulocytosis with CC Score 0-1 to 13+ . Activity used as weight and taken from NHS Cost Collection 2022/2023 total HRG data.	2,337.31	
Leukopenia	SA35A-E: Weighted average of non-elective spells for agranulocytosis with CC Score 0-1 to 13+. Activity used as weight and taken from NHS Cost Collection 2022/2023 total HRG data	2,337.31	
Lymphopenia	Assumed the same as leukopenia	2,337.31	
Neutropenia	SA35A-E: Weighted average of non-elective spells for agranulocytosis with CC Score 0-1 to 13+. Activity used as	2,337.31	

AE	HRG code	Unit cost, £	Source
	weight and taken from NHS Cost Collection 2022/2023 total HRG data		
Pneumonia	DZ11K-V: Weighted average of non-elective spells for lobar, atypical or viral pneumonia, with or without interventions and all CC scores. Activity used as weight and taken from NHS Cost Collection 2022/2023 total HRG data	2,662.50	
Thrombocytopenia	SA12G-K: Weighted average of non-elective spells for thrombocytopenia with CC Score 0-1 to score 8+. Activity used as weight and taken from NHS Cost Collection 2022/2023 total HRG data	2,384.59	
COVID-19 pneumonia	DX11A - COVID-19 Infection, with Pneumonia, 19 years and over - Weighted average of non-elective spells (both long stay and short stay)	2,803.47	
COVID-19	DX01A (Covid-19 infection with Major Manifestations, 19 years and over) AND DX21A (Covid-19 injection, 19 years and over) - Weighted average of non-elective spells (both long stay and short stay)	2,870.05	
Rash maculo-papular	This is a skin manifestation observed in patients with Covid. Assumed that the cost of treating it is included in the HRG for COVID-19	0.00	
Neutrophil count decreased	Assumed the same as neutropenia	2,337.31	
White blood cell count decreased	Assumed the same as leukopenia	2,337.31	
Lymphocyte count decreased	Assumed the same as lymphopenia	2,337.31	
Hypertension	EB04Z - Hypertension - Weighted average of non-elective spells (both long stay and short stay)	735.07	

Abbreviations: AE, adverse event; CC, critical care; HRG, healthcare resource group; NHS, National Health Service.

For lab-based AEs (based on results from blood tests, e.g. decreased neutrophil count), the model assumes the same utility decrement and cost as for the associated condition [e.g. neutropenia]).

AE unit costs were applied to the AE incidence for each treatment arm (Table 45) and the resulting one-off costs can be found in Table 71.

B.3.6.4 Miscellaneous unit costs and resource use

B.3.6.4.1 End-of-life costs

HCRU for palliative care is different from the resource use during post-progression management of the disease. Accordingly, end-of-life costs were included as a one-off cost, applied at the time of death.

When reviewing the previous NICE TAs in 1L and R/R MCL, different sources of end-of-life costs were used (Table 73).

Table 73: Terminal care cost components

NICE TA	Indication	Intervention/ comparator	Reported cost in NICE TA, £	Population	Study type	Source
TA502 (2016) (45)	2L MCL	Ibrutinib versus R-CHOP	7,352.00 (2015)	All deaths in UK, with cancer subgroup analysis	Retrospective cohort analysis	Georghiou and Bardsley 2014 (76)
TA370 (2015) (23)	1L MCL	VR-CAP versus R-CHOP	6,018.00 (2014)	Cancer and other terminal illnesses (Marie Curie Cancer Care)	Retrospective analysis	Addicot and Dewar 2008 (77)
TA677 (2021) (46)	3L MCL	KTE-X19 versus post-BTKi standard of care	4,540.95 (2019)	Breast, colorectal, lung and prostate cancers	Modelling-based approach using publicly available data	Round et al 2015 (78)

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; BTKi, Bruton's tyrosine kinase inhibitor; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, and prednisolone; TA, technology appraisal; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

Given the recent nature of the TA and the original cost source used, end-of-life costs were sourced from Round et al 2015 (78), consistent with TA677 (46) (Table 74).

Table 74: Terminal care weighted average cost in Round et al 2015

Cancer type	Mean (95% CI), £				
	Health care	Social care	Charity care	Informal care	Total
Breast	4,346 (395 to 12,545)	2,843 (84 to 10,170)	480 (7 to 1,845)	4,868 (18 to 21,818)	12,663 (1,249 to 38,712)
Colorectal	4,854 (413 to 14,485)	1,489 (44 to 5,350)	470 (6 to 1,833)	2,850 (10 to 13,350)	9,760 (1,037 to 29,545)
Lung	3,157 (332 to 8,944)	1,358 (39 to 4,838)	459 (6 to 1,775)	2,420 (9 to 11,153)	7,467 (855 to 21,663)
Prostate	6,687 (535 to 20,257)	2,728 (83 to 9,588)	482 (6 to 1,906)	4,814 (18 to 21,981)	14,859 (1,391 to 46,424)
Mean	**4,254**	**1,829**	**468**	**3,265**	**9,914**

Note: Mean weighted by the proportion of deaths due to each cancer in the total population.
Abbreviations: CI, confidence interval.
Note: Mean weighted by the proportion of deaths due to each cancer in the total population.
Reference: Round et al 2015 (78).

End-of-life costs combining the healthcare and social care perspectives were used, taking the mean cost across the four cancer types (£4,254+£1,829=£6,083). The mean cost was then adjusted for inflation to 2024 GBP by using the CPI Health Index from the Office of National Statistics (65), resulting in a mean cost of end-of-life care of £7,441.00.

B.3.7 Severity

MCL remains a largely incurable type of NHL, with poor survival and high relapse rates placing a high burden on patients. The goal of treating MCL patients with BTKis, such as acalabrutinib, in 1L, is to achieve long-term benefits while limiting toxicities that are associated with non-targeted agents currently used.

The QALY shortfall calculator developed by Schneider et al 2021 (79) was used to generate absolute and proportional QALY shortfall estimates using the reference case HRQoL norms (HSE 2017–18 EQ-5D-5L mapped to EQ-5D-3L using the Hernandez Alava et al algorithm (2023) (58)). Patient characteristics used in the analysis were consistent with those informing the base case economic analysis.

ABR did not meet the criteria for a severity weight. Table 75 displays that, based on the expected total QALYs for the general population and the total QALYs for patients with previously untreated MCL, the absolute and proportional QALY shortfalls do not result in qualification for a severity weight.

Table 75: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
8.71 (calculated based on the average patient age [71.0 years] and percentage male [71%] used in the model, using the calculator by Scheider et al 2021 (79))	Treated with BR: [redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted] QALY weight: x1
	Treated with R-CHOP: [redacted]	Absolute shortfall: [redacted] Proportional shortfall: [redacted] QALY weight: x1

Abbreviations: BR, bendamustine + rituximab; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

B.3.8 Uncertainty

Uncertainty in the available evidence base has been thoroughly explored where possible through evaluation of the associated parameter uncertainty and testing of the various structural assumptions made within the economic model. The key areas of uncertainty in the economic analysis are considered to be the following:

- The independent modelling of OS and PFS curves within a PSM framework only implicitly accounts for the transition from the progressed disease state to death, limiting the possibility to model multiple subsequent lines of treatment. While the inclusion of progression-free and progressed disease states for R/R MCL would have allowed for a more detailed analysis of treatment costs and outcomes, their absence from the model is not expected to materially impact model results. To address the costs of progression during R/R MCL treatment, the costs assigned to the progressed disease state included up to two additional lines of treatment. The OS data used to estimate the proportion of patients in the PD state were derived from the ECHO trial and encompassed the survival effects of subsequent treatment lines in ECHO

- The long-term extrapolations of OS for ABR and BR are based on data with a maturity of 21.4% and 26.8%, respectively, from the 15th of February 2024 data cut of ECHO (censoring COVID-19 deaths). To reduce uncertainty in the long-term extrapolation, the selection of parametric curves that were applied to OS data were validated by UK clinical experts, and a range of scenario analyses were performed to explore the model results given alternative survival choices.
- No head-to-head trials were conducted to compare ABR and R-CHOP, therefore efficacy data for R-CHOP were taken from an ITC. This is a commonly used approach to ensure that all clinically relevant comparators are included in the base-case analysis. HRs derived from the ITC are varied in sensitivity analyses to understand the impact of uncertainty in these estimates
- [redacted] extensive scenario analyses have been undertaken to explore the impact of using different utility values, using a combination of the reported values from ECHO and the literature

B.3.9 Managed access proposal

This submission proposes ABR is commissioned for routine use in patients within its expected licensed population based on the robust clinical evidence provided by the pivotal Phase 3 ECHO trial; however, it may become relevant that a managed access proposal is needed if areas of clinical uncertainty are identified during the appraisal process.

B.3.10 Summary of base-case analysis inputs and assumptions

B.3.10.1 Summary of base-case analysis inputs

A summary of the key parameters used in the economic evaluation is presented in Table 76.

Information on the uncertainty of each parameter, such as standard error (SE), CIs and sample sizes, was taken from the original source where available. Where uncertainty information was not reported, the SE was assumed to be 10% of the mean value.

A normal distribution was used for resource use frequencies, and durations. A gamma distribution was used for costs. A log-normal distribution was used for HRs. A beta distribution was used for probabilities, proportions, and utilities, acknowledging that such parameters can never be negative and cannot exceed one. A multivariate normal distribution (using variance covariance matrices) was used to capture uncertainty in correlated parameters, such as survival parameters.

Inputs not associated with parameter uncertainty, such as alternative modelling assumptions, were investigated in the scenario analysis only.

Table 76: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
Baseline characteristics			
Age	71.6	Normal: 71.23, 71.97	
Proportion of male	70.74%	Beta: 67.00%, 74.00%	
Weight	77.04	Normal: 76.27, 77.81	
Height	168.38	Normal: 167.03, 169.73	
BSA	1.90	Normal: 1.53, 2.27	
Clinical efficacy			
OS, PFS, and TTD parametric models: ABR and PBR	Various	Multivariate normal distributions, per the variance-covariance matrices	B.3.4.1
R-CHOP HR: PFS	[redacted]	Log-normal: [redacted]	
R-CHOP HR: OS	[redacted]	Log-normal: [redacted]	
Acalabrutinib + BR- Proportion of non-fatal PFS	[redacted]	Beta: [redacted]	B.3.6.1.3
BR- Proportion of non-fatal PFS	[redacted]	Beta: [redacted]	
R-CHOP- Proportion of non-fatal PFS	[redacted]	Beta: [redacted]	
Ibrutinib duration of subsequent treatment	22.00	Normal: 15.00, 29.10	
R-CHOP duration of subsequent treatment	5.52	Normal: 4.44, 6.6	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
CAR-T duration of subsequent treatment	1.00	Not varied	
R-BAC duration of subsequent treatment	10.10	Normal: 6.9, 13.3	
VR-CAP duration of subsequent treatment	30.50	Normal: 24.52, 36.48	
Dosing regimens			
RDI of Acalabrutinib in Acalabrutinib + BR	89.08%	Gamma: 87.00%, 91.00%	B.3.6.1
RDI of bendamustine in acalabrutinib + BR	86.36%	Gamma: 84.00%, 89.00%	
RDI of rituximab in acalabrutinib + BR	92.81%	Gamma: 91.00%, 95.00%	
RDI of bendamustine in BR	86.53%	Gamma: 84.00%, 89.00%	
RDI of rituximab in BR	91.04%	Gamma: 88.00%, 94.00%	
RDI of rituximab in R-CHOP	96.00%	Gamma: 95.00%, 97.00%	
RDI of doxorubicin in R-CHOP	96.00%	Gamma: 95.00%, 97.00%	
RDI of vincristine in R-CHOP	71.50%	Gamma: 71.00%, 72.00%	
RDI of cyclophosphamide in R-CHOP	96.00%	Gamma: 95.00%, 97.00%	
RDI of prednisolone in R-CHOP	93.50%	Gamma: 92.00%, 95.00%	
RDI of rituximab in R-maintenance	76.75%	Gamma: 76.00%, 77.00%	
RDI of ibrutinib in Ibrutinib	94.38%	Gamma: 91.00%, 97.00%	
RDI of other included treatments	100.00%	Not varied	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
Adverse events			
Acalabrutinib + BR: Anaemia	9.40%	Beta: 6.0%, 13.0%	B.3.5.3
Acalabrutinib + BR: Febrile neutropenia	5.10%	Beta: 3.0%, 8.0%	
Acalabrutinib + BR: Leukopenia	5.70%	Beta: 3.0%, 9.0%	
Acalabrutinib + BR: Lymphopenia	2.70%	Beta: 1.0%, 5.0%	
Acalabrutinib + BR: Neutropenia	35.40%	Beta: 30.0%, 41.0%	
Acalabrutinib + BR: Pneumonia	8.80%	Beta: 6.0%, 12.0%	
Acalabrutinib + BR: Thrombocytopenia	6.10%	Beta: 4.0%, 9.0%	
Acalabrutinib + BR: COVID-19 pneumonia	15.50%	Beta: 12.0%, 20.0%	
Acalabrutinib + BR: COVID-19	13.50%	Beta: 10.0%, 18.0%	
Acalabrutinib + BR: Rash maculo-papular	10.10%	Beta: 7.0%, 14.0%	
Acalabrutinib + BR: Neutrophil count decreased	15.50%	Beta: 12.0%, 20.0%	
Acalabrutinib + BR: White blood cell count decreased	10.10%	Beta: 7.0%, 14.0%	
Acalabrutinib + BR: Lymphocyte count decreased	6.40%	Beta: 4.0%, 9.0%	
Acalabrutinib + BR: Hypertension	5.40%	Beta: 3.0%, 8.0%	
BR: Anaemia	10.10%	Beta: 7.0%, 14.0%	
BR: Febrile neutropenia	2.40%	Beta: 1.0%, 4.0%	
BR: Leukopenia	6.10%	Beta: 4.0%, 9.0%	
BR: Lymphopenia	5.40%	Beta: 3.0%, 8.0%	
BR: Neutropenia	37.00%	Beta: 32.0%, 43.0%	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
BR: Pneumonia	6.40%	Beta: 4.0%, 9.0%	
BR: Thrombocytopenia	5.40%	Beta: 3.0%, 8.0%	
BR: COVID-19 pneumonia	10.10%	Beta: 7.0%, 14.0%	
BR: COVID-19	10.40%	Beta: 7.0%, 14.0%	
BR: Rash maculo-papular	3.70%	Beta: 2.0%, 6.0%	
BR: Neutrophil count decreased	10.10%	Beta: 7.0%, 14.0%	
BR: White blood cell count decreased	3.70%	Beta: 2.0%, 6.0%	
BR: Lymphocyte count decreased	9.80%	Beta: 7.0%, 13.0%	
BR: Hypertension	8.40%	Beta: 6.0%, 12.0%	
BR: Platelet count decreased	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Anaemia	13.60%	Beta: 10.0%, 18.0%	
R-CHOP: Febrile neutropenia	13.60%	Beta: 10.0%, 18.0%	
R-CHOP: Leukopenia	29.30%	Beta: 24.0%, 35.0%	
R-CHOP: Lymphopenia	8.70%	Beta: 6.0%, 13.0%	
R-CHOP: Neutropenia	66.90%	Beta: 61.0%, 73.0%	
R-CHOP: Pneumonia	4.50%	Beta: 2.0%, 7.0%	
R-CHOP: Thrombocytopenia	5.80%	Beta: 3.0%, 9.0%	
R-CHOP: COVID-19 pneumonia	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: COVID-19	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Rash maculo-papular	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Neutrophil count decreased	0.00%	Beta: 0.00%, 0.00%	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
R-CHOP: White blood cell count decreased	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Lymphocyte count decreased	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Hypertension	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Rash maculo-papular	0.00%	Beta: 0.00%, 0.00%	
R-CHOP: Neutrophil count decreased	0.00%	Beta: 0.00%, 0.00%	
Utilities			
Disutility: Anaemia	-0.01	Beta: -0.006, -0.008	B.3.5.3.1
Disutility: Febrile neutropenia	-0.01	Beta: -0.011, -0.017	
Disutility: Leukopenia	-0.04	Beta: -0.034, -0.051	
Disutility: Lymphopenia	-0.07	Beta: -0.053, -0.078	
Disutility: Neutropenia	-0.03	Beta: -0.026, -0.039	
Disutility: Pneumonia	-0.06	Beta: -0.047, -0.07	
Disutility: Thrombocytopenia	-0.04	Beta: -0.031, -0.046	
Disutility: COVID-19 pneumonia	-0.03	Beta: -0.026, -0.039	
Disutility: COVID-19	-0.03	Beta: -0.026, -0.039	
Disutility: Rash maculo-papular	-0.03	Beta: -0.026, -0.039	
Disutility: Neutrophil count decreased	-0.03	Beta: -0.026, -0.039	
Disutility: White blood cell count decreased	-0.04	Beta: -0.034, -0.051	
Disutility: Lymphocyte count decreased	-0.07	Beta: -0.053, -0.078	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
Disutility: Hypertension	-0.16	Beta: -0.132, -0.196	
Duration: Anaemia	9.73 days	Normal: 7.82, 11.64	
Duration: Infections	14.00 days	Normal: 11.26, 16.74	
Duration: Leukopenia	9.45 days	Normal: 7.6, 11.3	
Duration: Lymphopenia	16.73 days	Normal: 13.45, 20.01	
Duration: Neutropenia	9.10 days	Normal: 7.32, 10.88	
Duration: Pneumonia	16.03 days	Normal: 12.89, 19.17	
Duration: Thrombocytopenia	10.08 days	Normal: 8.1, 12.06	
Duration: COVID-19 pneumonia	23.78 days	Normal: 19.12, 28.44	
Duration: COVID-19	23.78 days	Normal: 19.12, 28.44	
Duration: Rash maculo-papular	23.78 days	Normal: 19.12, 28.44	
Duration: Neutrophil count decreased	9.10 days	Normal: 7.32, 10.88	
Duration: White blood cell count decreased	9.45 days	Normal: 7.6, 11.3	
Duration: Lymphocyte count decreased	16.73 days	Normal: 13.45, 20.01	
Duration: Hypertension	15.09 days	Normal: 12.13, 18.05	
Utility progression-free (varied prior to capping)	[redacted]	Beta: [redacted]	B.3.5.4
Utility progressed disease (varied prior to capping)	[redacted]	Beta: [redacted]	
Costs			
Cost of acalabrutinib	£[redacted]	Not varied	B.3.6.1.1
Cost of bendamustine	£127.14	Gamma: £103.45, £153.24	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
Cost of rituximab	£1,344.65	Not varied	
Cost of cyclophosphamide	£13.11	Gamma: £11.8, £14.48	
Cost of doxorubicin	£17.67	Gamma: £16.13, £19.28	
Cost of vincristine	£38.42	Gamma: £5.33, £103.51	
Cost of prednisolone	£12.78	Gamma: £8.70, £17.63	
Cost of ibrutinib	£5,723.20	Not varied	
Cost of cytarabine	£30.79	Gamma: £6.08, £75.13	
Cost of brexucabtagene autoleucel	£316,118.00	Not varied	
Cost of bortezomib	£48.00	Gamma: £39.05, £57.85	
Simple parenteral chemotherapy at first attendance	£412.00	Gamma: £335.22, £496.58	
Subsequent elements of a chemotherapy cycle	£392.00	Gamma: £318.95, £472.47	
Oral administration	£0.00	Gamma: £0.00, £0.00	
CAR-T administration	£41,101.00	Gamma: £33,441.42, £49,538.60	
Unit cost: Full blood count	£2.75	Gamma: £2.24, £3.31	B.3.6.2
Unit cost: X-ray	£41.00	Gamma: £33.36, £49.42	
Unit cost: Blood glucose	£1.61	Gamma: £1.31, £1.94	
Unit cost: Lactate dehydrogenase	£1.61	Gamma: £1.31, £1.94	
Unit cost: Lymphocyte count	£2.75	Gamma: £2.24, £3.31	
Unit cost: Bone marrow exam	£487.00	Gamma: £396.24, £586.98	
Unit cost: Haematologist visit	£201.43	Gamma: £163.89, £242.78	
Unit cost: Inpatient visit (medical)	£3,447.80	Gamma: £2,805.27, £4,155.6	
Unit cost: Biopsy	£492.00	Gamma: £400.31, £593.	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
Unit cost: Blood transfusion	£453.00	Gamma: £368.58, £546.	
Unit cost: Platelet transfusion	£453.00	Gamma: £368.58, £546.	
Unit cost: Anaemia	£2,914.41	Gamma: £2,371.28, £3,512.71	B.3.6.3
Unit cost: Febrile neutropenia	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Leukopenia	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Lymphopenia	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Neutropenia	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Pneumonia	£2,662.50	Gamma: £2,166.32, £3,209.09	
Unit cost: Thrombocytopenia	£2,384.59	Gamma: £1,940.2, £2,874.12	
Unit cost: COVID-19 pneumonia	£2,803.47	Gamma: £2,281.01, £3,378.99	
Unit cost: COVID-19	£2,870.05	Gamma: £2,335.19, £3,459.25	
Unit cost: Rash maculo-papular	£0.00	Gamma: £0.00, £0.00	
Unit cost: Neutrophil count decreased	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: White blood cell count decreased	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Lymphocyte count decreased	£2,337.31	Gamma: £1,901.73, £2,817.14	
Unit cost: Hypertension	£735.07	Gamma: £598.08, £885.97	
Unit cost: End of life care	£7,441.00	Gamma: £6,054.29, £8,968.56	B.3.6.4.1, B.3.6.2
PFS frequency: Full blood count	0.50	Normal: 0.40, 0.60	
PFS frequency: X-ray	0.08	Normal: 0.06, 0.10	
PFS frequency: Blood glucose	0.00	Normal: 0.00, 0.00	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
PFS frequency: Lactate dehydrogenase	0.33	Normal: 0.27, 0.39	
PFS frequency: Lymphocyte count	0.50	Normal: 0.40, 0.60	
PFS frequency: Bone marrow exam	0.08	Normal: 0.06, 0.10	
PFS frequency: Haematologist visit	0.50	Normal: 0.40, 0.60	
PFS frequency: Inpatient visit (medical)	0.08	Normal: 0.07, 0.10	
PFS frequency: Biopsy	0.08	Normal: 0.06, 0.10	
PFS frequency: Blood transfusion	0.08	Normal: 0.06, 0.10	
PFS frequency: Platelet transfusion	0.00	Normal: 0.00, 0.00	
PD frequency: Full blood count	0.75	Normal: 0.60, 0.90	
PD frequency: X-ray	0.080	Normal: 0.06, 0.1	
PD frequency: Blood glucose	0.000	Normal: 0.00, 0.00	
PD frequency: Lactate dehydrogenase	0.420	Normal: 0.34, 0.50	
PD frequency: Lymphocyte count	0.750	Normal: 0.60, 0.90	
PD frequency: Bone marrow exam	0.000	Normal: 0.00, 0.00	
PD frequency: Haematologist visit	0.750	Normal: 0.60, 0.90	
PD frequency: Inpatient visit (medical)	0.167	Normal: 0.13, 0.20	
PD frequency: Biopsy	0.000	Normal: 0.00, 0.00	
PD frequency: Blood transfusion	0.330	Normal: 0.27, 0.39	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
PD frequency: Platelet transfusion	0.170	Normal: 0.06, 0.10	
Subsequent treatments			
Total use of 1L subsequent treatment from acalabrutinib + BR group	[redacted]	Beta: [redacted]	B.3.6.1.3.1
Total use of 1L subsequent treatment from BR group	[redacted]	Beta: [redacted]	
Total use of 1L subsequent treatment from R-CHOP group	[redacted]	Beta: [redacted]	
Acalabrutinib + BR: Subsequent 1L ibrutinib	0%	Dirichlet	
Acalabrutinib + BR: Subsequent 1L R-CHOP	74%	Dirichlet	
Acalabrutinib + BR: Subsequent 1L RBAC	11%	Dirichlet	
Acalabrutinib + BR: Subsequent 1L VR-CAP	14%	Dirichlet	
BR: Subsequent 1L ibrutinib	100%	Dirichlet	
BR: Subsequent 1L R-CHOP	0%	Dirichlet	
BR: Subsequent 1L R-BAC	0%	Dirichlet	
BR: Subsequent 1L VR-CAP	0%	Dirichlet	
R-CHOP: Subsequent 1L ibrutinib	100%	Dirichlet	
R-CHOP: Subsequent 1L R-CHOP	0%	Dirichlet	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
R-CHOP: Subsequent 1L RBAC	0%	Dirichlet	
R-CHOP: Subsequent 1L VR-CAP	0%	Dirichlet	
Total use of 2L subsequent treatment from acalabrutinib + BR group	[redacted]	[redacted]	
Total use of 2L subsequent treatment from BR group	[redacted]	[redacted]	
Total use of 2L subsequent treatment from R-CHOP group	[redacted]	[redacted]	
Acalabrutinib + BR: Subsequent 2L R-CHOP	17%	Dirichlet	
Acalabrutinib + BR: Subsequent 2L ibrutinib	0%	Dirichlet	
Acalabrutinib + BR: Subsequent 2L CAR-T	50%	Dirichlet	
Acalabrutinib + BR: Subsequent 2L RBAC	17%	Dirichlet	
Acalabrutinib + BR: Subsequent 2L VR-CAP	17%	Dirichlet	
BR: Subsequent 2L R-CHOP	16%	Dirichlet	
BR: Subsequent 2L ibrutinib	16%	Dirichlet	
BR: Subsequent 2L CAR-T	38%	Dirichlet	
BR: Subsequent 2L RBAC	16%	Dirichlet	
BR: Subsequent 2L VR-CAP	16%	Dirichlet	

Variable	Value	Measurement of uncertainty and distribution (distribution: lower bound, upper bound)	Reference to section in submission
R-CHOP: Subsequent 2L R-CHOP	16%	Dirichlet	
R-CHOP: Subsequent 2L iR-CHOPutinib	16%	Dirichlet	
R-CHOP: Subsequent 2L CAR-T	38%	Dirichlet	
R-CHOP: Subsequent 2L RBAC	16%	Dirichlet	
R-CHOP: Subsequent 2L VR-CAP	16%	Dirichlet	

Abbreviations: 1L, first-line; 2L, second-line; BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor T-cell; OS, overall survival; PD, progressed disease; PFS, progression-free survival; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDI, Relative dose intensity ; TTD, time-to-discontinuation; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

B.3.10.2 Assumptions

In the absence of all required data, it was necessary to introduce key assumptions in order to minimise potential bias in the analysis. A summary of the model assumptions is presented in Table 77.

Table 77: Model assumptions

Model input	Assumption	Rationale
Model structure	The three-state PSM structure captures the health states that are important to patient health outcomes and NHS/PSS costs.	The model type and structure are optimal for use with the data issuing from the ECHO trial, as well as consistent with those accepted for decision making in both identified NICE TAs in R/R MCL (45, 46). In the one TA that was identified for 1L MCL (23), the structure used was a STM; however, the health states used and considered relevant to the patient population at hand were consistent with our economic model. Furthermore, a PSM was suggested by the experts in the advisory board (33). Section B.3.3.2
Survival outcomes	The COVID-19-censored OS and PFS endpoints from the ECHO trial were used to inform model efficacy	When comparing the ECHO OS data for the PBR arm with the placebo arm from the SHINE study (conducted pre-pandemic)

Model input	Assumption	Rationale
	in the base-case analysis, rather than the FAS population, as it removes the effect of the pandemic on the trial results.	(37), it is clear that the ECHO COVID-19-censored OS KM better aligns with the SHINE OS KM when compared with the ECHO FAS OS KM. This suggests that the effect of COVID-19 deaths on the ECHO trial was not aligned with survival data observed outside of the pandemic. Section B.3.4.1.1
	To model OS and PFS for ABR and PBR, independent parametric models were used.	Independent models were chosen in the base-case analysis over joint models (i.e. fitting one parametric model to the entire dataset, with treatment group included as a covariate) as the proportional hazards assumption was not comfortably met. Given this was not clear cut, joint models have been explored in scenario analyses. Section B.3.4.2 and B.3.4.3
	The expected clinical effectiveness of ABR in terms of OS and PFS is captured by ECHO COVID-19-censored data that was extrapolated over a lifetime perspective using standard parametric curves. These curves are capped by the age-adjusted ONS general population survival data.	This approach makes best use of the ECHO trial data and is consistent with both NICE DSU TSD guidance and previous NICE Appraisals. The long-term OS and PFS projections were scrutinized via internal validity checks and were further validated by considering input from haematology-oncology consultants (3). Section B.3.4.1
Relative efficacy	An NMA including the ECHO trial and various comparator trials was performed to assess the clinical efficacy of R-CHOP compared to ABR and BR in an ITC. Analyses were run using the FAS as well as the COVID-19-censored analysis of ECHO, where patients who experienced a COVID-19 death were censored for both PFS and OS outcomes. HRs derived from the NMA, utilising the COVID-19-censored analysis, were applied to the selected parametric survival curves for BR and used to generate OS and PFS curves for R-CHOP.	R-CHOP was not included as a treatment arm in the ECHO trial and, therefore, indirect methods of treatment comparison were conducted using robust methodologies. However, due to limitations in the available evidence for inclusion in the ITC, there are a number of uncertainties related to the inputs and assumptions used; therefore, alternative HRs were explored in scenario analyses. Section B.3.4.5
Time on treatment	For acalabrutinib, the observed TTD data from the ECHO trial was used to determine time on treatment. For BR components of PBR and ABR, the observed TTD data from the ECHO trial was used to determine time on treatment. For R-CHOP, the rituximab TTD data from the ECHO trial was used to determine time on treatment.	Where possible, the ECHO trial was used to determine time on treatment to accurately model the duration over which patients incurred drug costs. Section B.3.4.4 and B.3.6.1.2

Model input	Assumption	Rationale
Subsequent treatments	In the base case analysis, subsequent treatment distributions, at 2L and 3L, were based on expert clinical input.	Although patients in the ECHO trial went on to receive subsequent lines of treatment, the therapies that those patients received were not aligned with available and commonly used treatments given in NHS England clinical practice. Therefore, the distributions of treatments received in 2L and 3L were informed via discussion with clinical experts (3). Section B.3.6.1.3
Utility values	For the progression-free utility value, the ECHO trial data is used in the base-case analysis. To inform the progressed disease utility value, the difference between the HSUVs for the progression-free and progressed disease health states in the most recent 1L MCL NICE technology appraisal, TA502 (45), was estimated and applied to the progression-free utility value estimated in the ECHO trial.	[redacted] Progression free utility values were capped by the age- and gender-adjusted general population value. Section B.3.5.4
AEs	TEAEs, derived from the ECHO trial, are used in the base-case analysis to inform the safety impact – in terms of its associated costs and utility decrements – of ABR and BR. For R-CHOP, TEAEs were derived from LYM-3002 (75). Disutility values were sources from prior TAs, and costs were sourced from standard UK cost sources.	TEAEs from the ECHO trial were used as these are consistent with what is reported in the publication used for R-CHOP. To explore the impact of this, TRAEs were explored in a scenario analysis. Disutility values were sourced from prior TAs in the absence of direct data from the ECHO trial. Section B.3.5.3
Vial sharing	The assumption of vial sharing is employed in the base case analysis. Specifically, this the functionality to assume vial sharing is only applied to rituximab.	Vial sharing is applied to rituximab costs in the base case analysis, given the wide-spread use of rituximab and therefore the perceived likelihood that vials would not be wasted after each use. This assumption is only applied to rituximab for simplicity, as this is the only treatment that is dosed based on body surface area and has a high cost. Other BSA-based drugs are relatively cheap, and, therefore, we have assumed that the impact of vial sharing would be negligible. Section B.3.6.1

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; BSA, body surface area; DSU, decision support unit; FAS, full analysis set; HSUV, health state utility value; ITC, indirect treatment comparison; KM, Kaplan–Meier; MCL, mantle cell lymphoma; NHS, National Health Service; NMA, network meta-analysis; ONS, Office of National Statistics; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; PSM, partitioned survival model; R/R, relapsed refractory; STM, state transition model; TA, technology appraisal; TEAE, treatment-emergent adverse event; TSD, technical support document; TTD, time to treatment discontinuation.

B.3.11 Base case results

B.3.11.1 Base case deterministic incremental cost-effectiveness analysis results

Table 78 displays base case cost-effectiveness results, including total costs, LYs, QALYs, and incremental cost per QALY gained for ABR versus BR and R-CHOP. Results in terms of net health benefit (NHB) are summarised in Table 79. These results are based on the current patient access scheme price for acalabrutinib. All numbers have been rounded up to the nearest integer.

Compared with BR, ABR incurs £[redacted] in additional costs and improves health outcomes per patient by [redacted] QALYs over the period modelled, resulting in an ICER of £10,153 per QALY. Expressed as NHB, this translates into a positive NHB of [redacted] at the cost-effectiveness threshold of £20,000 per QALY, and a positive NHB of [redacted] at a cost-effectiveness threshold of £30,000 per QALY. These results show ABR to be cost effective at the thresholds of £20,000 to £30,000 per QALY.

Compared with R-CHOP, ABR incurs £[redacted] in additional costs and improves health outcomes per patient by [redacted] QALYs over the period modelled, resulting in an ICER of £2,486 per QALY. Expressed as NHB, this translates into a positive NHB of [redacted] at a cost-effectiveness threshold of £20,000 per QALY and a positive NHB of [redacted] at the threshold of £30,000 per QALY. These results show ABR to be cost-effective at the cost-effectiveness threshold of between £20,000 and £30,000 per QALY.

With a fully incremental analysis, R-CHOP is dominated (Table 80).

Table 78: Deterministic base case results (discounted): Pairwise ICER

Technologies	Total costs, £†	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,153
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,486

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 79: Deterministic NHB (discounted)

Technologies	Total costs, £†	Total QALYs	Incremental costs, £	Incremental QALYs	NHB at £20,000	NHB at £30,000
ABR	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; NHB, net health benefit; PAS, patient access scheme; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 80: Deterministic base case results (discounted): incremental analysis

Technologies	Total costs, £†	Total QALYs	Regimen versus comparator	Incremental costs, £	Incremental QALYs	Incremental ICER, £/QALY
R-CHOP	[redacted]	[redacted]				Dominated
BR	[redacted]	[redacted]	N/A	N/A	N/A	-
ABR	[redacted]	[redacted]	BR	[redacted]	[redacted]	10,153

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LYs, life years; N/A, not applicable; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential patient access scheme for acalabrutinib.

B.3.11.2 Probabilistic incremental cost-effectiveness analysis results

Probabilistic results are presented in Table 81 and Table 82. These results are based on the current PAS price for acalabrutinib.

All key parameters were assigned probability distributions, as specified in Table 76. Point estimates were drawn using Monte Carlo simulation techniques. The probabilistic sensitivity analysis (PSA) was run for 1,000 iterations for the base case analyses. Uncertainty around cost-effectiveness is accounted for in the cost-effectiveness plane (Figure 31). The cost-effectiveness acceptability curve showing the incremental costs and QALYs for ABR against BR and R-CHOP is presented in Figure 32, which shows ABR as most likely to be considered cost-effective from a threshold of £20,000 per QALY.

Compared with BR, ABR incurs £[redacted] in additional costs and improves health outcomes per patient by [redacted] QALYs over the period modelled, resulting in an ICER of £11,914 per QALY. Expressed as NHB, this translates into a NHB of [redacted] at the cost-effectiveness threshold of £20,000 per QALY, and a NHB of [redacted] at a cost-effectiveness threshold of £30,000 per QALY. These results show ABR to be cost effective at both thresholds.

Compared with R-CHOP, ABR is associated with a cost savings of £[redacted], and improves health outcomes per patient by [redacted] QALYs over the period modelled, resulting in a dominant ICER. Expressed as NHB, this translates into a positive NHB of [redacted] at the cost-effectiveness threshold of £20,000 per QALY and a positive NHB of [redacted] at a cost-effectiveness threshold of £30,000 per QALY. These results show ABR to be cost effective at the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY.

The probabilistic results for R-CHOP are shown to vary more than those for ABR and BR. This is due to the wide CIs around the relative efficacy estimates for R-CHOP compared to BR, resulting in very varied HRs for R-CHOP in the PSA. Furthermore, the probabilistic ICER is negative (ABR is dominant vs R-CHOP), whilst the deterministic is positive. Owing to this observed discrepancy between the

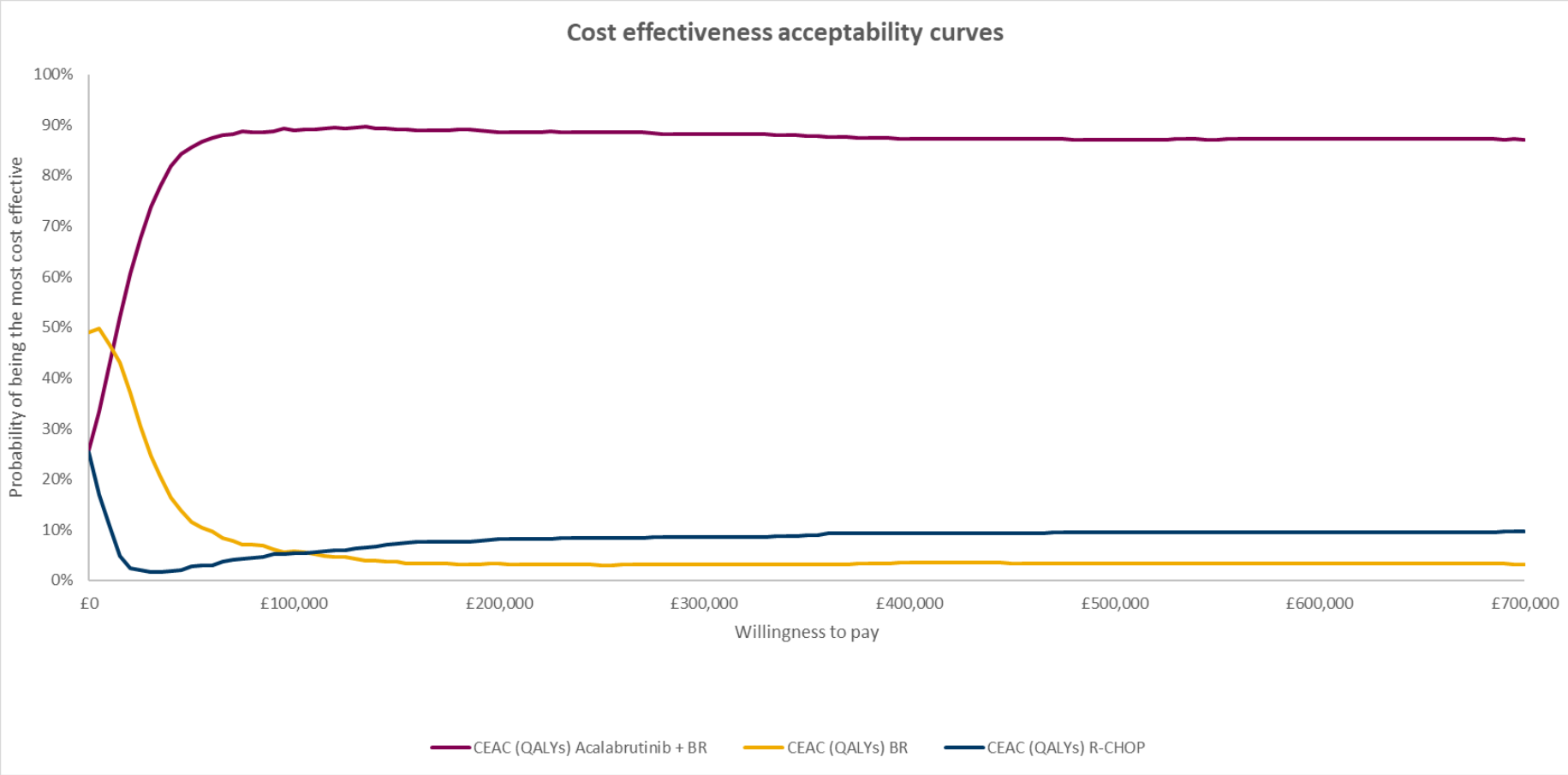
probabilistic and deterministic results, alternative HRs are explored in the scenario analysis.

With a fully incremental analysis, R-CHOP is dominated (Table 83).

Figure 31: Cost-effectiveness plane

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; PAS, patient access scheme; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Figure 32: Cost-effectiveness acceptability curve



Abbreviations: BR, bendamustine + rituximab; CEAC, cost-effectiveness acceptability curve; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 81: Probabilistic base case results (discounted): Pairwise

Technologies	Mean total costs, £†	Mean total LYs	Mean Total QALYs	Mean incremental costs, £	Mean incremental LYG	Mean incremental QALYs	Pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,914
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ABR is dominant

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LY, life year; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 82: Probabilistic NHB (discounted)

Technologies	Mean total costs, £†	Mean total QALYs	Mean incremental costs, £	Mean incremental QALYs	NHB at £20,000	NHB at £30,000
ABR	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 83: Probabilistic base case results (discounted): Incremental analysis

Technologies	Mean total costs, £†	Mean Total QALYs	Regimen versus comparator	Incremental costs, £	Incremental QALYs	Incremental ICER, £/QALY
R-CHOP	[redacted]	[redacted]				
BR	[redacted]	[redacted]	N/A	N/A	N/A	N/A
ABR	[redacted]	[redacted]	BR	[redacted]	[redacted]	11,914

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LY, life year; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

B.3.12 Exploring uncertainty

B.3.12.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) was conducted around the deterministic cost-effectiveness results of ABR as compared to BR, at a base case ICER of £10,153 per QALY. The model parameters are varied between the upper and lower 95% CIs of the expected values, or by ±10% if the CI was not available.

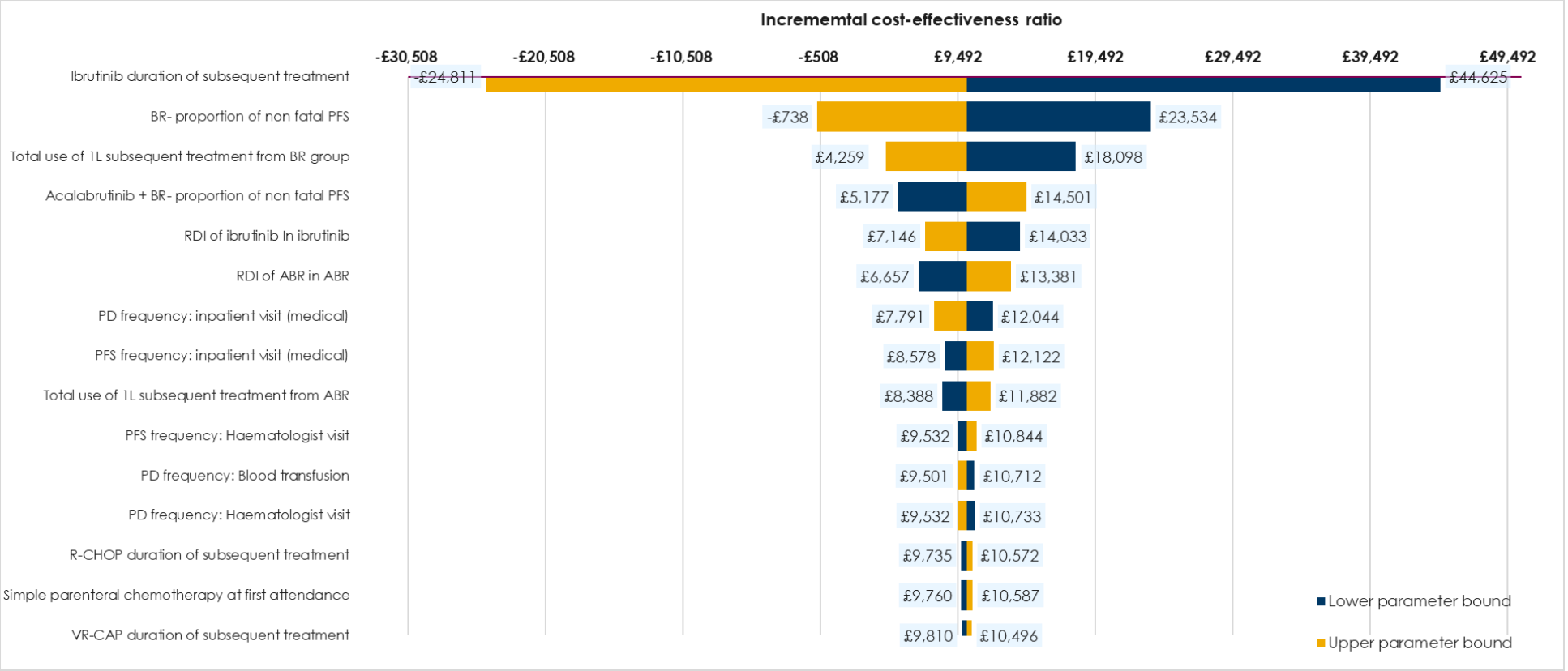
The parameters included in the DSA are presented in Table 84. The results for the top 10 parameters are presented in a tornado diagram in Figure 33. A DSA was not run for ABR as compared to R-CHOP since the fully incremental analysis demonstrated that R-CHOP is dominated.

Table 84: Parameters highlighted in the DSA

Input	ICER (lower value), £/QALY	ICER (upper value) £/QALY	Difference, £/QALY
Ibrutinib duration of subsequent treatment	44,625	-24,811	69,436
BR- proportion of non-fatal PFS	23,534	-738	24,272
Total use of 1L subsequent treatment from BR group	18,098	4,259	13,840
Acalabrutinib + BR- proportion of non-fatal PFS	5,177	14,501	-9,323
RDI of ibrutinib in ibrutinib	14,033	7,146	6,887
RDI of acalabrutinib in acalabrutinib + BR	6,657	13,381	-6,725
PD frequency: Inpatient visit (medical)	12,044	7,791	4,253
PFS frequency: Inpatient visit (medical)	8,578	12,122	-3,544
Total use of 1L subsequent treatment from acalabrutinib + BR group	8,388	11,882	-3,493
PFS frequency: Haematologist visit	9,532	10,844	-1,311
PD frequency: Blood transfusion	10,712	9,501	1,211
PD frequency: Haematologist visit	10,733	9,532	1,201
R-CHOP Duration of subsequent treatment	9,735	10,572	-838
Simple parenteral chemotherapy at first attendance	9,760	10,587	-828
VR-CAP Duration of subsequent treatment	9,810	10,496	-686

Abbreviations: 1L, first-line; BR, bendamustine + rituximab; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; RDI, relative dose intensity; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.
† Includes confidential PAS for acalabrutinib.

Figure 33: Tornado chart – DSA base case of ABR versus BR



Abbreviations: 1L, first-line; ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; DSA, deterministic sensitivity analysis; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PAS, patient access scheme; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDI, relative dose intensity; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.
† Includes confidential PAS for acalabrutinib.

The main drivers of the cost-effectiveness results are the duration of subsequent treatment with ibrutinib, and the proportion of non-fatal PFS in both the BR and the ABR arms. In the base case, these parameters are derived from the ECHO trial and are therefore directly reflective of the modelled population.

Other influential factors include the total use of subsequent treatment in patients initiating treatment with BR. In the model base case, the subsequent treatment distributions were determined by clinical experts in the UK (3), in order to best represent UK clinical practice.

B.3.12.2 Scenario analysis

The scenario analyses reported here test the sensitivity of the cost-effectiveness results to the methodological, parameter, and structural uncertainties in the cost-effectiveness analysis, and form an important element of this submission.

Table 85 describes the different scenarios tested, the rationale behind each, and documents the ICER associated with each scenario in turn. The most impactful scenario is the use of an alternative distribution to estimate acalabrutinib TTD. Overall, the ICER is fairly stable in all explored scenarios, illustrating the robustness of the model base case.

Table 85: Scenario analyses

Base case equivalent	Scenario detail	Brief rationale	ABR versus BR ICER, £/QALY	ABR versus R-CHOP ICER, £/QALY
Base case			10,153	2,486
Population: COVID-19-censored population	ITT population, using exponential for OS and PFS for ABR and BR, and log-logistic for TTD for ABR	Alternative population using the best-fitting survival extrapolations (see Appendix Q): note these have not been clinically validated	21,287	11,041
Curve selection: OS and PFS for ABR and BR: Gamma	OS and PFS for ABR and BR: exponential (most conservative long-term projection)	Alternative structural survival models	8,721	3,989
Curve selection: TTD for acalabrutinib: Weibull	TTD for acalabrutinib: log-normal (best statistical fit)		29,934	12,962
Independent models for OS and PFS	Joint models for OS and PFS (using Gamma, per the base case curve selection)	Alternative structural survival models	5,771	427
PFS HR for R-CHOP against BR: [redacted]	Alternative HR of [redacted] to estimate R-CHOP's PFS	The lower confidence interval of the HR derived from the ITC is used to demonstrate the sensitivity of the model's results to relative efficacy estimates	10,153	10,256
Age-adjusted utility values	No age adjustment for utility values	Alternative utility assumptions	10,153	2,486

Base case equivalent	Scenario detail	Brief rationale	ABR versus BR ICER, £/QALY	ABR versus R-CHOP ICER, £/QALY
Utilities are capped by general population utility	PFS and PD health state utilities are uncapped by general population utility		9,631	2,358
PF utility sourced from ECHO trial PD utility sourced from ECHO trial and adjusted by the difference between PF and PD in TA502	Use TA502 utility values for PF and PD		10,149	2,471
	Use ECHO utility values for PF and PD		11,849	3,212
Vial sharing applied	No vial sharing	Alternative cost assumptions	11,945	3,967
Adverse events for lab-based abnormalities incur cost and disutility of the associated condition (e.g. neutropenia)	Adverse events for lab-based abnormalities incur cost and disutility of 0	Conservative scenario for adverse events reported as blood-test results	9,872	1,918
Discount rate of 3.5%	Discount rate (costs) = 1.5%	Alternative discount rate	11,455	8,214
	Discount rate (outcomes) = 1.5%		8,476	2,084
End of life costs included	End of life care costs excluded	Alternative cost assumption	10,452	2,754

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; DSA, deterministic sensitivity analysis; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention to treat; OS, overall survival; PAS, patient access scheme; PBR, placebo, bendamustine, rituximab; PD, progressed disease; PF, progression free; PFS, progression-free survival; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDI, relative dose intensity; TTD, time to treatment discontinuation.
† Includes confidential PAS for acalabrutinib.

B.3.13 Subgroup analysis

No subgroup cost-effectiveness analyses were conducted.

B.3.14 Benefits not captured in the QALY calculation

ABR has improved PFS and OS rates compared with the current established SoC options. These improvements benefit the patient themselves, as captured in the QALY calculations, in addition to their caregivers and/or family members. This benefit to caregivers/family members would be captured via a societal perspective; however, this perspective is not included in the economic analysis.

B.3.15 Validation

B.3.15.1 Validation of cost-effectiveness analysis

B.3.15.1.1 Validation with external clinical experts

As described in Section B.2.3.8, an advisory board was conducted in July 2024 with three HCPs and three health economists based in the UK, Canada, and Sweden. The objective of the advisory board was to review and appraise the clinical evidence and health economic models for ABR in previously untreated MCL, including discussion of:

- The treatment pathway for patients with previously untreated MCL
- ECHO trial results and the positioning of ABR in the treatment pathway
- Model structure, health states of interest, key modelling assumptions, and missing model inputs

A further four one-to-one interviews were conducted with clinical experts (consultant haematologists) based in England to support clinical assumptions and statements used for this submission (3).

Insights from the advisory board and clinician interviews are provided throughout the dossier. The reports, which are qualitative in nature, are provided as confidential ‘Data on File’ references. Further details are provided Appendix N.

B.3.15.1.2 Technical validation

A health economist, independent to the team involved in the submission, formally validated the cost-effectiveness analysis for internal accuracy. This included checking technical design, calculation implementation, formula accuracy, and extreme value testing. Distributions in the probabilistic analysis were examined, and model structure and inputs were compared with previous NICE appraisals. To ensure a thorough validation, a checklist was used, aligning with the published Technical Verification (TECH-VER) checklist (80). Errors identified during validation were corrected and integrated into the model.

Furthermore, the methodology described throughout this submission followed the NICE guide for health technology evaluations (2022) (52).

B.3.16 Interpretation and conclusions of economic evidence

MCL is an aggressive cancer typically with poor prognosis, and a relapsing course. The addition of targeted agents, such as BTKis, to chemoimmunotherapy, is a key area of advancement in the treatment of MCL and represents a statistically significant and clinically meaningful improvement in PFS.

When considering the efficacy benefits associated with ABR alongside the direct costs, this economic analysis demonstrates the cost effectiveness of ABR as compared with BR and R-CHOP for the treatment of adult patients with pathologically confirmed, previously untreated MCL who are considered unsuitable candidates for ASCT. The deterministic base case analysis indicates that ABR is more costly and more efficacious against both comparators, with an ICER of £10,153 and £2,486 for BR and R-CHOP, respectively.

Aligned with the deterministic base case results, the probabilistic analysis similarly indicated that ABR was cost effective against BR and R-CHOP. For ABR versus BR, the ICER was £11,914. For ABR versus R-CHOP, ABR was shown to be dominant, as ABR is both less costly and more efficacious in this analysis. The probabilistic results for ABR as compared against BR are aligned with the deterministic results. Due to the high CIs in the R-CHOP efficacy data, the probabilistic results for ABR as compared against R-CHOP show notable differences. However, the overall

conclusion of cost effectiveness against R-CHOP holds true. The cost-effectiveness acceptability curve shows that ABR emerges as likely to be considered cost effective from a threshold of £20,000 per QALY onwards. The DSA results show that the ICER is most impacted by variations in the duration of subsequent treatment with ibrutinib and R-BAC, the proportions of non-fatal PFS for both arms, and the total use of 2L subsequent treatments in the BR arm.

The key strengths of the economic assessment are:

- The model structure uses a transparent and flexible framework within which it harnesses the latest available ECHO trial data and best available comparative data from published sources, benefitting from relevant NICE DSU TSD recommendations and consistent with the NICE reference case and the decision problem at hand.
- Several alternative scenarios are presented, allowing for the assessment of uncertainty, including the use of alternative parametric survival models, sources to inform HRQoL inputs, and methods for estimating relative treatment effects.
- The generalisability of the evidence underpinning the economic evaluation to the NHS England treatment setting is strong and has been validated by UK haematology-oncology consultants. The ECHO patient demographics and disease characteristics at baseline were considered by clinical experts to be representative of the targeted patient population of patients with untreated MCL who are considered to be ineligible for ASCT.
- Furthermore, the UK clinical experts also validated the model OS and PFS extrapolations, ensuring external validity was adhered to, alongside the robust internal validity checks that were conducted.
- The model underwent extensive technical review and quality control processes such as TECH-VER and stress-testing (80).

In summary, ABR represents a cost-effective use of UK NHS resources and in the context of a disease that remains incurable ECHO represents a significant and clinically meaningful improvement over currently available SoC for the treatment of patients with previously untreated MCL, considered unsuitable for ASCT.

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B.4 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Addendum to company evidence submission

January 2026

File name	Version	Contains confidential information	Date
ID6155 Acalabrutinib MCL addendum [noCON]	**V1.0**	**Yes**	**5th January 2026**

Contents

Tables and figures

Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
ABR	Acalabrutinib, bendamustine, rituximab
AE	Adverse event
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BR	Bendamustine + rituximab
BTKi	Bruton tyrosine kinase inhibitor
CAR-T	Chimeric antigen receptor – T cell
CI	Confidence interval
DCO1	Data cut off 1 – 15th February 2024
DCO2	Data cut off 2 – 15th February 2025
FAS	Full analysis set
HR	Hazard ratio
IRC	Independent review committee
ITT	Intent-to-treat
IXRS	Interactive voice/web response system
MCL	Mantle cell lymphoma
KM	Kaplan-Meier
NE	Not estimable
NHB	Net health benefit
OS	Overall survival
PBR	Placebo, bendamustine, rituximab
PFS	Progression-free survival
PFS2	Time to second disease progression
PH	Proportional hazards
SAE	Serious adverse event
TTD	Time to treatment discontinuation
TTNT2	Time to next treatment 2

1 Clinical effectiveness

In the original company submission (November 2024), data from the Phase 3 ECHO trial comparing acalabrutinib in combination with bendamustine and rituximab (ABR) to placebo plus bendamustine and rituximab (PBR) in patients with previously untreated mantle cell lymphoma (MCL) were available from an interim data cut (referred to as DCO1: 15th February 2024). Updated efficacy and safety data are now available with an additional 12 months of follow-up (referred to as DCO2: 15th February 2025) and are provided in this addendum.

Data from DCO2 are drawn from multiple sources:

- Wang ML, et al. abstract from 67th ASH Annual Meeting[1] – data in the public domain
- Wang ML, et al. poster presentation at 67th ASH Annual Meeting[2] – data in the public domain
- AstraZeneca Data on File. ID: REF-299562. December 2025[3] – confidential information
- AstraZeneca 2.5 Clinical Overview. CALQUENCE® for the Treatment of Patients with Previously Untreated Mantle Cell Lymphoma 2025[4] – confidential information

1.1 Primary efficacy outcome: progression-free survival (PFS) by independent review committee (IRC)

1.1.1 Full analysis set (FAS) population

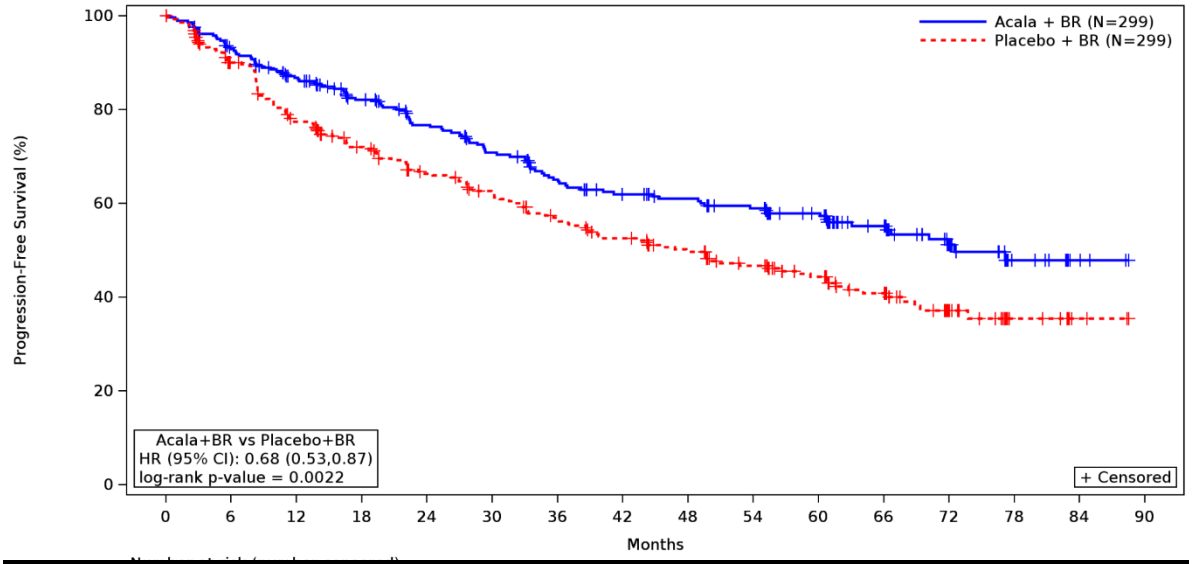
Based on DCO2 (15th February 2025), with a median follow up of 60.8 months, median PFS by IRC was 72.5 months with ABR versus 47.8 months with PBR (absolute difference of 24.7 months), corresponding to a 32% reduction in risk of progression or death (hazard ratio [HR]: 0.68; 95% confidence intervals [CI]: 0.53, 0.87; p=0.002) (see Table 1). The Kaplan-Meier (KM) plot is shown in Figure 1.

Table 1: Analysis of PFS by IRC assessment (FAS): DCO2 (15th February 2025)

	ABR (N=299)	PBR (N=299)
Patient status		
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
PFS (months)		
Median (95% CI)	72.5 (60.7, NE)	47.8 (36.1, 60.8)
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	0.68 (0.53, 0.87)	-
p-value§	0.0022	-
Unstratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	[redacted]	-
p-value§	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.
† Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0–3], Intermediate Risk [4–5], High Risk [6–11]) as collected via IXRS.
‡ Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively.
§ Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375. Time to event (or time to censor for censored patients) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
"+" indicates a value from a censored patient.
Sources: AstraZeneca. Data on File. ID: REF-299562. December 2025[3]; Wang ML, et al. 67th ASH Annual Meeting.[2]

Figure 1: KM plot for PFS by IRC assessment (FAS): DCO2 (15th February 2025)



[redacted]

Abbreviations: Acala + BR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; DCO2, data cutoff 2; HR, hazard ratio; IXRS, Interactive Voice/Web Response System; MIPI, Mantle Cell Lymphoma International Prognostic Index; Placebo + BR, placebo, bendamustine, rituximab; OS, overall survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors simplified MIPI score as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025[3]; Wang ML, et al. 67th ASH Annual Meeting.[2]

1.1.2 PFS COVID-19-censored

Because ECHO occurred during the COVID-19 pandemic, a pre-specified sensitivity analysis was conducted, in which deaths related to COVID-19 were censored. After censoring COVID-19-related deaths at DCO2, median PFS improved to [redacted] for ABR versus [redacted] for PBR (Table 2). The stratified HR was [redacted], translating into a [redacted] % reduction in the risk of progression or death. The KM plot is shown in Figure 2.

Table 2: Analysis of PFS by IRC assessment (FAS: censoring confirmed/suspected COVID-19 death): DCO2 (15th February 2025)

	ABR (N=299)	PBR (N=299)
Patient status		
Events, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Progression-free survival (months)		
Median (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	[redacted]	-
p-value§	[redacted]	-
Unstratified analysis (versus PBR)†		
Hazard ratio (95% CI)‡	[redacted]	-
p-value§	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimable; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.
† Stratified/unstratified by randomisation stratification factors: Geographic Region (North America, Western Europe, Other) and simplified MIPI Score (Low Risk [0–3], Intermediate Risk [4–5], High Risk [6–11]) as collected via IXRS.
‡ Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively.
§ Estimated based on stratified or unstratified log-rank test for p-value, respectively.
Months are derived as days/30.4375. Time to event (or time to censor for censored patients) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
"+" indicates a value from a censored patient.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025.[3]

Figure 2: KM plot for PFS by IRC assessment (FAS: censoring confirmed/suspected COVID-19 death): DCO2 (15th February 2025)

Abbreviations: acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; MIPI, Mantle Cell Lymphoma International Prognostic Index.
HR (95% CI) are based on stratified Cox-Proportional-Hazards model, stratified by randomisation stratification factor Simplified MIPI Score as recorded in IXRS.
P-value is based on stratified log-rank test, stratified by randomisation stratification factor Simplified MIPI Score as recorded in IXRS.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025.[3]

1.1.3 Clinical interpretation and comparison with DCO1

With an additional 12 months follow-up (DCO2), the magnitude of PFS benefit increased beyond what was observed and presented in the original submission (DCO1). In the FAS population, the reduction in risk of progression or death increased from 27% (HR: 0.73; 95% CI: 0.57, 0.94; p=0.0160) to 32% (HR: 0.68; 95% CI: 0.53, 0.87; p=0.002), with a corresponding widening of the absolute difference between arms to 24.7 months, compared with 16.8 months at DCO1. When deaths related to COVID-19 were censored, the risk of disease progression or death increased from 36% at DCO1 to [redacted] % at DCO2. The results of the sensitivity analysis evaluating the impact of COVID-19 deaths confirm the robustness of the primary analysis and indicate that the clinical benefit of ABR over PBR was not compromised despite the number of COVID-19 deaths reported in the study.

These updated data demonstrate that the benefit of ABR is durable, underscoring the robustness and clinical relevance of early Bruton tyrosine kinase inhibitor (BTKi) use in this population. The favourable PFS benefit is maintained when COVID-19 deaths

are censored, affirming the validity of the treatment effect. The updated PFS analysis confirms that ABR provides a clinically meaningful extension of remission, with a median PFS approximately 2 years longer than PBR.

1.2 Secondary efficacy outcome: overall survival (OS)

1.2.1 FAS

Based on DCO2 (15th February 2025), there was a positive OS trend in favour of ABR for the FAS. With an OS maturity rate of [redacted] % ([redacted] target events), the HR was 0.87 (95% CI: 0.67, 1.13).

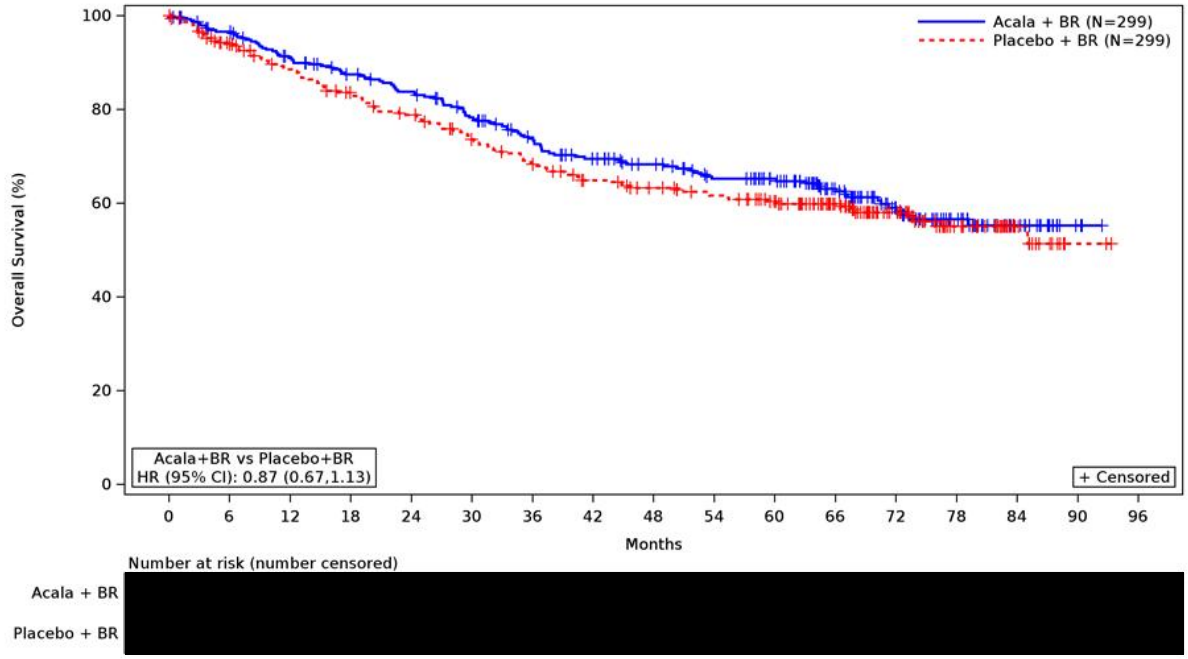
With a median follow-up of 51.9 months, there were an additional 11 deaths in the ABR arm (108 total deaths) and 10 additional deaths in the PBR arm (116 total deaths) versus DCO1. Median OS was not reached in either arm. The KM plot is provided in Figure 3.

Table 3: Analysis of OS (FAS): DCO2 (15th February 2025)

	ABR (N=299)	PBR (N=299)
Patient status		
Total deaths, n (%)†	108 (36.1%)	116 (38.8%)
Censored, n (%)	[redacted]	[redacted]
Overall survival (months)		
Median (95% CI)	NE (73.3, NE)	NE (73.8, NE)
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	0.87 (0.67, 1.13)	-
Unstratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; IXRS, interactive voice/web response system; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab.
† Death from any cause.
‡ Based on stratified or unstratified Cox proportional hazards model, by randomisation stratification factors as recorded in IXRS if stratified.
§ Based on stratified or unstratified log-rank test, by randomisation stratification factors as recorded in IXRS if stratified.
Months are derived as days/30.4375. Time to event (or time to censor for censored patient) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
'+' indicates a value from a censored patient.
Source: AstraZeneca Clinical Overview Calquence® for MCL[4]; Wang ML, et al. 67th ASH Annual Meeting.[2]

Figure 3: KM plot for OS (FAS): DCO2 (15th February 2025)



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; KM, Kaplan–Meier; OS, overall survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.
Source: AstraZeneca Clinical Overview Calquence® for MCL[4]; Wang ML, et al. 67th ASH Annual Meeting.[2]

1.2.2 OS COVID-19-censored

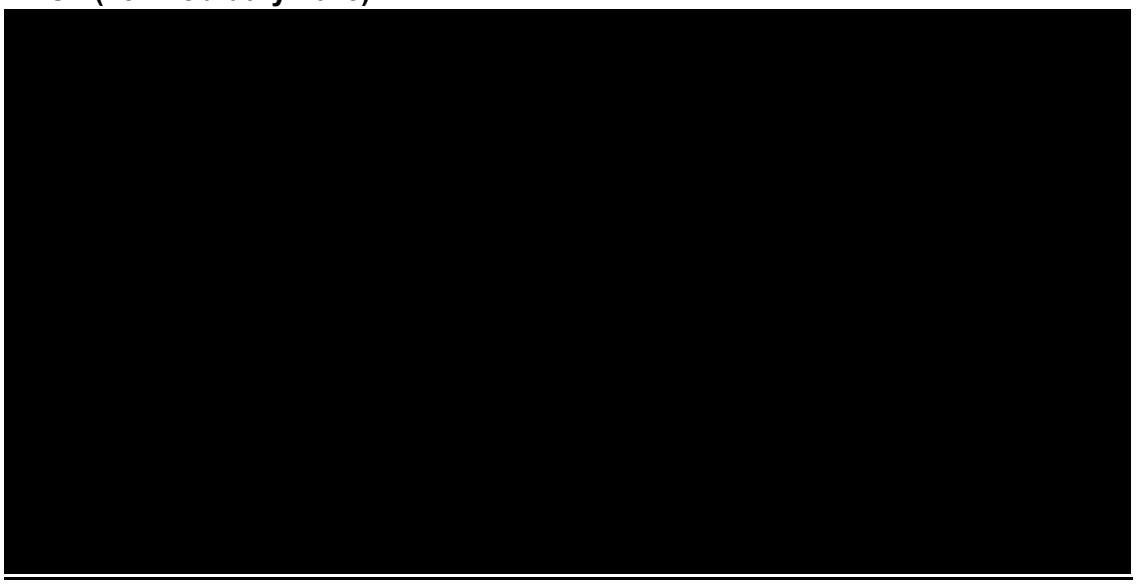
After censoring for COVID-19-related deaths, the OS HR was [redacted] (95% CI: [redacted]), consistent with the main analysis and supporting the conclusion that the clinical benefit of ABR over PBR is maintained despite the confounding effect of COVID-19 mortality (Table 4).

Table 4: Analysis of OS (FAS: censoring confirmed/suspected COVID-19 death): DCO2 (15th February 2025)

	ABR (N=299)	PBR (N=299)
Patient status		
Total deaths, n (%)†	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
COVID-19 death††	[redacted]	[redacted]
Lost to follow-up immediately after randomisation	[redacted]	[redacted]
Not known to have died at or prior to data cut-off date	[redacted]	[redacted]
Not known to have died at or prior to lost to follow-up or study exit 48	[redacted]	[redacted]
Overall survival (months)		
Median (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
Stratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	[redacted]	-
p-value¶	[redacted]	-
Unstratified analysis (versus PBR) ‡		
Hazard ratio (95% CI)§	[redacted]	-
p-value¶	[redacted]	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; IXRS, interactive voice/web response system; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab.
† Death from any cause.
‡ Based on stratified or unstratified Cox proportional hazards model, by randomisation stratification factors as recorded in IXRS if stratified.
§ Based on stratified or unstratified log-rank test, by randomisation stratification factors as recorded in IXRS if stratified.
¶ Estimated based on stratified or unstratified log-rank test for p-value.
Months are derived as days/30.4375. Time to event (or time to censor for censored patient) was calculated as date of disease progression or death (censoring date for censored patients) – randomisation date + 1.
†† COVID-19 deaths include all grade 5 Confirmed/Suspected COVID-19 infection AEs and deaths due to a reason specified as COVID-19.
'+' indicates a value from a censored patient.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025.[3]

Figure 4: KM plot for OS (FAS: censoring confirmed/suspected COVID-19 death): DCO2 (15th February 2025)



Abbreviations: acala, acalabrutinib; BR, bendamustine and rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; KM, Kaplan-Meier; MIPI, Mantle Cell Lymphoma International Prognostic Index.
HR (95% CI) are based on stratified Cox-Proportional-Hazards model, stratified by randomisation stratification factor Simplified MIPI Score.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025.[3]

1.2.3 Clinical interpretation and comparison with DCO1

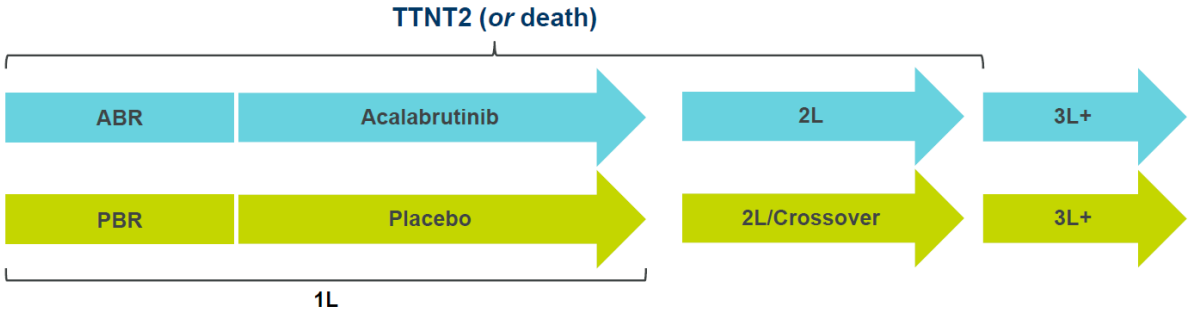
OS results were consistent with the previous analysis. At DCO2, data maturity had increased to [redacted] % (from 34% at DCO1). Median OS was still not reached in either arm, and a consistent positive trend was observed in favour of ABR, in line with the data from DCO1 presented in the original company submission (HR: 0.87 [95% CI: 0.67, 1.13] at DCO2 vs 0.86 [95% CI: 0.658, 1.13; p=0.2742] at DCO1). The results of the sensitivity analysis censoring for COVID-19 deaths were consistent with the main analysis, supporting the conclusion that the clinical benefit of ABR over PBR is maintained despite the confounding effect of COVID-19 mortality. Importantly, the last reported COVID-19-related deaths in the ABR and PBR arms occurred in June 2023 and October 2023, respectively, underscoring the positive impact of COVID-19 vaccination on mitigating the mortality associated with COVID-19 for these patients.

1.3 Post-hoc analysis: time to next treatment 2 (TTNT2): DCO2

1.3.1 FAS

To further understand the impact of treatment sequencing after ABR/PBR in first-line (1L) MCL, a post-hoc analysis of TTNT2 was conducted based on DCO2. TTNT2 is defined as time from randomisation to second subsequent (third-line [3L]) therapy after discontinuation of randomised treatment, or death, as presented in Figure 5. TTNT2 may be considered a surrogate for PFS2 (time from initial treatment to second disease progression). Analysis of TTNT2 was not available at the time of the original company submission.

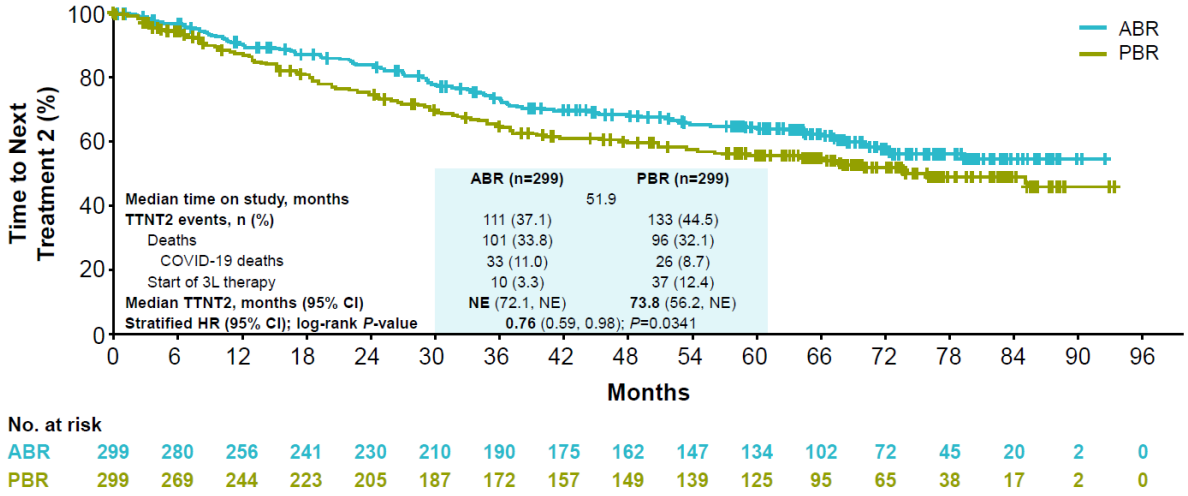
Figure 5: Time to next treatment 2 (TTNT2)



Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; PBR, placebo, bendamustine, rituximab; TTNT2, time to next treatment 2.
Source: Wang ML, et al. 67th ASH Annual Meeting.[2]

At DCO2, ABR lowered the risk of needing 3L therapy by 24% compared with PBR (HR: 0.76, 95% CI: 0.59, 0.98; p=0.0341). The median TTNT2 was not reached in the ABR arm (95% CI: 72.1, NE), compared with 73.8 months (56.2, NE) in the PBR arm (Figure 6).

Figure 6: KM plot for TTNT2 (FAS): DCO2 (15th February 2025)



Abbreviations: 3L, third-line; ABR, acalabrutinib, bendamustine, rituximab; CI, confidence interval; DCO2, data cut off 2; FAS, full analysis set; HR, hazard ratio; NE, not estimable; PBR, placebo, bendamustine, rituximab; TTNT2, time to next treatment 2.
Source: Wang ML, et al. 67th ASH Annual Meeting.[2]

1.3.2 TTNT2 COVID-19-censored

When COVID-19-related deaths were censored, the HR for TTNT2 further improved to a 33% reduction in risk of needing 3L therapy with ABR compared with PBR (HR: 0.67; 95% CI: 0.50, 0.89; median TTNT2 NR in either arm).

1.3.3 Clinical interpretation

Despite crossover, TTNT2 was prolonged in the ABR arm (~24% risk reduction), emphasising the clinical value of combining acalabrutinib with BR in 1L, rather than reserving it for later lines.

1.4 Subsequent treatment: DCO2

Subsequent therapy was required by only 11% of patients in the ABR arm, compared with 33% in the PBR arm, as outlined in Table 5.

Table 5: Subsequent treatments in ECHO: DCO2 (15th February 2025)

Number of patients	ABR (N=299)	PBR (N=299)
≥1 subsequent anticancer therapy	33	100
2L anticancer therapy	33	100
BTKi	12	79
Chemotherapy	11	13

Number of patients	ABR (N=299)	PBR (N=299)
Non-BTKi targeted therapy	9	6
Others	1	3
3L anticancer therapy	10	37
BTKi	3	7
Chemotherapy	4	19
Non-BTKi targeted therapy	3	11
4L+ anticancer therapy	3	14
BTKi	0	5
Chemotherapy	2	7
Non-BTKi targeted therapy	1	7

Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; ABR, acalabrutinib, bendamustine, rituximab; BTKi, Bruton tyrosine kinase inhibitor; DCO2, data cut off 2; PBR, placebo, bendamustine, rituximab.
Source: Wang ML, et al. 67th ASH Annual Meeting.[2]

Patients in the PBR arm required approximately twice as many high-impact therapies such as chimeric antigen receptor T cell therapy (CAR-T), autologous stem cell transplant (ASCT), or bispecific antibodies ([redacted] % of ABR patients versus [redacted] % of PBR patients; Figure 7), which carry substantial acute and chronic toxicities. With ABR, subsequent therapy was needed less often and later, reflecting deeper, more durable disease control. This two-fold difference is clinically meaningful, underscoring that patients randomised to ABR were not only less likely to require multiple lines of therapy, but also less likely to be exposed to the substantial risks associated with intensive salvage strategies.

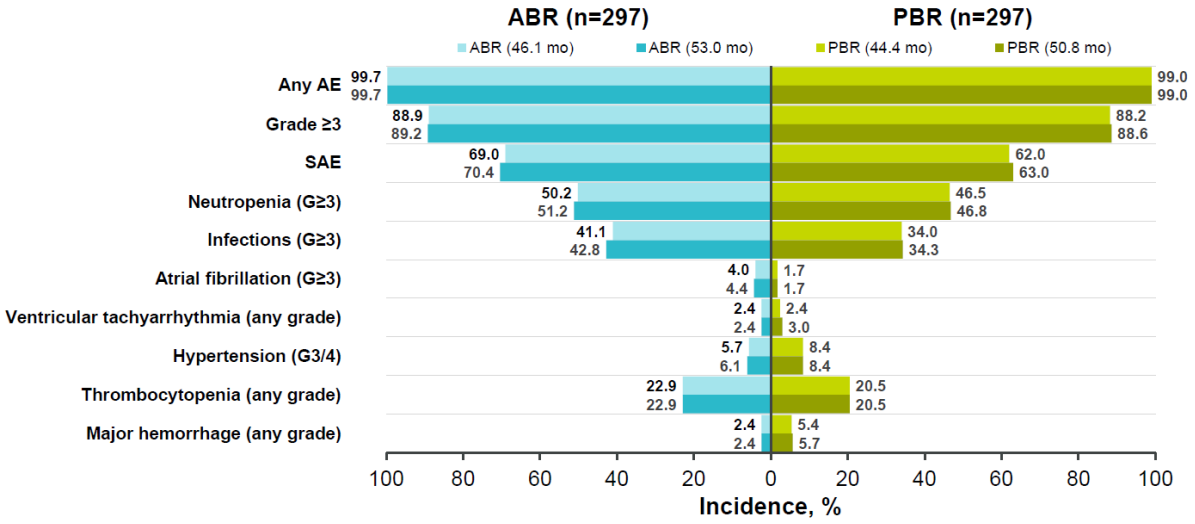
Figure 7: Subsequent high-impact therapies in ECHO: DCO2 (15th February 2025)

Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; DCO2, data cut off 2.
Source: AstraZeneca. Data on File. ID: REF-299562. December 2025.[3]

1.5 Safety

At DCO2, the safety profile remained favourable and similar between arms with longer follow-up, with no new signals despite continuous acalabrutinib therapy in the ABR arm (Figure 8). Rates of grade 3 adverse events (AEs) and serious adverse events (SAEs) in the ABR arm were comparable to previously reported rates, indicating that prolonged acalabrutinib exposure does not appear to result in cumulative toxicities. Three new cases of grade 3/4 neutropenia were reported, with no marked changes in the rates of grade ≥3 or serious infections. The rate of grade ≥3 cardiac events remained consistent with the primary analysis. In the ABR arm, 1 new case of grade 3/4 atrial fibrillation and 1 new case of grade 3/4 hypertension were reported. Rates of thrombocytopenia, major haemorrhage, and ventricular tachyarrhythmia remained unchanged.

Figure 8: Summary of AEs in ECHO: DCO2 (15th February 2025)



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AE, adverse event; DCO2, data cut off 2; G, grade; PBR, placebo, bendamustine, rituximab; SAE, serious adverse event.
Source: Wang ML, et al. 67th ASH Annual Meeting.[2]

1.6 Conclusion

For patients with MCL aged ≥65 years who are ineligible for ASCT, ABR delivered a durable, clinically meaningful improvement in disease control, which was maintained for an additional 12 months after the initial DCO presented in the original company submission. IRC-assessed median PFS was approximately 25 months longer versus PBR (Section 1.1), with consistent, directionally favourable OS signals (Section 1.2) despite the impact of COVID-19. ABR delays the need for subsequent therapy, with lower reliance on high-impact interventions, such as CAR-T and bispecific antibodies (Sections 1.3 and 1.4).

This consistent and clinically meaningful efficacy is achieved with a safety profile that is anticipated and manageable. Infections and cytopenias are the most frequent events (mainly driven by COVID-19 during peak pandemic) and are generally mitigated by monitoring, prophylaxis, and dose modification. Importantly, the absence of newly reported COVID-19-related deaths since DCO1 highlights the effectiveness of current mitigation strategies for managing COVID-19 infections in this patient population. The safety profile remained similar with longer follow-up, with no new signals at DCO2 despite continuous acalabrutinib therapy in the ABR arm (Section 1.5).

Combined with the data provided in the original company submission, the comprehensive and updated data provided in this addendum further substantiate the benefits of ABR in this population. In ECHO, ABR delivered superior disease control (~32% reduction in risk of progression or death) and reduced reliance on salvage therapies (~3-fold fewer subsequent lines), including intensive interventions (~2-fold fewer high-impact therapies). Thus, ABR optimises 1L efficacy while lowering cumulative toxicity risk across the treatment journey.

2 Cost effectiveness

2.1 ECHO trial data cut off: 15th February 2025

This section includes updated survival analysis derived from the second data cut of ECHO (15th February 2025) for the censored COVID-19 deaths and FAS (i.e. intent-to-treat [ITT]) analyses. All endpoints used are the same as those defined in the company submission. Throughout this addendum, the interim data cut (15th February 2024) is referred to as DCO1, with the latest data cut (15th February 2025) referred to as DCO2.

2.1.1 Censored COVID-19 deaths analysis

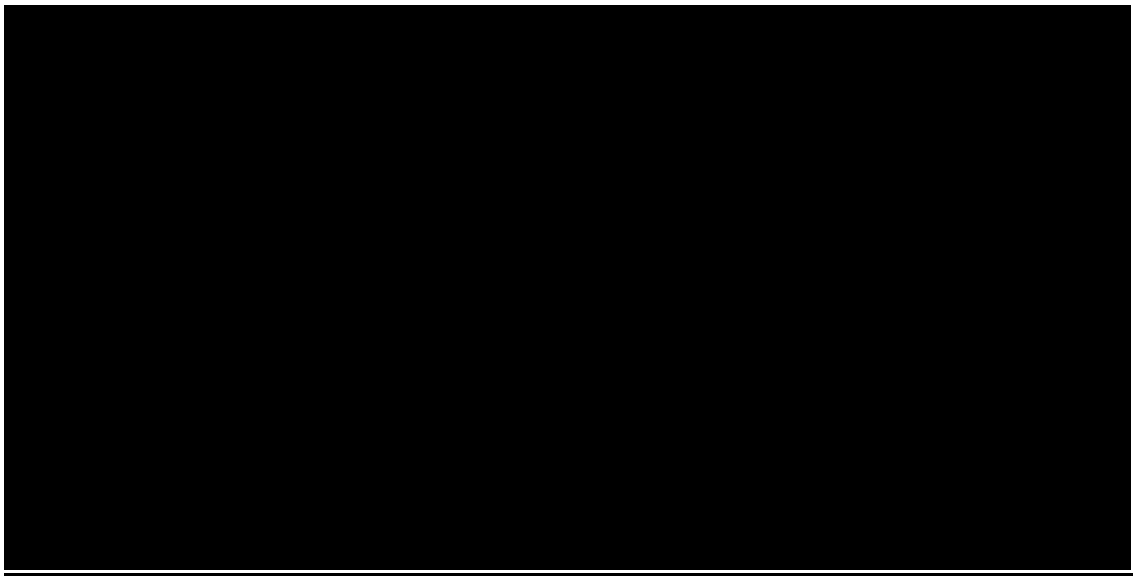
2.1.1.1 PFS

PFS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for PFS from the ECHO trial (censored COVID-19 deaths) (DCO2: 15th February 2025). The observed trial data and corresponding KM curve are presented in Section 1.1.2.

2.1.1.1.1 Diagnostic assessment

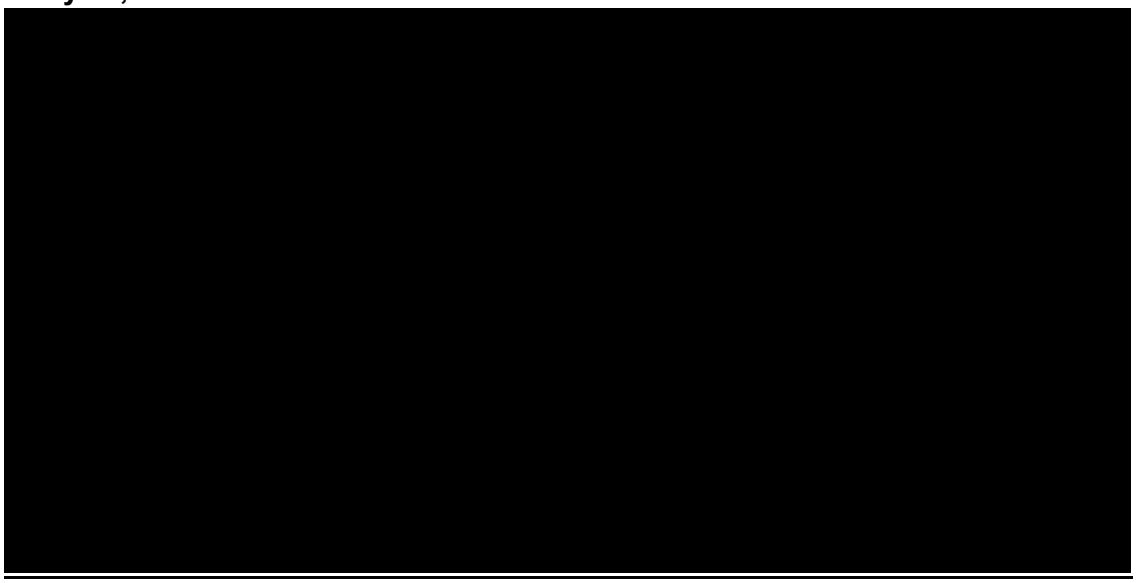
Aligned with the company submission, the methods outlined in NICE DSU TSD 14 were followed to determine the appropriate method of extrapolation of the PFS data over the lifetime horizon.[5] First, assessment of proportional hazards (PH) between the two arms was undertaken using Schoenfeld residuals (Figure 9) and log-cumulative hazards plots (Figure 10). Similar to DCO1, the Schoenfeld residual test reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. However, the visual inspection of the log-cumulative hazard curves do not appear to be parallel over time, with crossing of hazards observed. While the Schoenfeld residuals plot shows a relatively linear gradient over time, there are deviations at the tails and a non-zero gradient for residuals is observed over the follow-up period, therefore indicating that proportionality may not be reasonable to assume. Given the totality of the diagnostic assessment indicating a possibility for PH to be violated, independent parametric models were fitted to the patient-level PFS data from the ECHO trial, aligned with the approach taken for DCO1.

Figure 9: Schoenfeld residual plots for PFS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; PFS, progression-free survival.

Figure 10: Log-cumulative hazard plots for PFS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: BR, bendamustine + rituximab; DCO2, data cut off 2 – 15th February 2025; PFS, progression-free survival.

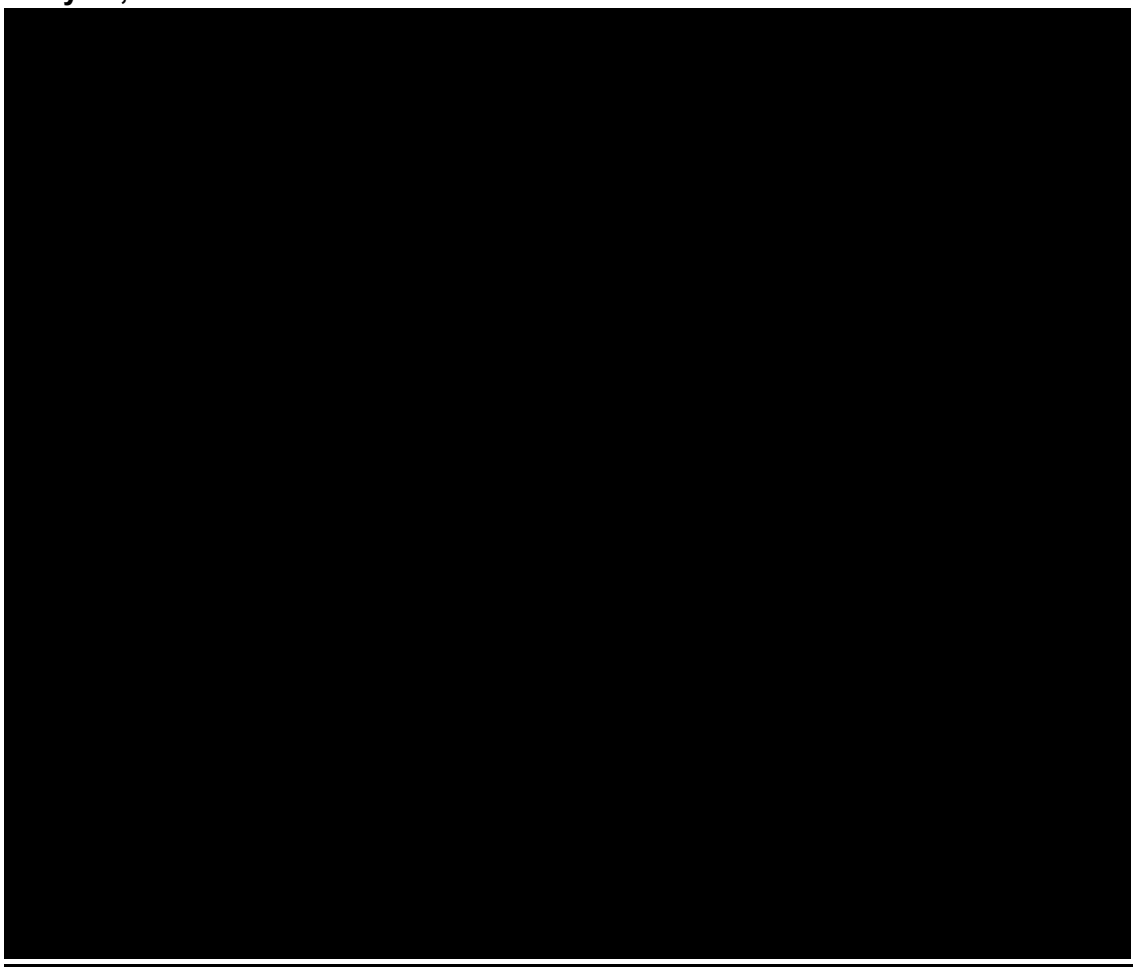
2.1.1.1.2 Visual and statistical fit

Next, parametric survival models were fitted to patient-level PFS data for each arm of the ECHO study and assessed for goodness-of-fit. Aligned with DCO1, the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma and Gompertz) were considered. Based on visual inspection of the

extrapolations fitted in Figure 11 and Figure 12, all models provide a relatively similar fit in to the KM estimates in the initial three years.

All but the exponential model provide a reasonable fit to the KM in both the PBR and ABR arms.

Figure 11: PBR KM and parametric curves for PFS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; KM, Kaplan–Meier; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Figure 12: ABR KM and parametric curves for PFS data: censored COVID-19 deaths analysis, DCO2

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; KM, Kaplan–Meier; PFS, progression-free survival.

The statistical fit of each distribution was assessed using both the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) goodness-of-fit statistics, with the results summarised in Table 6. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. For all models used for ABR and PBR, the AIC and BIC statistics were similar, which suggests that the parametric models fit relatively well to the observed portion of the PFS data. The log-normal curve provided the best statistical fit for ABR, with the log-logistic providing the best fit for PBR. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 6: AIC and BIC scores for parametric curves for PFS data: censored COVID-19 deaths analysis, DCO2

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

2.1.1.1.3 Landmark and external validation

To externally validate the PFS extrapolations, landmark estimates of PFS from ECHO DCO2 were assessed.

PFS extrapolations at different landmarks are displayed in Table 7 for PBR and Table 8 for ABR. Based on the latest available landmark at approximately 6 years from ECHO DCO2, the exponential, Weibull, and gamma distributions provided the most closely aligned predictions within the observed data range.

Table 7: PBR landmark PFS proportions for parametric curves: censored COVID-19 deaths analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	[redacted]	[redacted]	[redacted]	-
SHINE	80.0%	68.2%	43.5%	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO2, data cut off 2 – 15th February 2025; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Table 8: ABR landmark PFS proportions for parametric curves: censored COVID-19 deaths analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; PFS, progression-free survival.

2.1.1.1.4 PFS curve selection conclusion

Four UK clinical experts with experience of treating MCL were consulted previously to estimate long-term PFS in this population. The experts noted they would expect PFS at 10 years to be between 20–25% in the cohort of patients with previously untreated MCL treated with BR.[6] As presented in Table 7, PFS extrapolations using the exponential, Weibull and gamma distributions resulted in long-term projections that best aligned with the expert viewpoint at Year 10.

For the long-term PFS estimates of ABR, there was no clear consensus among the clinical experts on a reasonable long-term estimation for PFS. They did, however, highlight that in alignment with the observed PFS benefit in the ECHO trial for the ABR arm, a clinical benefit in favour of ABR compared with BR would be expected in 1L MCL.[6]

The selection of an appropriate parametric distribution to PFS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness-of-fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14,[5] the same distribution was preferred across both treatment arms; therefore, the final selection considered models that were appropriate to select for both treatment arms.

Based on the goodness-of-fit assessment, none of the distributions had a substantially improved fit relative to others. However, when expert feedback was

considered, the log-normal, Gompertz, generalised gamma and log-logistic were deemed to overestimate long-term PFS and could therefore be excluded. Among the remaining exponential, Weibull and gamma distributions, most clinical experts preferred the relatively more conservative long-term estimate of PFS based on the exponential distribution. However, the expert preference for an exponential curve for both treatment arms is at odds with the diagnostic assessments, which suggested the possibility for the PH assumption to be violated for PFS. On this basis, the gamma distribution was selected for the base case extrapolation of PFS.

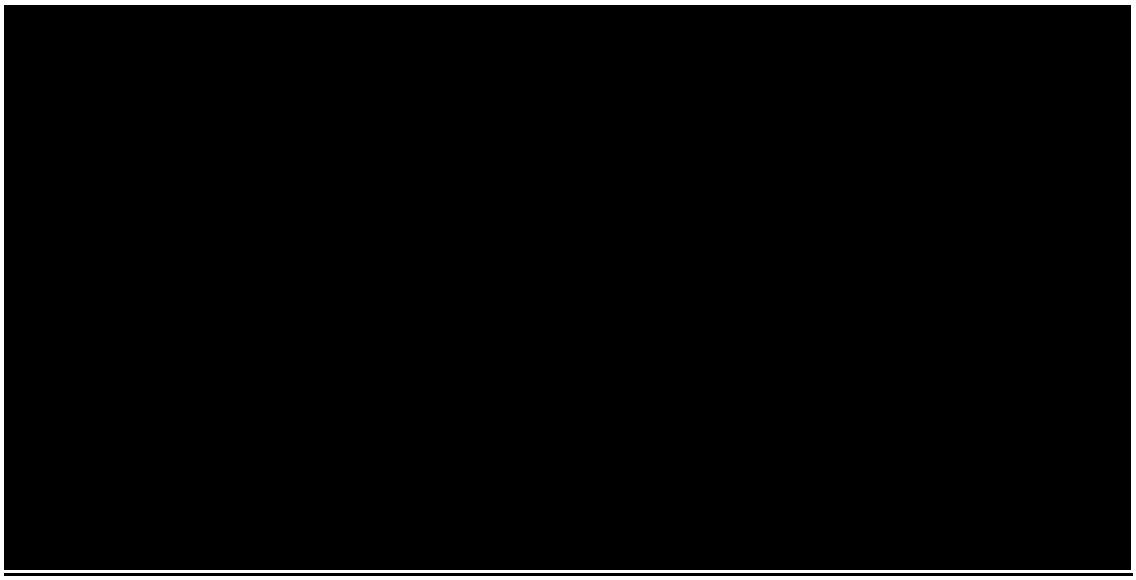
2.1.1.2 OS

OS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for OS from the ECHO trial (censored COVID-19 deaths) (DCO2: 15th February 2025). A summary of the observed trial data and corresponding KM curve is presented in Section 1.2.2.

2.1.1.2.1 Diagnostic assessment

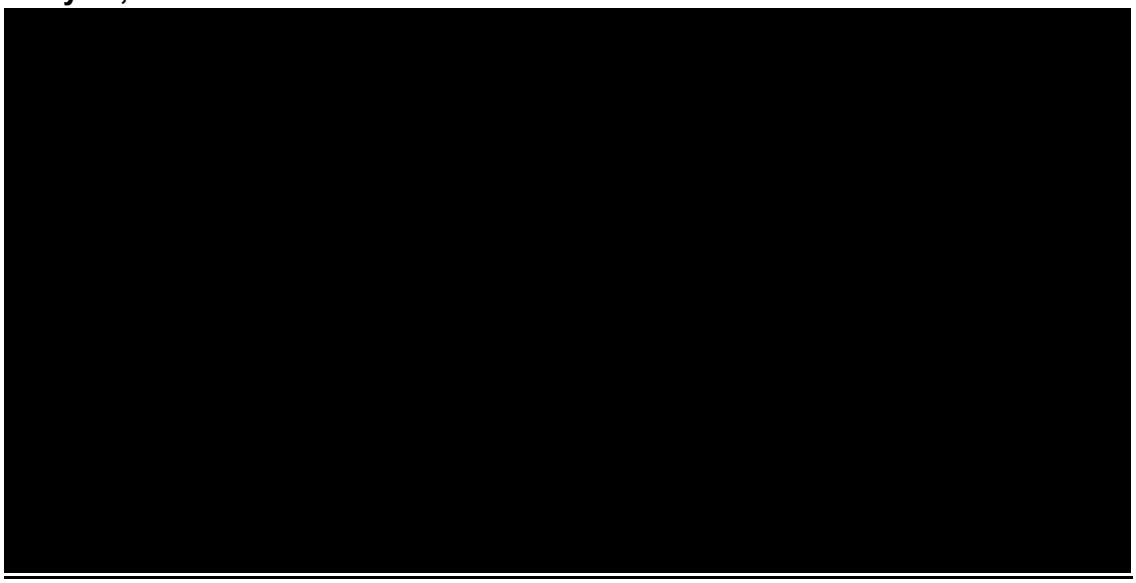
Aligned with the company submission, and approach taken for PFS, assessment of PH between the two arms was undertaken using Schoenfeld residuals (Figure 13) and log-cumulative hazards plots (Figure 14). Similar to DCO1, the Schoenfeld residual test, reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. However, the visual inspection of the log-cumulative hazard curves does not appear to be generally parallel, with the curves converging over time. Further, the Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals emerges at the tail of the plot, therefore indicating that proportionality may not be reasonable to assume. On balance, the diagnostic assessment implies a possibility for PH to be violated, and for consistency with the approach taken for PFS, independent parametric models were fitted to the patient-level OS data from the ECHO trial, aligned with the approach taken for DCO1.

Figure 13: Schoenfeld residual plots for OS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; OS, overall survival.

Figure 14: Log-cumulative hazard plots for OS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; BR, bendamustine + rituximab; OS, overall survival.

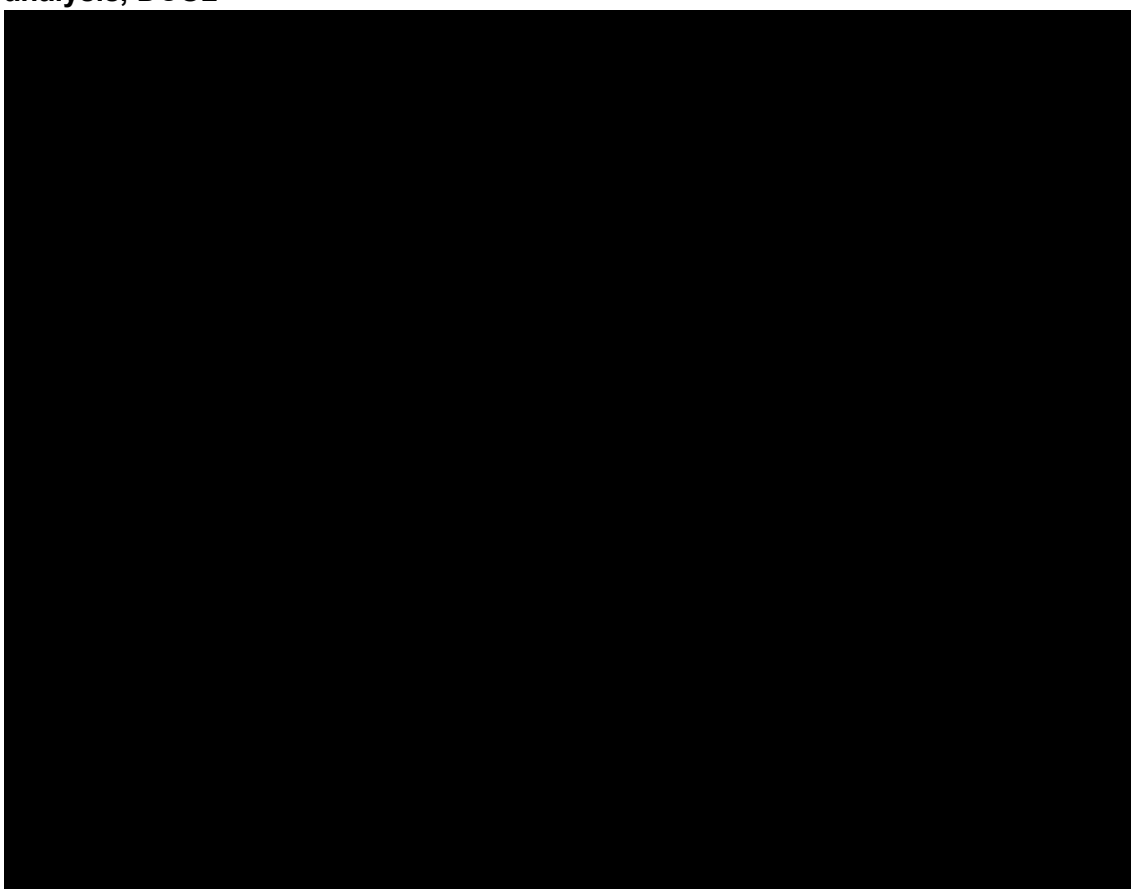
2.1.1.2.2 Visual and statistical fit

Parametric survival models were fitted to patient-level OS data for each arm of the ECHO study and assessed for goodness-of-fit. Aligned with DCO1, the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma and Gompertz) were considered. Based on visual inspection of the extrapolations fitted in Figure 15 and Figure 16, all models align closely with the KM

estimates in the initial three years, with the exception of the exponential curve, which initially overestimates survival and later underestimates relative to the KM curve.

The log-normal, generalised gamma, Gompertz, and log-logistic curves in both the PBR and ABR arms provide a slightly better fit compared to the other curves available.

Figure 15: PBR KM and parametric curves for OS data: censored COVID-19 deaths analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; KM, Kaplan–Meier; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Figure 16: ABR KM and parametric curves for OS data: censored COVID-19 deaths analysis, DCO2

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; KM, Kaplan–Meier; OS, overall survival.

The statistical fit of each distribution was assessed using both the AIC and the BIC goodness-of-fit statistics, with the results summarised in Table 9. For all models used for ABR and PBR, the AIC and BIC statistics were similar, which suggests that the parametric models fit relatively well to the observed portion of the PFS data. The log-normal and exponential curves provided the best statistical fit for ABR, with the Gompertz providing the best fit for PBR. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 9: AIC and BIC scores for parametric curves for OS data: censored COVID-19 deaths analysis, DCO2

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; OS, overall survival; PBR, placebo, bendamustine, rituximab.

2.1.1.2.3 Landmark and external validation

To externally validate the OS extrapolations, landmark estimates of OS from ECHO DCO2 were assessed. OS extrapolations at different landmarks are displayed in Table 10 for PBR and Table 11 for ABR. Based on the latest available landmark at approximately 6 years from ECHO DCO2, the log-normal, Gompertz and generalised gamma distributions provided the most closely aligned predictions within the observed data range for PBR, though all extrapolations estimated relatively similar OS at 6 years - particularly for ABR.

Table 10: PBR landmark OS proportions for parametric curves: censored COVID-19 deaths analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	[redacted]	[redacted]	[redacted]	
SHINE	87.5%	83.0%	63.1%	-
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO2, data cut off 2 – 15th February 2025; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Table 11: ABR landmark OS proportions for parametric curves: censored COVID-19 deaths analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; OS, overall survival.

2.1.1.2.4 OS curve selection conclusion

Four UK clinical experts with experience of treating MCL were consulted previously to estimate long-term OS in this population. The experts noted they would expect survival at 10 years for those treated with BR to be between 45–50%. As presented in Table 10, OS extrapolations using the exponential, Weibull and gamma distributions resulted in long-term projections that best aligned with the expert viewpoint at Year 10.

Similar to the feedback for PFS, experts shared that an OS benefit in favour of ABR was clinically plausible but that there was no single consensus on the long-term expectations of OS for ABR based on the ECHO study.

The selection of an appropriate parametric distribution to OS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness-of-fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14,[5] the same distribution was preferred across both treatment arms; therefore, the final selection considered models that were appropriate to select for both treatment arms.

Based on visual assessment, the exponential curve provided a relatively worse fit to the observed OS data. The goodness-of-fit assessment, however, suggested that none of the distributions had a substantially improved fit relative to others. When expert feedback is considered, the log-normal, Gompertz, generalised gamma, and

log-logistic models were deemed to overestimate long-term OS and could therefore be excluded. Among the remaining distributions, the exponential and gamma distributions provided the most conservative long-term estimate of OS. Given that the exponential is a poor reflection of the KM curve in the observed period, and the diagnostic assessment for OS was suggestive of PH violation, the gamma distribution was selected for the base case extrapolation of OS.

2.1.1.3 Time to treatment discontinuation

For time to treatment discontinuation (TTD), aligned with the company submission, the acalabrutinib component of ABR was modelled over the time horizon in the model by fitting parametric curves to patient-level data from the ECHO DCO2 (censored COVID-19 deaths), consistent with OS and PFS.

2.1.1.3.1 Visual and statistical fit

The visual and goodness-of-fit of the fitted patient-level data from the ECHO trial for the censored COVID-19 deaths analysis was assessed for TTD. With the exception of the exponential curve, all the extrapolations (Figure 17) provided relatively reasonable visual fit to the ABR arm. The exponential showed an overestimation in the first 24 months, with tendency to underestimate TTD towards the tail end of the KM period.

Figure 17: Acalabrutinib KM data and parametric curves for TTD data: censored COVID-19 deaths analysis, DCO2

Abbreviations: DCO2, data cut off 2 – 15th February 2025; KM, Kaplan–Meier; TTD, time to discontinuation.

The statistical fit of each distribution was assessed based on AIC and BIC goodness-of-fit statistics, with the results summarised in Table 12. Similar to the visual assessment, the exponential based on its AIC and BIC scores was the worst-fitting curve to the observed TTD data for ABR. All other curves provided a reasonable fit.

Table 12: AIC and BIC scores for parametric curves for TTD data: censored COVID-19 deaths analysis, DCO2

Distribution	Acalabrutinib			
	AIC		BIC	
	Result	Rank	Result	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; TTD, time to discontinuation.

2.1.1.3.2 TTD curve selection conclusion

The selection of an appropriate parametric distribution to TTD data for acalabrutinib was based on a combination of visual inspection of the fitted curves and comparison of statistical goodness of fit. Based on the AIC and BIC scores, the log-normal, log-logistic and generalised gamma distributions resulted in the lowest scores, indicating best statistical fit. However, these curves alongside the Gompertz model generate a long tail in the extrapolated curve for ABR, which was not considered plausible.

Given the known trend for TTD in the ECHO study and the summary of product characteristics for ABR, it is recommended that treatment is continued until either disease progression or toxicity is observed. The Weibull distribution for treatment discontinuation, which does not exceed PFS extrapolation over the time horizon, was deemed appropriate for the base case. A cap was also applied to all treatment discontinuation curves in the model, such that time on treatment does not exceed PFS over the time horizon.

2.1.2 ITT (FAS) analysis

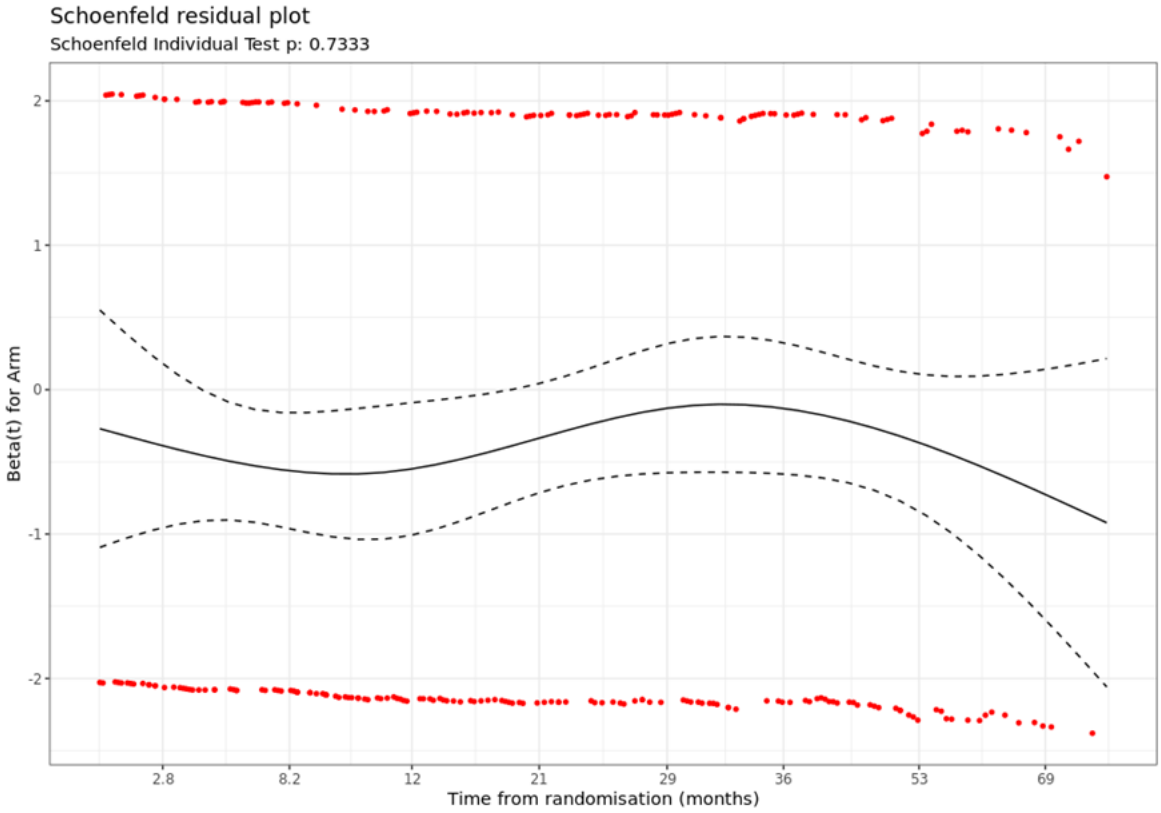
2.1.2.1 PFS

PFS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for PFS from the ECHO trial (FAS) (DCO2: 15th February 2025). The observed trial data and corresponding KM curve is presented in Section 1.1.1.

2.1.2.1.1 Diagnostic assessment

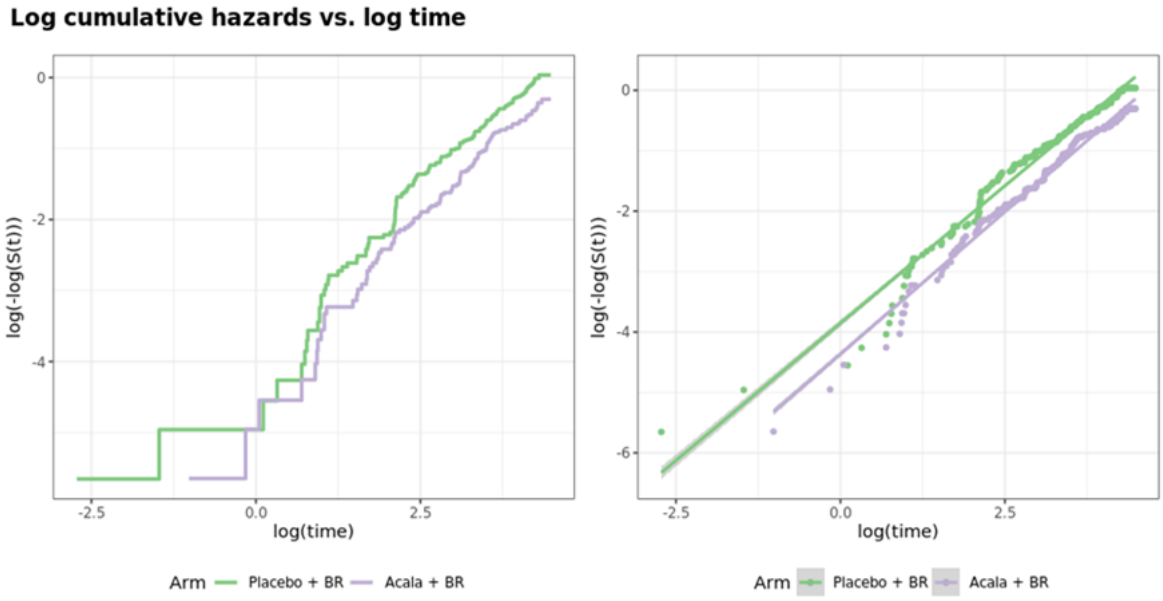
Aligned with the company submission, the methods outlined in NICE DSU TSD 14 were followed to determine the appropriate method of extrapolation of the PFS data over the lifetime time horizon.[5] First, assessment of PH between the two arms was undertaken using Schoenfeld residuals (Figure 18) and log-cumulative hazards plots (Figure 19). Similar to DCO1, the Schoenfeld residual test reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. Likewise, the visual inspection of the log-cumulative hazard curves appear to be generally parallel over time, however, there is with marginal narrowing at the tail end of the line of best fit. These results are unclear as to whether the proportional hazards assumption is violated. However, the Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals over the follow-up period, therefore indicating that proportionality may not be reasonable to assume. Given the totality of the diagnostic assessment indicating a possibility for PH to be violated, independent parametric models were fitted to the patient-level PFS data from the ECHO trial, aligned with the approach taken for DCO1.

Figure 18: Schoenfeld residual plots for PFS data: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; PFS, progression-free survival.

Figure 19: Log-cumulative hazard plots for PFS data: ITT analysis, DCO2



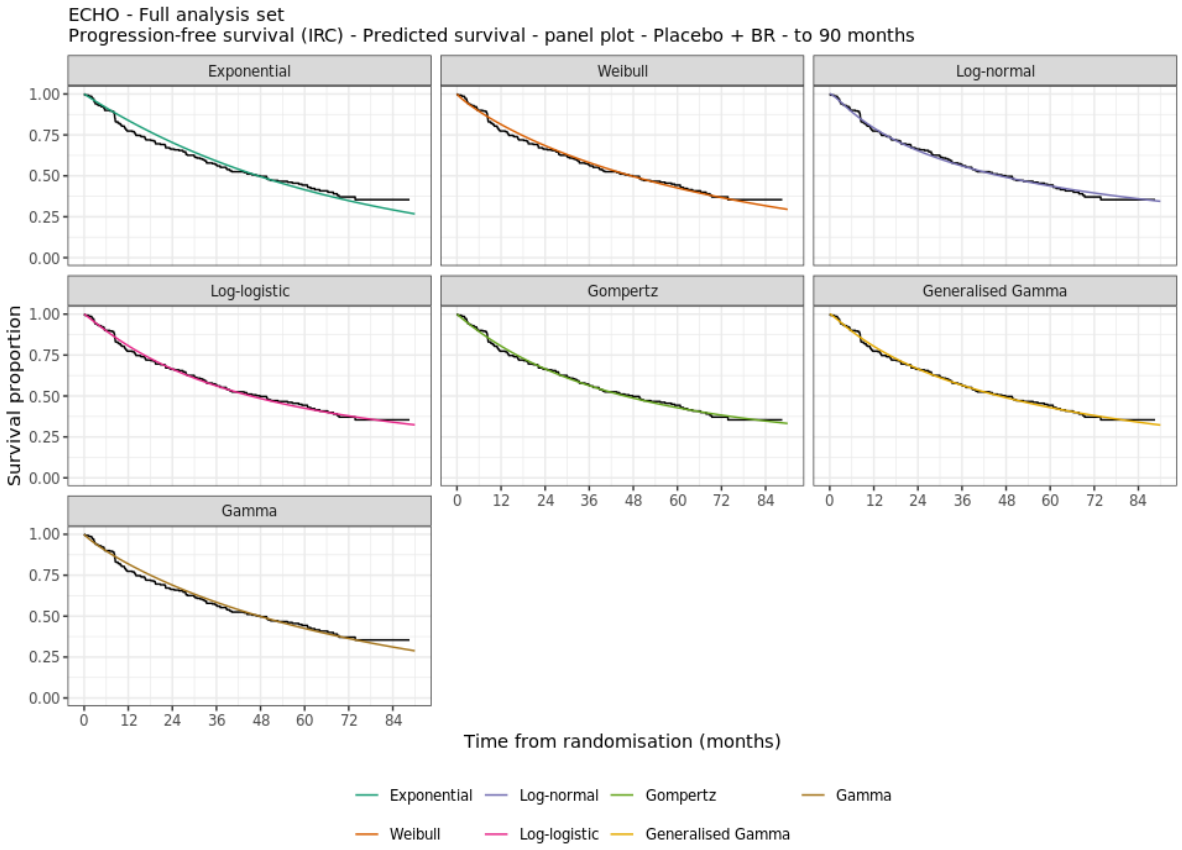
Abbreviations: BR, bendamustine + rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; PFS, progression-free survival.

2.1.2.1.2 Visual and statistical fit

Next, parametric survival models were fitted to patient-level PFS data for each arm of the ECHO study and assessed for goodness of fit. Aligned with DCO1, the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma and Gompertz) were considered. Based on visual inspection of the extrapolations fitted in Figure 20 and Figure 21, all models provide a relatively similar fit to the KM estimates in the initial three years.

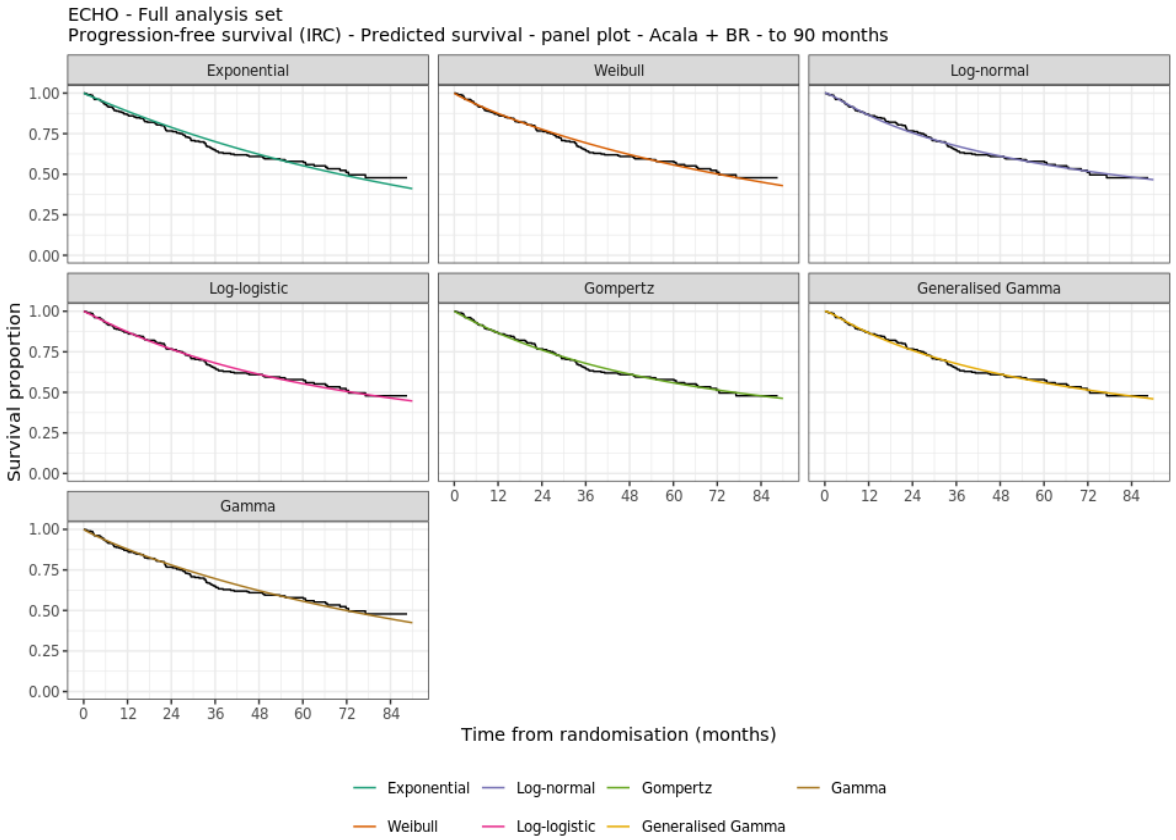
The log-normal, generalised gamma, Gompertz and log-logistic curves in both the PBR and ABR arms provide a relatively better fit compared to the other curves available.

Figure 20: PBR KM and parametric curves for PFS data: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; KM, Kaplan–Meier; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Figure 21: ABR KM and parametric curves for PFS data: ITT analysis, DCO2



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; KM, Kaplan–Meier; PFS, progression-free survival.

The statistical fit of each distribution was assessed using both the AIC and the BIC goodness-of-fit statistics, with the results summarised in Table 13. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. For all models used for ABR and PBR, the AIC and BIC statistics were all similar, which suggests that the parametric models fit relatively well to the observed portion of the PFS data. The log-normal and exponential curves provided the best statistical fit for ABR, with the log-logistic providing the best fit for PBR. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 13: AIC and BIC scores for parametric curves for PFS data: ITT analysis, DCO2

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	1282.8	5	1286.5	1	1548.2	7	1551.9	3
Weibull	1283.5	6	1290.9	5	1547.0	5	1554.4	5
Log-normal	1279.5	1	1286.9	2	1544.8	4	1552.2	4
Log-logistic	1280.6	4	1288.0	7	1542.8	1	1550.2	1
Gompertz	1280.9	2	1288.3	3	1543.7	2	1551.1	2
Generalised gamma	1281.3	3	1292.4	4	1544.6	3	1555.7	7
Gamma	1284.0	7	1291.4	6	1547.9	6	1555.3	6

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

2.1.2.1.3 Landmark and external validation

To externally validate the PFS extrapolations, landmark estimates of PFS from ECHO DCO2 were assessed.

PFS extrapolations at different landmarks are displayed in Table 15 for ABR and Table 14 for PBR. Based on the latest available landmark at approximately 6 years from ECHO DCO2, the Weibull, log-logistic, and gamma distributions provided the most closely aligned predictions within the observed data range.

Table 14: PBR landmark PFS proportions for parametric curves: ITT analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	77.4%	66.3%	37.1%	-
Exponential	83.9%	70.5%	35.0%	17.4%
Weibull	81.5%	68.5%	36.8%	20.8%
Log-normal	79.3%	65.5%	39.6%	28.4%
Log-logistic	80.7%	66.5%	37.9%	26.1%
Gompertz	80.5%	66.6%	38.4%	27.7%
Generalised Gamma	80.4%	66.6%	38.2%	25.3%
Gamma	81.9%	69.0%	36.5%	19.8%

Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival.

Table 15: ABR landmark PFS proportions for parametric curves: ITT analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	86.7%	76.7%	52.3%	-
Exponential	88.9%	79.0%	49.2%	30.7%
Weibull	87.5%	77.7%	50.3%	33.4%
Log-normal	86.4%	75.6%	51.9%	40.1%
Log-logistic	87.3%	76.7%	50.7%	37.4%
Gompertz	86.6%	76.2%	51.6%	40.2%
Generalised Gamma	86.7%	75.9%	51.5%	39.0%
Gamma	87.8%	78.1%	50.0%	32.6%

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; PFS, progression-free survival.

2.1.2.1.4 PFS curve selection conclusion

Four UK clinical experts with experience of treating MCL were consulted previously to estimate long-term PFS in this population. The experts noted they would expect PFS at 10 years to be between 20–25% in the cohort of patients with previously untreated MCL treated with BR.[6] As presented in Table 14, PFS extrapolations using the Weibull and generalised gamma distributions resulted in long-term projections that best aligned with expert viewpoint at Year 10.

For the long-term PFS estimates of ABR, there was no clear consensus among the clinical experts on a reasonable long-term estimation for PFS. They did, however, highlight that in alignment with the observed PFS benefit in the ECHO trial for the ABR arm, a clinical benefit in favour of ABR compared with BR would be expected in 1L MCL.[6]

The selection of an appropriate parametric distribution to PFS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness-of-fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14,[5] the same distribution was preferred across both treatment arms; therefore, the final selection considered models that were appropriate to select for both treatment arms.

Based on the goodness-of-fit assessment, none of the distributions had a substantially improved fit relative to others. However, when expert feedback was

considered, the log-normal, Gompertz, and log-logistic were deemed to overestimate long-term PFS and could therefore be excluded. Among the remaining exponential, Weibull, generalised gamma and gamma distributions, the Weibull distribution was selected for the base case extrapolation of PFS.

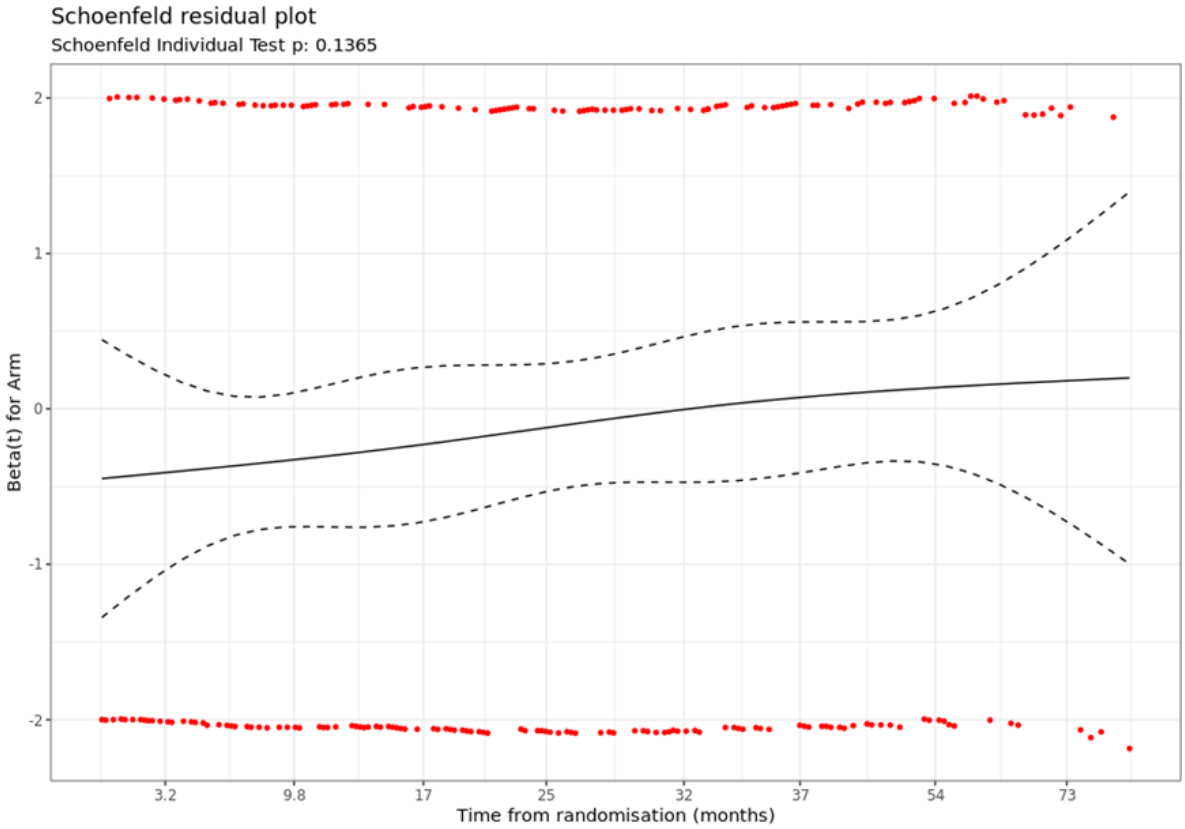
2.1.2.2 OS

OS for ABR and PBR was modelled based on parametric curves fitted to the patient-level data for OS from the ECHO trial (ITT) (DCO2: 15 February 2025). The observed trial data and corresponding KM curve is presented in Section 1.2.1.

2.1.2.2.1 Diagnostic assessment

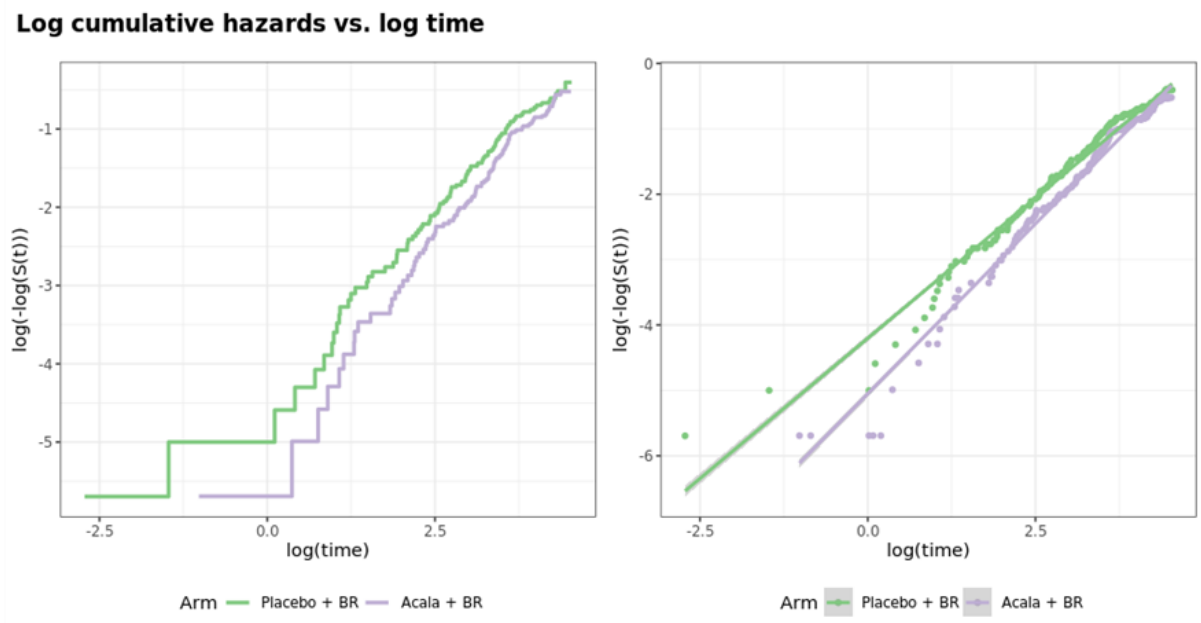
Aligned with the company submission, and approach taken for PFS, assessment of PH between the two arms was undertaken using Schoenfeld residuals (Figure 22) and log-cumulative hazards plots (Figure 23). Similar to DCO1, the Schoenfeld residual test reports a p-value >0.05, suggesting no statistically significant evidence to reject the null hypothesis of PH. However, the visual inspection of the log-cumulative hazard curves appear to converge over time, while the Schoenfeld residuals plot shows a non-linear and non-zero gradient for residuals emerges at the tail of the plot indicating that proportionality may not be reasonable to assume. On balance, the diagnostic assessment implies PH to be violated, therefore, independent parametric models were fitted to the patient-level OS data from the ECHO trial, aligned with the approach taken for DCO1.

Figure 22: Schoenfeld residual plots for OS data: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival.

Figure 23: Log-cumulative hazard plots for OS data: ITT analysis, DCO2



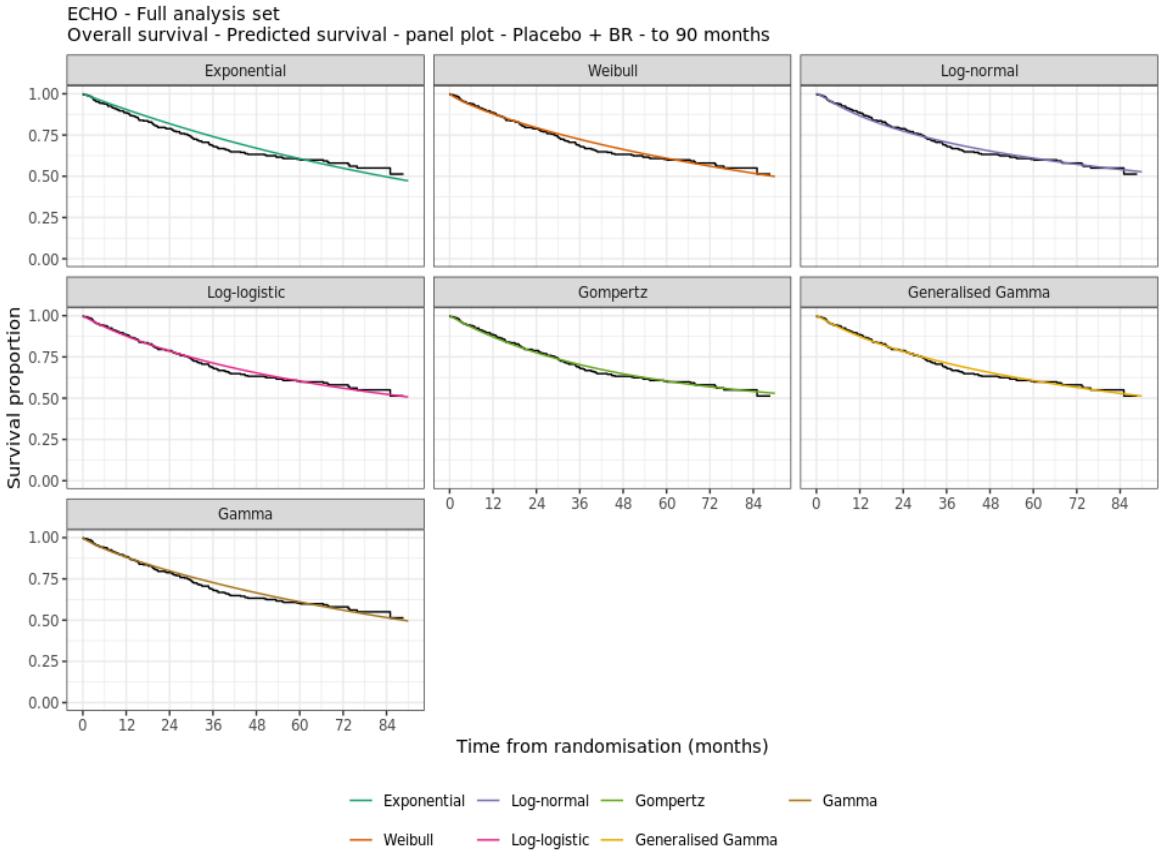
Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; BR, bendamustine + rituximab; OS, overall survival.

2.1.2.2.2 Visual and statistical fit

Parametric survival models were fitted to patient-level OS data for each arm of the ECHO study and assessed for goodness-of-fit. Aligned with DCO1, the standard parametric functions (exponential, Weibull, log-logistic, log-normal, generalised gamma, gamma and Gompertz) were considered. Based on visual inspection of the extrapolations fitted in Figure 24 and Figure 25, all models provide a relatively similar fit in to the KM estimates in the initial three years.

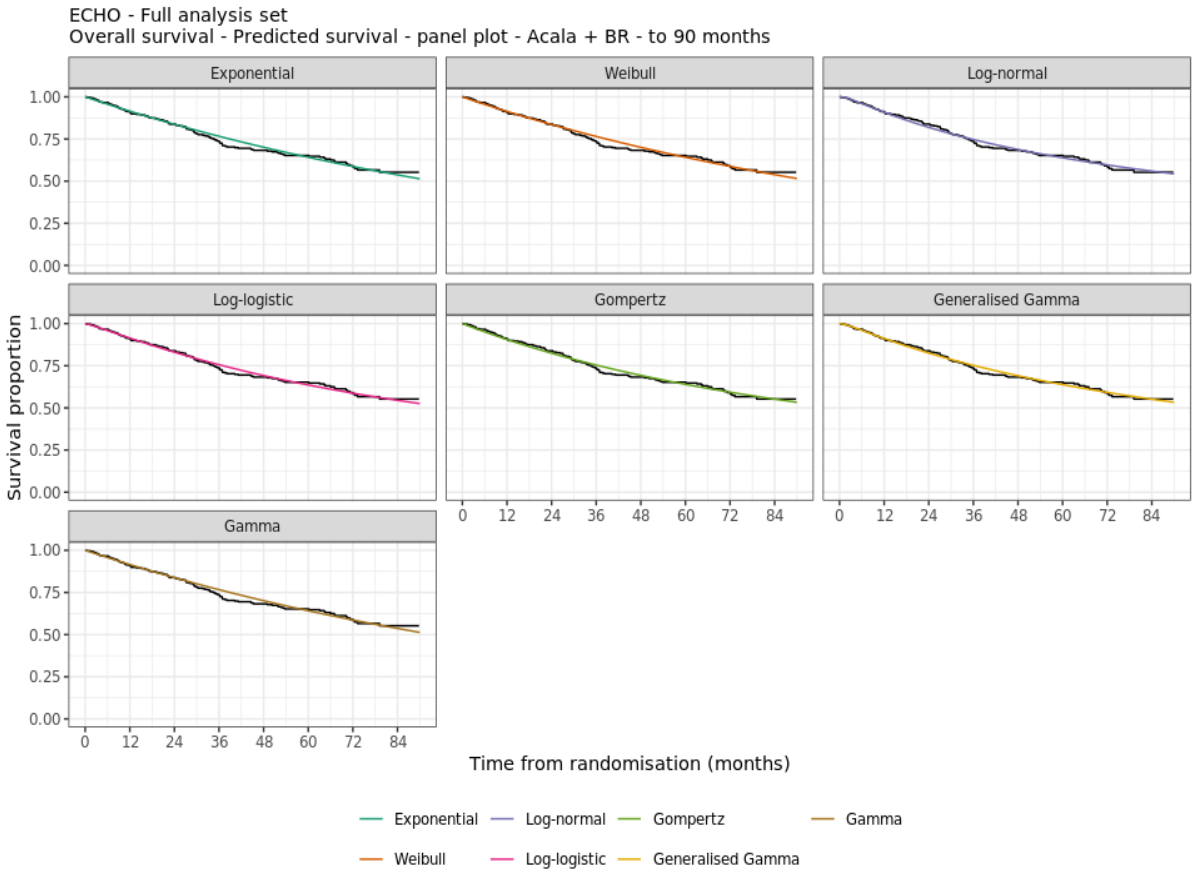
The log-normal, generalised gamma and log-logistic curves in both the PBR and ABR arms provide a relatively better fit compared to the other curves available.

Figure 24: PBR KM and parametric curves for OS data: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Figure 25: ABR KM and parametric curves for OS data: ITT analysis, DCO2



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival.

The statistical fit of each distribution was assessed using both the AIC and the BIC goodness-of-fit statistics, with the results summarised in Table 16. The best statistical fits are distributions with the lowest values indicating the most parsimonious fit to the data. For all models used for ABR and PBR, the AIC and BIC statistics were similar, which suggests that the parametric models fit relatively well to the observed portion of the OS data. The log-logistic and exponential curves provided the best statistical fit for ABR, with the Gompertz providing the best fit for PBR. In both arms, the AIC and BIC scores for all distributions fell within a 10-point range, indicating that none of the distributions had a substantially improved fit relative to others.

Table 16: AIC and BIC scores for parametric curves for OS data: ITT analysis, DCO2

Distribution	ABR				PBR			
	AIC		BIC		AIC		BIC	
	Result	Rank	Result	Rank	Result	Rank	Result	Rank
Exponential	1277.8	2	1281.5	1	1344.6	7	1348.3	4
Weibull	1279.8	6	1287.2	5	1341.8	5	1349.2	5
Log-normal	1277.8	2	1285.2	3	1340.7	3	1348.1	3
Log-logistic	1277.6	1	1285.0	2	1338.6	2	1346.0	2
Gompertz	1278.8	4	1286.2	4	1336.9	1	1344.3	1
Generalised gamma	1279.1	5	1290.2	7	1341.0	4	1352.1	7
Gamma	1279.8	6	1287.2	5	1342.6	6	1350.0	6

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival; PBR, placebo, bendamustine, rituximab.

2.1.2.2.3 Landmark and external validation

To externally validate the OS extrapolations, landmark estimates of OS from ECHO DCO2 were assessed.

OS extrapolations at different landmarks are displayed in Table 18 for ABR and Table 17 for PBR. Based on the latest available landmark at approximately 6 years from ECHO DCO2, the log-normal, Gompertz and generalised gamma distributions provided the most closely aligned predictions within the observed data range, though all extrapolations estimated relatively similar OS at 6 years.

Table 17: PBR landmark OS proportions for parametric curves: ITT analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	88.5%	79.1%	57.7%	0.0%
Exponential	90.5%	81.9%	55.0%	36.9%
Weibull	87.9%	79.5%	56.2%	41.4%
Log-normal	86.7%	77.5%	57.4%	46.8%
Log-logistic	87.7%	78.6%	56.1%	43.9%
Gompertz	87.2%	77.6%	57.0%	48.7%
Generalised Gamma	87.5%	78.4%	56.6%	44.4%
Gamma	88.2%	79.9%	56.1%	40.5%

Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival; PBR, placebo, bendamustine, rituximab.

Table 18: ABR landmark OS proportions for parametric curves: ITT analysis, DCO2

	Year 1, %	Year 2, %	Year 6, %	Year 10, %
ECHO	91.0%	83.8%	59.8%	0.0%
Exponential	91.5%	83.8%	58.8%	41.3%
Weibull	91.4%	83.6%	58.9%	41.6%
Log-normal	90.9%	81.9%	59.7%	47.4%
Log-logistic	91.4%	83.1%	58.8%	44.6%
Gompertz	90.6%	82.5%	59.4%	45.6%
Generalised Gamma	91.2%	82.6%	59.3%	45.6%
Gamma	91.6%	83.8%	58.8%	41.2%

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival.

2.1.2.2.4 OS curve selection conclusion

Four UK clinical experts with experience of treating MCL were consulted previously to estimate long-term OS in this population. The experts noted that they would expect survival at 10 years for those treated with BR to be between 45–50%. As presented in Table 17, OS extrapolations using the log-normal and Gompertz distributions resulted in long-term projections that best aligned with expert viewpoint at Year 10.

Similar to the feedback for PFS, experts shared that an OS benefit in favour of ABR was clinically plausible but that there was no single consensus on the long-term expectations of OS for ABR based on the ECHO study. On this basis, the Gompertz model could be ruled out owing to a lower estimate of OS at 10 years for ABR than PBR.

The selection of an appropriate parametric distribution to OS data for ABR and PBR was based on a combination of visual inspection of the fitted curves, comparison of statistical goodness-of-fit, and external validity checks through clinical input. In alignment with the guidance in NICE DSU TSD 14,[5] the same distribution was preferred across both treatment arms; therefore, the final selection considered models that were appropriate to select for both treatment arms.

Based on the goodness-of-fit assessment, none of the distributions had a substantially improved fit relative to others. However, when expert feedback was considered, the Gompertz was deemed to produce unrealistic comparative estimates

of OS and could therefore be excluded. Among the remaining distributions, the log-normal distribution was selected for the base case extrapolation of OS, based on alignment across visual fit, landmark assessment and clinical feedback.

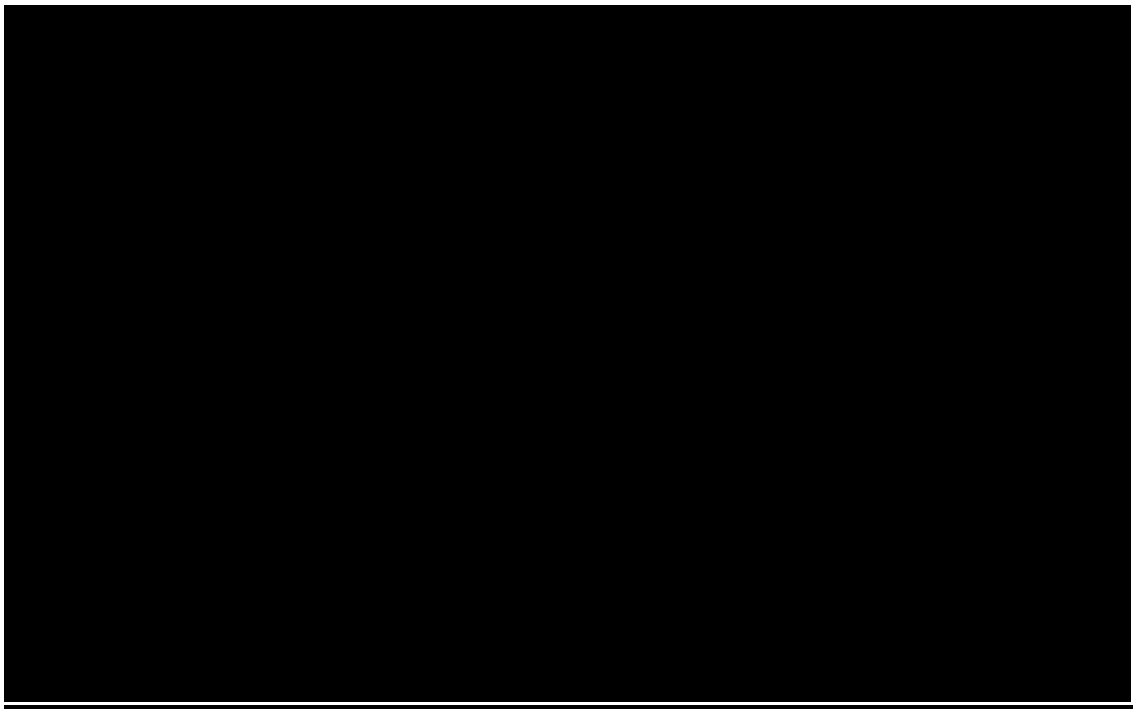
2.1.2.3 TTD

Aligned with the company submission, the acalabrutinib component of ABR was modelled over the time horizon in the model by fitting parametric curves to patient-level data from the ECHO DCO2 (FAS/ITT), consistent with OS and PFS.

2.1.2.3.1 Visual and statistical fit

The visual and goodness-of-fit of the fitted patient-level data from the ECHO trial for the ITT analysis was assessed for TTD. With the exception of the exponential curve, all the extrapolations (Figure 26) provided relatively reasonable visual fit to the ABR arm. The exponential showed an overestimation in the first 24 months, with tendency to underestimate TTD towards the tail end of the KM period.

Figure 26: Acalabrutinib KM data and parametric curves for TTD data: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; KM, Kaplan–Meier; TTD, time to discontinuation.

The statistical fit of each distribution was assessed based on AIC and BIC goodness-of-fit statistics, with the results summarised in Table 19. Similar to the visual assessment, the exponential based on its AIC and BIC scores was the worst-fitting curve to the observed TTD data for ABR. All other curves provided a reasonable fit.

Table 19: AIC and BIC scores for parametric curves for TTD data: ITT analysis, DCO2

Distribution	Acalabrutinib			
	AIC		BIC	
	Result	Rank	Result	Rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; TTD, time to discontinuation.

2.1.2.3.2 TTD curve selection conclusion

The selection of an appropriate parametric distribution to TTD data for acalabrutinib was based on a combination of visual inspection of the fitted curves and comparison of statistical goodness-of-fit. Based on the AIC and BIC scores, the log-logistic, Gompertz and log-normal distribution resulted in the lowest scores, indicating best statistical fit. However, the curves generate a long tail in the extrapolated curve for ABR. This assumption was not considered plausible and would result in the TTD curve crossing PFS in the long term, which lacks face validity and is not supported by clinical practice.

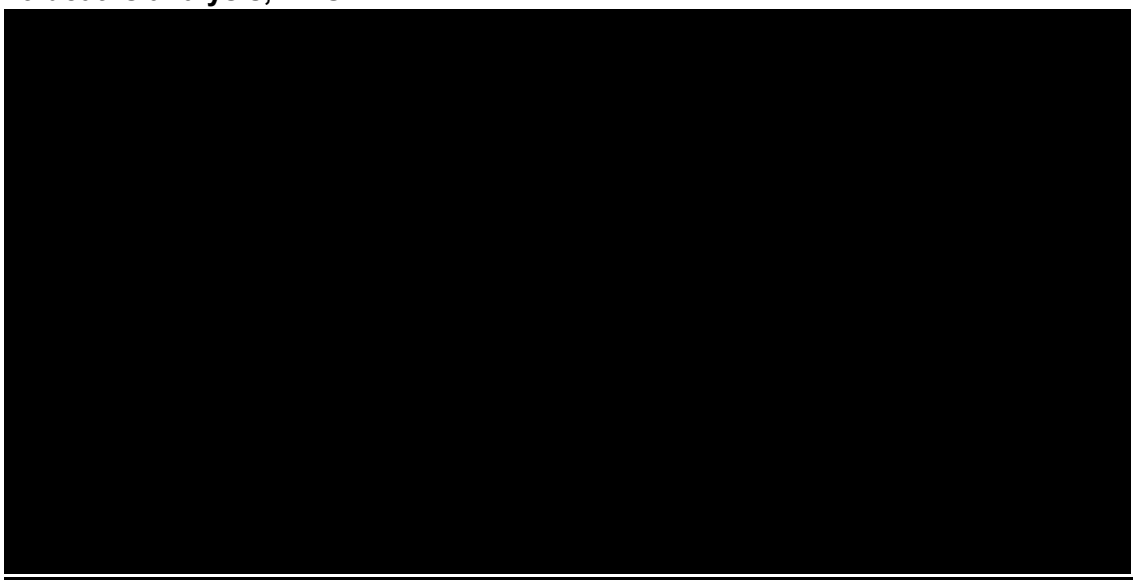
Given the known trend for TTD in the ECHO study and the summary of product characteristics for ABR, it is recommended that treatment is continued until either disease progression or toxicity is observed. The Weibull distribution for treatment discontinuation, which does not exceed PFS extrapolation over the time horizon, was deemed appropriate for the base case. A cap was also applied to all treatment discontinuation curves in the model, such that time on treatment does not exceed PFS over the time horizon.

2.1.3 Summary of selected survival models

The selected OS, PFS, and TTD curves for the ABR and the selected OS and PFS curves for the PBR arm are plotted in Figure 27 and Figure 28 for the censored COVID-19 deaths analysis. Consistent with the original submission, the gamma distribution is selected in the base case to extrapolate OS and PFS, with the Weibull distribution used to extrapolate acalabrutinib TTD.

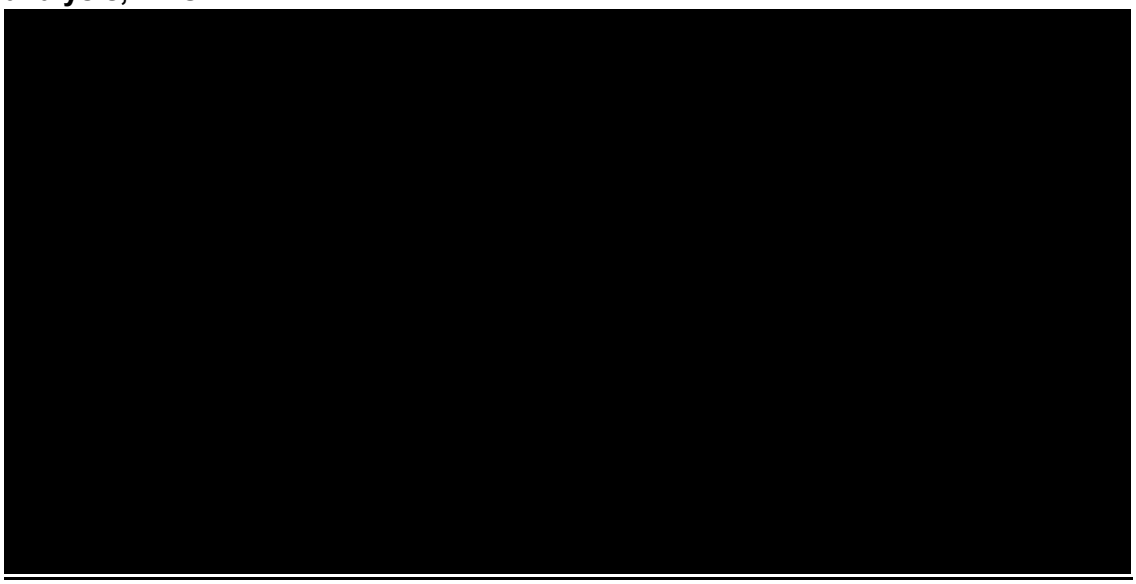
For the ITT analysis, the selected curves are plotted in Figure 29 and Figure 30. The Weibull distribution is selected to extrapolate PFS and acalabrutinib TTD, with the log-normal curve chosen to extrapolate OS.

Figure 27: ABR selected parametric curves for OS, PFS, & TTD data: censored COVID-19 deaths analysis, DCO2



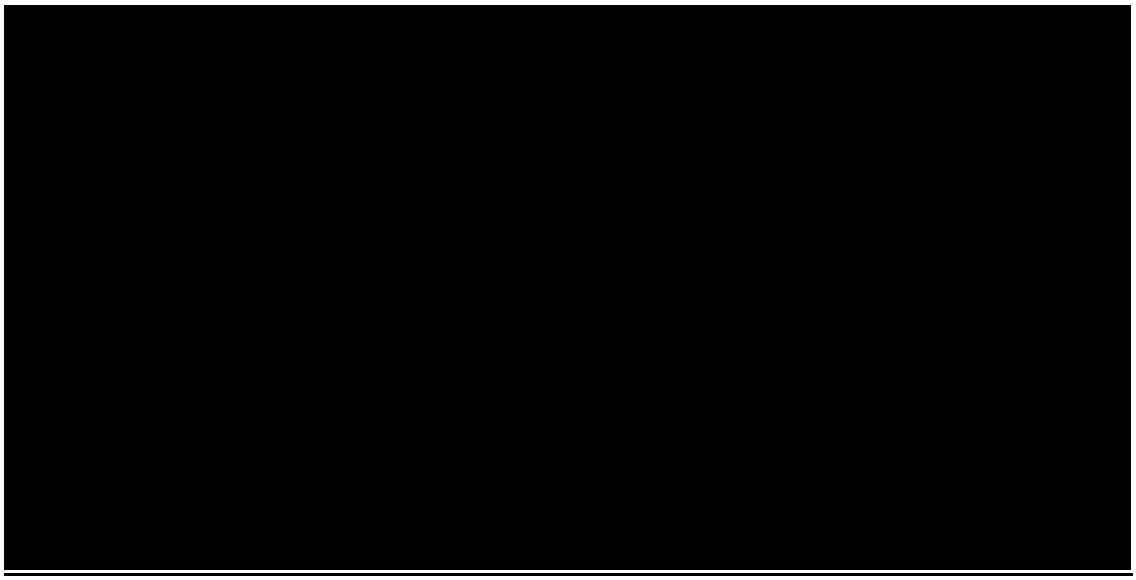
Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.
Note: Selected parametric curves presented here have been corrected for background mortality.

Figure 28: PBR selected parametric curves for OS, PFS: censored COVID-19 deaths analysis, DCO2



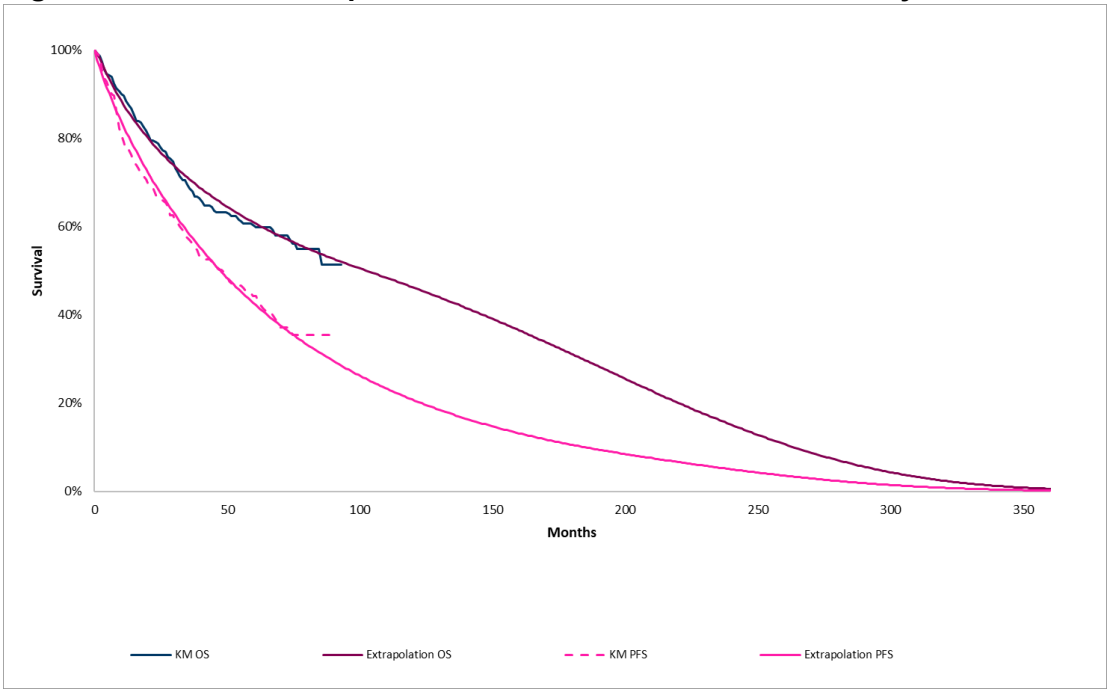
Abbreviations: DCO2, data cut off 2 – 15th February 2025; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; TTD, time to discontinuation.
Note: Selected parametric curves presented here have been corrected for background mortality.

Figure 29: ABR selected parametric curves for OS, PFS, & TTD data: ITT analysis, DCO2



Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; TTD, time to discontinuation.
Note: Selected parametric curves presented here have been corrected for background mortality.

Figure 30: PBR selected parametric curves for OS, PFS: ITT analysis, DCO2



Abbreviations: DCO2, data cut off 2 – 15th February 2025; ITT, intent-to-treat; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; TTD, time to discontinuation.
Note: Selected parametric curves presented here have been corrected for background mortality.

2.2 Subsequent treatments

The approach to calculating the proportion of patients receiving greater than 1 subsequent therapies in the model has been updated using data presented in Table 1 and Table 5. The calculations are as follows:

$$\%\ recieving\ subsequent\ therapy = \frac{N\ recieving\ 2L}{N\ with\ progression}$$

$$\%\ ABR\ recieving\ subsequent\ therapy = \frac{33}{59} = 55.9\%$$

$$\%\ PBR\ recieving\ subsequent\ therapy = \frac{100}{107} = 93.5\%$$

For further treatment lines (3L+), there were no additional data available to update the model. Therefore, these values remain aligned with the original submission.

2.3 Rationale for inclusion of 3L treatment in cost-effectiveness analysis

The evidence on TTNT2 available from DCO2 (Section 1.3 and 1.4) is of particular relevance to Issue 4 raised by the EAG. The EAG had several concerns regarding the assumptions and available data for the inclusion of subsequent treatments in the cost-effectiveness model.

At clarification stage, the EAG queried why a large proportion of patients with progressed disease, particularly in the ABR arm, were not deemed suitable for further lines of treatment after progression. At the time the original submission was made, the EAG indicated that longer follow-up data from the ECHO trial may resolve the uncertainty around proportions requiring 2L and in particular 3L treatments. Given the time taken to reach 3L treatment and small numbers progressing twice in the ECHO trial, the EAG did not consider the modelled differences in 3L treatment proportions to be evidence based. Due to the uncertainties, the EAG's preferred assumption was to remove 3L therapies from the model, which had a substantial impact on the ICER.

In DCO2, the available data on TTNT2 (Section 1.3) showed that despite crossover, there was a 33% reduction (HR: 0.67; 95% CI: 0.50, 0.89) in risk of needing 3L therapy with ABR versus PBR (data censored for COVID-19 deaths) in the ECHO trial. With ABR, subsequent therapy was needed less often and later, reflecting deeper, more durable disease control. This evidence significantly reduces the uncertainty in the model inputs associated with subsequent treatments and supports the inclusion of 3L therapies in the base case results.

2.4 Systemic Anti-Cancer Therapy dataset

The Systemic Anti-Cancer Therapy dataset collects information on the use of systemic anti-cancer therapies across all NHS Trusts in England. NICE provided AZ with the dataset to provide commentary on, and AZ have taken the opportunity to assess whether it could be of value to this technology appraisal. In brief, the SACT data presented patient demographics and OS among patients who have received a 1L treatment of BR and R-CHOP for MCL. The key exclusion criteria were receipt of ASCT.

Upon review, the company concluded that, given a number of limitations with the data, it would not be included in this addendum as it would require substantial adjustment and sensitivity analyses to be performed. Identified limitations include the following:

- Population age differences: The dataset's age distribution of the BR population (median age 75) differs from the ECHO trial population (median age 71). The ECHO trial is aligned with the Haematological Malignancy Research Network (HMRN; median age 72.2), as well as other clinical trials in MCL, such as the Maintain study,[7] (median age 70). The difference in age poses risks to comparability and may introduce selection bias
- Unaddressed COVID-19 period effects: The dataset covers diagnoses from 2017 to 2022, including the peak COVID-19 period. The analysis does not adjust for this, so results may not be a true reflection of disease or treatment outcomes
- Rituximab maintenance: The SACT includes all patients on 1L BR or R-CHOP, but does not distinguish whether the patient received rituximab maintenance therapy as well. The uptake of rituximab maintenance can vary widely depending on a number of factors and could not be estimated in the SACT data provided. Therefore, the dataset is not comparable to the ECHO trial, and any direct effectiveness or outcome comparisons would be confounded by differences in maintenance therapy.

2.5 Updated results of the cost-effectiveness analysis

2.5.1 Updated base case settings and key changes

The following changes have been made to the company's base case following the availability of the additional data from ECHO (DCO2), and in response to the EAG report:

- Subsequent treatments: Proportion of patients receiving ≥1 subsequent therapies (Section 2.2)
- Model corrections:
  - Corrected TEAE incidence rates (see response to clarification questions)
  - Subsequent treatment calculation (applied by the EAG)

Other assumptions (including curve selections) and inputs from the original base case were maintained, with further support for the inclusion of 3L therapies provided by the TTNT2 data, as discussed in Section 2.3.

2.5.2 Base case results

Table 20 contains the updated deterministic base case results using DCO2, with the censored COVID-19 deaths analysis. Results in terms of net health benefit (NHB) are summarised in Table 21. The results are based on the current patient access scheme price for acalabrutinib. Fully incremental results are presented in Table 22.

Equivalent results from the probabilistic analysis with 1,000 iterations are presented in Table 23 to Table 25.

Table 20: Deterministic base case results (discounted): Pairwise ICER

Technologies	Total costs, £†	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,849
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LY, life year; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 21: Deterministic NHB (discounted)

Technologies	Total costs, £†	Total QALYs	Incremental costs, £	Incremental QALYs	NHB at £20,000	NHB at £30,000
ABR	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; NHB, net health benefit; PAS, patient access scheme; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 22: Deterministic base case results (discounted): incremental analysis

Technologies	Total costs, £†	Total QALYs	Regimen versus comparator	Incremental costs, £	Incremental QALYs	Incremental ICER, £/QALY
R-CHOP	[redacted]	[redacted]				Dominated
BR	[redacted]	[redacted]	N/A	N/A	N/A	N/A
ABR	[redacted]	[redacted]	BR	[redacted]	[redacted]	£21,849

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LYs, life years; N/A, not applicable; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential patient access scheme for acalabrutinib.

Table 23: Probabilistic base case results (discounted): Pairwise

Technologies	Mean total costs, £†	Mean total LYs	Mean Total QALYs	Mean incremental costs, £	Mean incremental LYG	Mean incremental QALYs	Pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,450
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LY, life year; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 24: Probabilistic NHB (discounted)

Technologies	Mean total costs, £†	Mean total QALYs	Mean incremental costs, £	Mean incremental QALYs	NHB at £20,000	NHB at £30,000
ABR	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

Table 25: Probabilistic base case results (discounted): Incremental analysis

Technologies	Mean total costs, £†	Mean Total QALYs	Regimen versus comparator	Incremental costs, £	Incremental QALYs	Incremental ICER, £/QALY
R-CHOP	[redacted]	[redacted]				Dominated
BR	[redacted]	[redacted]	N/A	N/A	N/A	N/A
ABR	[redacted]	[redacted]	BR	[redacted]	[redacted]	£21,450

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; LY, life year; PAS, patient access scheme; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.
† Includes the existing confidential PAS for acalabrutinib.

3 References

1. Wang M, Paludo J, de Holanda Farias JS, Villa D, Forsyth C, John E, et al. Abstract 885. Time to Third-Line Treatment After Bendamustine-Rituximab With or Without Acalabrutinib in Patients With Previously Untreated Mantle Cell Lymphoma: Updated Analysis of the Phase 3 ECHO Trial After 50 Months of Follow-up. Presented at: American Society of Hematology (ASH) Annual Meeting; December 6–9, 2025; Orlando, Florida; 2025.
2. Wang M, Paludo J, de Holanda Farias JS, Villa D, Forsyth C, John E, et al. Poster Presentation 885. Time to Third-Line Treatment After Bendamustine-Rituximab With or Without Acalabrutinib in Patients With Previously Untreated Mantle Cell Lymphoma: Updated Analysis of the Phase 3 ECHO Trial After 50 Months of Follow-up. Presented at: American Society of Hematology (ASH) Annual Meeting; December 6–9, 2025; Orlando, Florida; 2025.
3. AstraZeneca. Data on File. ID: REF-299562. 2025.
4. AstraZeneca. 2.5 Clinical Overview. CALQUENCE® for the Treatment of Patients with Previously Untreated Mantle Cell Lymphoma 2025.
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6. AstraZeneca. Summary of clinician interviews to support the NICE HTA submission for acalabrutinib with bendamustine and rituximab in untreated mantle cell lymphoma [ID6155]. Data on File: REF-251322. 2024.
7. Rummel MJ, Knauf W, Goerner M, Soeling U, Lange E, Hertenstein B, et al. Two years rituximab maintenance vs. observation after first-line treatment with bendamustine plus rituximab (B-R) in patients with mantle cell lymphoma: First results of a prospective, randomized, multicenter phase II study (a subgroup study of the StiL NHL7-2008 MAINTAIN trial). J Clin Oncol. 216;34(15):7503.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Summary of Information for Patients (SIP)

November 2024

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
ID6155 Acalabrutinib MCL SIP vFINAL [noCON]	**V1.0**	**No**	**26th November 2024**

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 NICE for their treatment to be sold to the 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 IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Acalabrutinib (Calquence®) in combination with bendamustine and rituximab (BR)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population requested by AstraZeneca for appraisal is adults with previously untreated mantle cell lymphoma (MCL) who are unsuitable for autologous stem cell transplant (ASCT).

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.

The marketing authorisation for acalabrutinib is pending. Please refer to Section B.1.2 of the main submission document for more information.

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:

AstraZeneca UK Limited engages with the following patient advocacy groups in haematology, with the aims of strengthening patient insights and responding to requests for information: Blood Cancer UK, Lymphoma Action, Leukaemia Care. Funding provided to UK patient groups is published annually on our website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups

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.
Mantle cell lymphoma (MCL) is a rare type of non-Hodgkin lymphoma (NHL). Mantle cell lymphoma develops when B cells, a type of white blood cell that normally help fight infection, grow abnormally and build up in the lymph nodes and other parts of the body. Approximately 590 new cases are diagnosed each year in the UK (1). Mantle cell lymphoma is more common in males than females, and is more likely to occur at older ages (median age at diagnosis is 72 years (1)). Most cases of mantle cell lymphoma have a particular genetic change (mutation) in the abnormal cells, known as chromosome translocation t[11;14](q13;q32). Scientists don't know why this genetic change develops. The mutation means the B cells make too much of a protein called cyclin D1. Too much cyclin D1 makes the B cells grow out of control, and lymphoma develops. Mantle cell lymphoma is classified into stages based on how much the cancerous B cells have spread, with Stage I being the most localised disease, and Stage IV indicating wider spread to other parts of the body (2). Mantle cell lymphoma is often aggressive and fast growing, meaning most patients are diagnosed at advanced stages (3, 4). The most common symptom of mantle cell lymphoma is a lump, or lumps, which often develop in several parts of the body (5). These are swollen lymph nodes. Depending on the areas of the body affected, patients may experience reduced appetite, pain in the abdomen, fatigue, shortness of breath, diarrhoea and sickness, bruising and bleeding, or increased risk of infection (5). Some people experience unexplained weight loss, night sweats or fever. These are known as 'B symptoms' and can occur together (5). Despite available treatments, mantle cell lymphoma is generally incurable. How long mantle cell lymphoma stays under control (in remission) after successful treatment varies from person to person, but at some point, it usually relapses (5). The median duration of remission has been reported to be between 1.5 and 3 years (6). Survival is poor, with less than 50% of patients surviving 5 years after diagnosis (1). The focus of this submission is on patients with previously untreated mantle cell lymphoma who are considered unsuitable candidates for autologous stem cell transplant (ASCT), a key treatment option for many patients. This will be discussed further in (2c).

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?
Mantle cell lymphoma is typically diagnosed by a biopsy, a small procedure to remove a sample of tissue, such as a swollen lymph node (5). It also might be diagnosed through a blood test (5). A pathologist looks at the blood and tissue samples in the laboratory. In most cases of mantle cell

lymphoma, there are characteristic proteins and genetic features that help the pathologist confirm the diagnosis (5).

Other tests are used to find out which areas of the body are affected (staging). These may include (5):

- a CT or PET/CT scan
- a blood test
- a bone marrow biopsy
- a lumbar puncture (a procedure to take a sample of fluid from your spine using a thin needle) and MRI scan if the doctor suspects mantle cell lymphoma may be affecting the brain or spinal cord
- an endoscopy (a camera examination of your stomach or bowel using a thin, flexible tube passed through your mouth or bottom) if the doctor suspects mantle cell lymphoma in the digestive tract

Not everyone needs all of these tests.

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.

Treatment for mantle cell lymphoma depends on several factors, including the stage of disease, how quickly it is growing, what symptoms are present, the age and general health/fitness of the patient, any other conditions the patient has (comorbidities) and patient preference (5).

Patients with early-stage, slowly growing, asymptomatic mantle cell lymphoma typically receive radiotherapy, or a 'watch and wait' approach where they receive no treatment but are regularly monitored for any changes.

For patients with advanced disease, the doctor will assess whether they are considered suitable for a procedure known as autologous stem cell transplant (ASCT). Autologous stem cell transplant replaces damaged or destroyed stem cells (cells in the bone marrow that make new blood cells) with healthy stem cells (7). As this is an intensive form of treatment, the patient must be well enough to have one (7). A range of factors are considered in determining fitness for autologous stem cell transplant, including patient choice, the timing of relapse, age, previous treatment, comorbidities, and general health and fitness (8). Patients deemed transplant-suitable typically receive aggressive chemoimmunotherapy, followed by autologous stem cell transplant once in remission, and maintenance treatment with an immunotherapy drug called rituximab (4, 9).

The group of patients who are not deemed fit enough for autologous stem cell transplant are the focus of this submission. Currently, patients unsuitable for autologous stem cell transplant will be offered less aggressive chemoimmunotherapy as the first treatment (4, 9). This involves a combination of the immunotherapy drug rituximab and chemotherapy. There are several options of chemotherapy recommended in guidelines (4, 9):

- BR: bendamustine + rituximab
- R-CHOP: rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone
- R-BAC: rituximab, bendamustine and cytarabine
- VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone

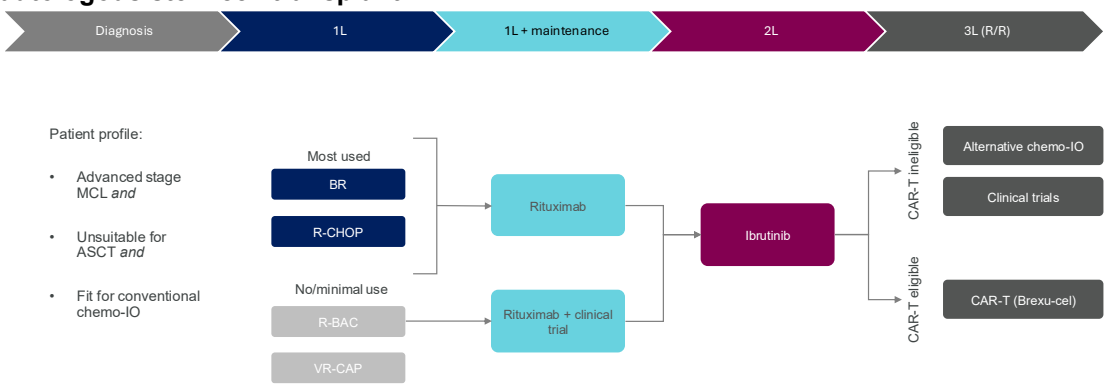
The choice of treatment is based on the individual circumstances for a patient, considering general health and fitness. Clinicians have highlighted that bendamustine plus rituximab is used in 60 to 75% of these patients and R-CHOP is used in 25 to 30% of patients (10), with R-BAC and VR-CAP rarely used due to issues with toxicity and side effects (10).

If the mantle cell lymphoma responds well to this initial chemotherapy treatment, patients will continue to receive rituximab as a maintenance treatment every two months to keep the lymphoma in remission (4).

After relapse, ibrutinib, a targeted drug known as a Bruton tyrosine kinase inhibitor (BTKi) is recommended as a second-line treatment (4). Following a further relapse, chimeric antigen receptor T-cell therapy (CAR-T), a personalised treatment, may be considered (4).

The current treatment pathway is shown in Figure 1.

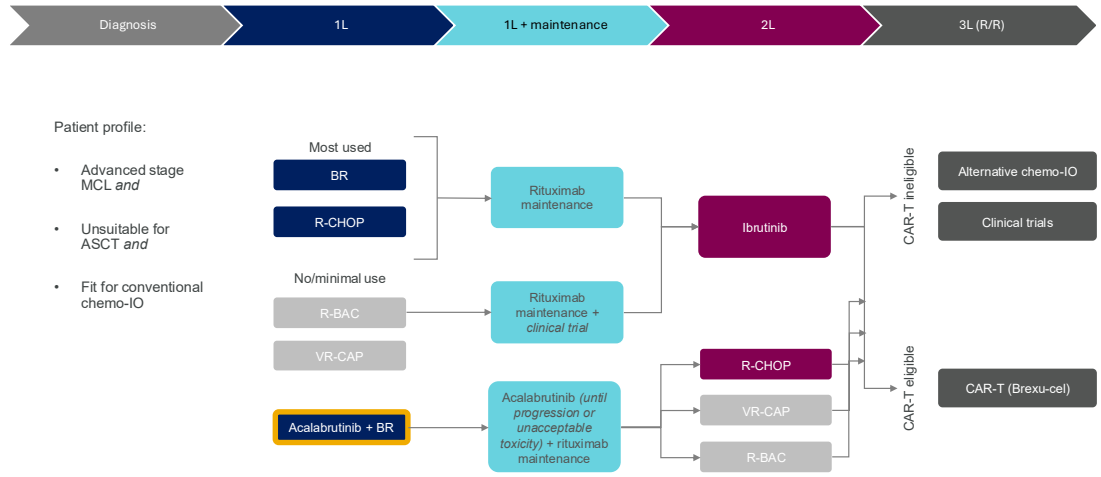
Figure 1: Current treatment pathway for advanced mantle cell lymphoma unsuitable for autologous stem cell transplant



Abbreviations: 1/2/3L, first/second/third-line; ASCT, autologous stem cell transplant; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor-T cell therapy; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
References: Eyre T et al. 2024 (4); NICE NG52 (9); AstraZeneca Data on File REF-251322, 2024 (10).

Acalabrutinib is a second-generation targeted Bruton tyrosine kinase inhibitor. The anticipated positioning of acalabrutinib in combination with bendamustine and rituximab (BR) is for use as the first treatment in patients with mantle cell lymphoma who are not suitable for autologous stem cell transplant, as shown in Figure 2.

Figure 2: Anticipated place in therapy for acalabrutinib plus bendamustine and rituximab



Abbreviations: 1/2/3L, first/second/third-line; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor-T cell therapy; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
References: Eyre T et al. 2024 (4); NICE NG52 (9); AstraZeneca Data on File REF-251322, 2024 (10).

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.

There is limited patient-based evidence about living with mantle cell lymphoma. However, as an incurable disease with poor survival and high rates of relapse, there is clearly a high burden on patients.

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.

The draft Summary of Product Characteristics (SmPC) is available in the reference pack provided to NICE.

Acalabrutinib plus bendamustine and rituximab is a novel combination therapy, with the individual components as follows:

- Acalabrutinib is a type of targeted cancer drug called a second-generation Bruton tyrosine kinase inhibitor (BTKi) (11). Tyrosine kinases are enzymes that help to send growth signals in cells. Bruton tyrosine kinase inhibitors block one of these enzymes, Bruton tyrosine kinase, therefore stopping the cells from growing and dividing (11).

- Bendamustine is a type of chemotherapy drug called an alkylating drug (12). It works by interfering with the DNA (genetic information that provides the instructions living things need to function, grow, and develop) in cancer cells, preventing them from dividing so the cancer can't grow (12).

- Rituximab is a type of targeted cancer drug called a monoclonal antibody, which targets a protein called CD20 on the surface of B cells, including the cancerous B cells (13). Rituximab attaches to all the CD20 proteins it finds. The cells of the immune system then pick out the marked cells and kill them (13).

One of the main areas of possible advancement in treating mantle cell lymphoma is adding targeted agents to standard chemoimmunotherapy treatment. The combination of bendamustine and rituximab is currently one of the most commonly used treatments in the UK for previously untreated mantle cell lymphoma patients who are unsuitable for autologous stem cell transplant (4, 10). Acalabrutinib is the first targeted Bruton tyrosine kinase inhibitor for use in patients with previously untreated MCL who are unsuitable for ASCT.

The addition of acalabrutinib to the existing treatment regimen with bendamustine and rituximab improves the anti-cancer effects (14).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

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.

Acalabrutinib is intended to be used in combination with bendamustine and rituximab. The individual mechanisms of action for these treatments are discussed in 3a. The combination of bendamustine and rituximab is currently one of the most commonly used treatments in the UK for previously untreated mantle cell lymphoma patients who are unsuitable for autologous stem cell transplant (4, 10). Despite treatment, most patients eventually relapse. The ECHO clinical trial (discussed further in 3d, 3e, 3f and 3g) has shown that the addition of acalabrutinib to bendamustine and rituximab can extend the time that patients survive without their disease progressing (14).

Like all medicines, acalabrutinib, bendamustine, and rituximab are associated with side effects. During the ECHO trial, nearly all participants experienced side effects (also called adverse events) of treatment, whether they received acalabrutinib in combination with bendamustine and rituximab or placebo plus bendamustine and rituximab (14). Side effects are discussed further in 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?

Acalabrutinib treatment should be started and supervised by a doctor with experience in the use of cancer medicines. It is available as tablets to be taken by mouth (15). The recommended dose is 100 mg taken twice a day (15). Acalabrutinib is continued as long as the cancer remains under control and there are no unacceptable side effects (15).

Bendamustine is delivered as a drip into the bloodstream (intravenously) at a hospital (12). It may be given through a long plastic tube that goes into a large vein in the chest (central line, PICC line, or portacath), which stays in place throughout the course of treatment (12). The dose of bendamustine depends on the body surface area of the patient. In the ECHO trial, bendamustine was given at a dose of 90 mg/m^2 on Days 1 and 2 of a 28-day cycle. Bendamustine was administered for a maximum of 6 cycles (15).

Rituximab is delivered as a drip into the bloodstream (intravenously) at a hospital (13). The dose of rituximab depends on the body surface area of the patient. In the ECHO trial, rituximab was given at a dose of 375 mg/m^2 on Day 1 of a 28-day cycle (15). Rituximab was administered for a maximum of 6 cycles alongside bendamustine (15). Patients whose mantle cell lymphoma responded to the treatment combination then continued to receive maintenance rituximab at the same dose every other cycle, for a maximum of 12 additional doses (15).

Given that bendamustine and rituximab are already an established treatment in clinical practice, there is likely to be minimal impact on patients and caregivers from adding acalabrutinib, with respect to administration and dosing. The addition of acalabrutinib will require patients to take two tablets by mouth each day, on top of the intravenous administration of bendamustine and rituximab at a hospital.

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.

ECHO is a global clinical trial assessing the efficacy and safety of acalabrutinib in combination with bendamustine and rituximab in patients with untreated mantle cell lymphoma who are likely considered unsuitable candidates for autologous stem cell transplant (as all patients are aged ≥65 years) (14). The trial compares acalabrutinib in combination with bendamustine and rituximab with placebo plus bendamustine and rituximab to determine the effect of adding acalabrutinib to current standard of care. Placebo is a 'dummy treatment' which looks exactly like the actual treatment (in this case, acalabrutinib) and is given the same way, to see if the actual treatment works.

Some results from the trial are available, although it is ongoing. Results presented in this submission were based on an analysis of data collected up to 15th February 2024 (14). A further analysis will be conducted when more data are available.

ECHO included patients with mantle cell lymphoma aged 65 years and older who had received no previous treatment for their mantle cell lymphoma (14). In total, 299 patients received acalabrutinib in combination with bendamustine and rituximab, and 299 patients received placebo plus bendamustine and rituximab (14).

The outcomes measured in the trial included (14):

- how long participants remained alive without disease progression (progression-free survival)
- how long participants remained alive (overall survival)
- the proportion of participants who responded to treatment (overall response rate)
- how long people survived from the time a response to treatment was recorded until their cancer got worse (duration of response)
- the time from patients being randomised to receive treatment to a response being recorded (time to response)

Further details on the study design and results from ECHO are available from Wang M, Mayer J, Belada D et al. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: results from the phase 3, double-blind, placebo-controlled ECHO trial. European Haematology Association (EHA) 2024;Abstract: LB3439.

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.

The ECHO trial showed that patients treated with acalabrutinib in combination with bendamustine and rituximab lived significantly longer without their disease progressing (median 66.4 months) than patients treated with placebo plus bendamustine and rituximab (median 49.6 months) (14). This equates to patients living approximately 17 months longer without disease progression. The addition of acalabrutinib to bendamustine and rituximab reduced the risk of disease progression or death by 27% (14). This was the key outcome being measured in the trial.

There was also a trend towards an improvement in how long participants remained alive with acalabrutinib in combination with bendamustine and rituximab; however, a lot of participants are still alive in both treatment groups and the trial will need to continue for longer for a final analysis of the difference in survival between the two treatments (14).

A high number of patients responded to treatment (≥88%) in both treatment groups in the trial, though no significant differences were found between the groups (14).

Given that the trial was ongoing during the COVID-19 pandemic, and a number of participants were enrolled and began receiving treatment before the COVID-19 vaccine was available, an analysis was conducted to understand whether deaths due to COVID-19 had an impact on the results of the study. When deaths due to COVID-19 were removed from the analysis, acalabrutinib plus bendamustine and rituximab reduced the risk of disease progression or death by 36% versus placebo plus bendamustine and rituximab (14). The trend towards an improvement in how long

participants remained alive also became more pronounced when COVID-19 deaths were removed (14).

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 in ECHO was assessed using a number of questionnaires that were completed by participants at different time points during the study. These included questionnaires on general health (EQ-5D), the impact of having cancer (EORTC-QLQ-C30), and on specific issues that are known to affect people with lymphoma (FACT-Lym) (14).

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.

Like all medicines, acalabrutinib, bendamustine, and rituximab are associated with side effects. During the ECHO trial, nearly all participants experienced side effects (also called adverse events) of treatment, whether they received acalabrutinib in combination with bendamustine and rituximab or placebo plus bendamustine and rituximab (14). The safety profile of acalabrutinib in combination with bendamustine and rituximab was in line with the known safety profiles of the individual drugs (14). The addition of acalabrutinib did not result in any new safety signals (14).

Severe side effects (categorised as Grade 3 or higher adverse events) due to any cause occurred in 88.9% of patients treated with acalabrutinib, bendamustine and rituximab, and 88.2% of patients treated with bendamustine rituximab. These side effects included severe (Grade 3 or higher) atrial fibrillation in 3.7% and 1.7% of patients, hypertension in 5.4% and 8.4%, major bleeding in 2.0% and 3.4%, neutropenia in 35.4% and 37.0%, infections in 41.1% and 34.0%, and pneumonia in 8.8% and 6.4%, respectively (14).

Any-grade COVID-19 events (other than pneumonia) were reported in 30.6% and 20.9% of patients in the acalabrutinib, bendamustine and rituximab, and placebo, bendamustine and rituximab arms respectively, with deaths reported in 2.7% and 2.0% of pts, respectively (14).

Discontinuation of acalabrutinib due to side effects was reported in 42.8% of patients, which was a difference of 11.8% versus the placebo arm (31.0%) (14). COVID-19 was the primary cause (14).

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 ECHO trial showed that for people with untreated mantle cell lymphoma who are likely considered unsuitable candidates for autologous stem cell transplant, adding acalabrutinib to the current standard treatment with bendamustine and rituximab significantly increases the time that people remain alive without disease progression (14). The trial also showed a trend towards improvement in life expectancy compared with using bendamustine and rituximab alone (14). In addition, acalabrutinib in combination with bendamustine and rituximab showed manageable side effects (14).

While many patients respond well to current treatment options, these treatments for patients with mantle cell lymphoma who are unsuitable for autologous stem cell transplant have limited efficacy in preventing patients relapsing. This results in high mortality, with less than 50% of patients surviving 5 years after diagnosis (1). Many existing treatments, such as R-BAC and VR-CAP (see 2c) have high toxicity rates and are not suitable for patients who are less fit or have other co-existing conditions.

Acalabrutinib in combination with bendamustine and rituximab has been shown to extend the time that people remain alive without their disease, and therefore delay relapse. The targeted mechanism of acalabrutinib (see 3a) enables these long-term benefits whilst limiting toxicity to patients.

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

Nearly all patients in the ECHO trial experienced side effects, and the proportion of participants that experienced a side effect that was considered to be caused by the treatment was higher with acalabrutinib plus bendamustine and rituximab than with placebo plus bendamustine and rituximab.
Severe side effects (categorised as Grade 3 or higher adverse events) due to any cause occurred in 88.9% of patients treated with acalabrutinib, bendamustine and rituximab, and 88.2% of patients treated with bendamustine rituximab. These side effects included severe (Grade 3 or higher) atrial fibrillation in 3.7% and 1.7% of patients, hypertension in 5.4% and 8.4%, major bleeding in 2.0% and 3.4%, neutropenia in 35.4% and 37.0%, infections in 41.1% and 34.0%, and pneumonia in 8.8% and 6.4%, respectively (14).
Whilst acalabrutinib can be taken orally at home, people who are treated with bendamustine and rituximab will need to visit a hospital for infusions each month for 6 months.

3i) 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.

How the model reflects the condition

An economic model was designed to simulate mantle cell lymphoma by modelling the different stages of the disease using categories called 'health states'. The health states used in the model were:

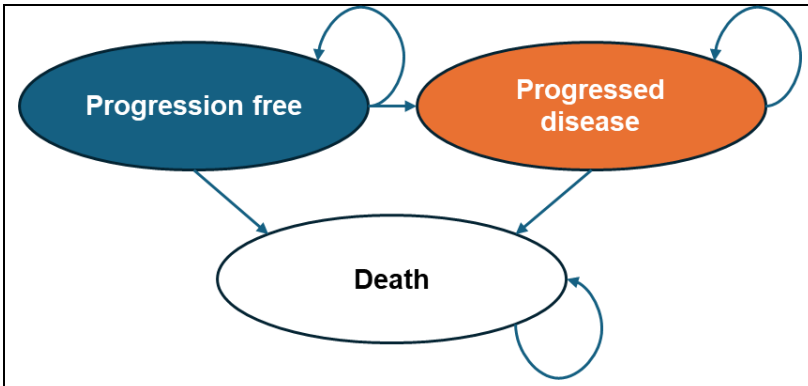
- Progression-free – the cancer is not getting worse
- Progressed disease – the cancer has got worse
- Death

In the model, patients start in the progression-free state, and then may either die, or experience worsening of the disease; once the patient has experienced worsening of the disease, they remain in this health state until they die (Figure 3). This reflects the real-life disease course.

The model assessed the cost-effectiveness of acalabrutinib plus bendamustine and rituximab followed by rituximab maintenance, compared with bendamustine and rituximab (and rituximab maintenance), and compared with R-CHOP followed by rituximab maintenance, in the first-line treatment of patients with mantle cell lymphoma who are unsuitable for autologous stem cell transplant.

The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment is, the more time patients will spend in the 'progression-free' health state. Patients accrue different costs depending on the health state they are in.

Figure 3: Model structure



Modelling how much a treatment extends life

Data from the ECHO trial were used to inform the efficacy of acalabrutinib plus bendamustine and rituximab, and bendamustine and rituximab alone (i.e. how long patients remained in the 'progression-free' or 'progressed disease' health state) in the cost-effectiveness model. In the base-case, the data from the ECHO trial in which COVID-19 deaths were removed was used, as the COVID-19 pandemic has now ended, so this was considered most representative going forward. Data for R-CHOP were taken from an analysis using published results from other clinical trials to indirectly estimate its relative efficacy.

As data from the clinical trial were only available for a relatively short length of time, statistical models were used to estimate the proportion of patients who would be in the 'progression-free' and 'progressed disease' health states over the course of 30 years.

Modelling how much a treatment improves quality of life

In the model, quality of life was determined by the health state that patients are in rather than the treatment they receive; patients in the 'progression-free' health state have a better quality of life than patients in the 'progressed disease' health state.

EQ-5D data from the ECHO trial were used to estimate the quality of life for patients in the 'progression-free' and 'progressed disease' health states.

The model also considered that side effects may have a negative impact on quality of life. The types of side effects and the number of patients experiencing them was informed by the ECHO trial and a clinical trial of R-CHOP, called LYM-3002. The impact of these side effects on quality of life was estimated from previous submissions to NICE.

Modelling how the costs of treatment differ with the new treatment

Costs that were considered in the cost-effectiveness model include those associated with medicines, treatment administration, resource use (costs for healthcare professionals and hospitals), costs of treating side effects, and costs of any subsequent treatments that patients receive after they stop first-line treatment.

Acalabrutinib plus bendamustine and rituximab displays better efficacy compared with bendamustine plus rituximab alone and is estimated to have better efficacy compared with R--CHOP. This translates into patients spending more time in the 'progression-free' health state, with a lower resource requirement on the healthcare professionals used when patients progress, and a lower proportion of patients dying. Patients progressing to the death health state are assumed to receive terminal care and accrue end-of-life costs.

Uncertainty

Uncertainty in the model inputs and structure was explored using sensitivity and scenario analyses; these analyses assessed the impact on the model outputs when inputs are varied by a defined amount and model assumptions changed.

3j) 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 combination of acalabrutinib with bendamustine and rituximab provides an opportunity to build on the efficacy of the current standard of care, treatment with bendamustine and rituximab alone, with a treatment regimen that can maximise long-term outcomes for adults with previously untreated mantle cell lymphoma who are unsuitable for autologous stem cell transplant. The addition of acalabrutinib to bendamustine and rituximab delayed disease progression for these patients by approximately 17 months in the ECHO trial, whilst limiting any additional toxicity (the frequency of side effects was similar in the two treatment groups) (14).

In the US, the New Drug Application for acalabrutinib in patients with previously untreated mantle cell lymphoma has been granted Priority Review by the FDA, the regulatory body for medicines in the US (16). Priority Review is granted to applications for medicines that, if approved, would offer significant improvements over available options by demonstrating safety or efficacy improvements, preventing serious conditions, or enhancing patient compliance (16).

3k) 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

Use of acalabrutinib in combination with bendamustine and rituximab is not expected to raise any equality issues.

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.

Useful resources for mantle cell lymphoma:

- Cancer Research UK: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell
- Macmillan Cancer Support: https://www.macmillan.org.uk/cancer-information-and-support/lymphoma/non-hodgkin/types/mantle-cell
- Lymphoma Action: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/mantle-cell-lymphoma

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

Autologous stem cell transplant	A procedure that replaces damaged or destroyed stem cells (cells in the bone marrow that make new blood cells) with healthy stem cells
B cells	A type of white blood cell
Biopsy	A small procedure to remove a sample of tissue
Bendamustine plus rituximab	The most commonly used treatment for patients with untreated mantle cell lymphoma who are unsuitable for autologous stem cell transplant
Cyclin D1	A protein involved in regulating cell growth
DNA	Genetic information that provides the instructions living things need to function, grow, and develop
Duration of response	How long people survived from the time a response to treatment was recorded until their cancer got worse
Endoscopy	A camera examination of your stomach or bowel using a thin, flexible tube passed through your mouth or bottom
EORTC-QLQ-C30	A questionnaire on the impact of having cancer
EQ-5D	A questionnaire on general health, used to assess quality of life
FACT-Lym	A questionnaire on specific issues that are known to affect people with lymphoma
First-line treatment	The first treatment given for a disease
Lumbar puncture	A procedure to take a sample of fluid from your spine using a thin needle

Mantle cell lymphoma	A rare type of non-Hodgkin lymphoma that develops when B cells, a type of white blood cell that normally help fight infection, grow abnormally and build up in the lymph nodes and other parts of the body
Mutation	A genetic change
Non-Hodgkin lymphoma	A type of cancer that develops in the lymphatic system, a network of vessels and glands that form part of the immune system
Overall response rate	The proportion of participants who respond to treatment
Overall survival	The average length of time patients are alive after the start of treatment
Progression-free survival	The average length of time after the start of treatment in which a person is alive, and their cancer does not grow or spread
R-CHOP	Rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone, a treatment currently used for mantle cell lymphoma
Resource use	Costs for healthcare professionals and hospitals
Time to response	The time from patients being randomised to receive treatment to a response being recorded
Treatment-emergent adverse events	Side effects that are reported during the clinical trial
Treatment-related adverse events	Side effects considered to be caused by the treatment given
Tyrosine kinase	Enzyme that helps to send growth signals in cells

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. HMRN. Factsheets: mantle cell lymphoma. Available from: https://hmrn.org/factsheets#mantle_cell_lymphoma. Accessed on: 20 November 2024
2. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(27):3059-68.
3. Cancer Research UK. Mantle cell lymphoma. Available from: https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/mantle-cell. Accessed on: 20 November 2024
4. Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology guideline. British journal of haematology. 2024;204(1):108-26.
5. Lymphoma Action. Mantle cell lymphoma. Available from: https://lymphoma-action.org.uk/types-lymphoma-non-hodgkin-lymphoma/mantle-cell-lymphoma. Accessed on: 20 November 2024
6. Leukemia & Lymphoma Society. Mantle cell lymphoma. 2023. Available from: https://www.lls.org/sites/default/files/2023-05/FS4_Mantle_Cell_Facts_0423rev.pdf. Accessed on: 20 November 2024
7. Lymphoma Action. Self (autologous) stem cell transplants. Available from: https://lymphoma-action.org.uk/about-lymphoma-treatment-lymphoma-stem-cell-transplants/self-stem-cell-transplants. Accessed on: 20 November 2024
8. Myeloma UK. High-dose therapy and autologous stem cell transplantation: Treatments and tests infoguide. 2023.

9. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management. NG52. 2016. Available from: https://www.nice.org.uk/guidance/ng52.
10. AstraZeneca. Summary of clinician interviews to support the NICE HTA submission for acalabrutinib with bendamustine and rituximab in untreated mantle cell lymphoma [ID6155]. Data on File: REF-251322. 2024.
11. Cancer Research UK. Acalabrutinib (Calquence). Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/acalabrutinib. Accessed on: 20 November 2024
12. Cancer Research UK. Bendamustine (Levact). Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/bendamustine. Accessed on: 20 November 2024
13. Cancer Research UK. Rituximab. Available from: https://www.cancerresearchuk.org/about-cancer/treatment/drugs/rituximab. Accessed on: 20 November 2024
14. Acerta Pharma/AstraZeneca. Phase 3, randomized, double-blind, placebo-controlled, multicenter study of bendamustine and rituximab (BR) alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated mantle cell lymphoma (ECHO). Interim Clinical Study Report. Data on file. 2024.
15. AstraZeneca. Calquence draft SmPC. Data on file 2024.
16. Calquence granted Priority Review in the US for patients with untreated mantle cell lymphoma [press release]. 2024.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Clarification questions

December 2024

File name	Version	Contains confidential information	Date
ID6155 acalabrutinib Clarification Letter 111224IM [CON]	**V1.0**	**Yes**	**16th January 2025**

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 A: Clarification on effectiveness data

Statistical analyses

A1. PRIORITY Document B, Section B.2.6.2 p46. In the PBR arm 51/299=17% of participants crossed over to acalabrutinib monotherapy. Please clarify whether any sensitivity analysis of the overall survival was undertaken. The EAG would suggest an analysis such as Inverse Probability of Censoring Weights or Rank Preserving Structural Failure Time Model and would draw attention to the TSD16 (Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching, 2014. Available from http://www.nicedsu.org.uk).

Further analysis of crossover was not performed on the ECHO trial because the results of the intention to treat analysis, which accounted for subsequent BTKi therapy, were considered representative of UK clinical practice. Adjusting overall survival to exclude the effects of crossover therapy would reflect a hypothetical scenario where eligible patients in the PBR treatment arm did not receive BTKi therapy after progression. However, in UK clinical practice, all eligible patients receiving BR in 1L are expected to receive a BTKi therapy after progression, aligning with the intention to treat results of ECHO.

As requested by the EAG, a further post-hoc analysis exploring the impact of crossover on OS results was conducted. A rank preserving structural failure time (RPSFT) analysis that exclusively adjusted for crossover therapy was performed.

Following NICE TSD16 and TSD24, the updated RPSFT analysis was conducted using an 'as treated' (effect applies while on therapy only) approach and an 'ever treated' (effect continues beyond end of therapy) approach, and with and without re-censoring. In all scenarios, a log-rank test statistic was used to identify the value of psi where counterfactual survival times were on average, equal across arms. Visual inspection of the Kaplan-Meier plots of counterfactual survival times in each group confirmed that survival estimates were equal at the psi value (Figure 1 to Figure 4). The effect of treatment after crossover adjustment was estimated by stratified Cox regression analysis, with stratification factors of region and simplified MIPI score. The 95% confidence interval for treatment effect was estimated using the p-value from the intention to treat analysis (p=0.2743).

Table 1 shows the results of the updated RPSFTm analysis of crossover therapy.

Figure 1: Counterfactual KM plots: On treatment (without recensoring)

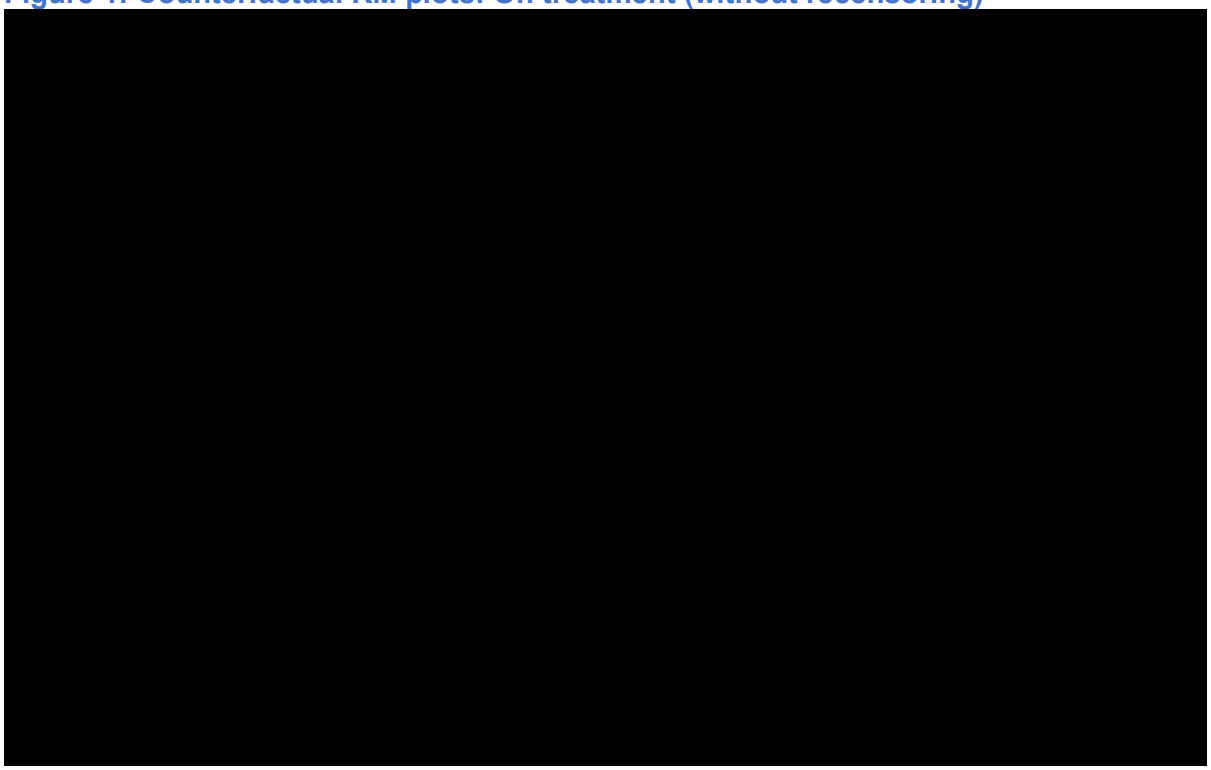


Figure 2: Counterfactual KM plots: On treatment (with recensoring)

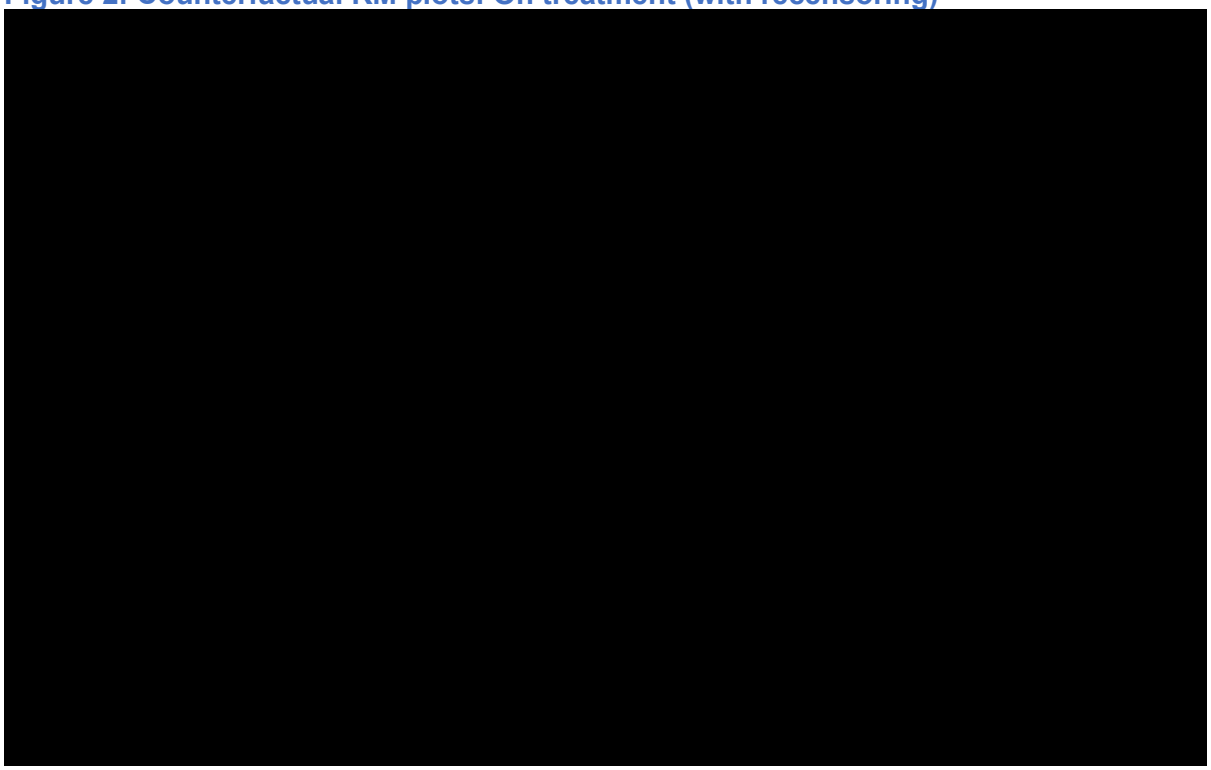


Figure 3: Counterfactual KM plots: Treatment group (without recensoring)

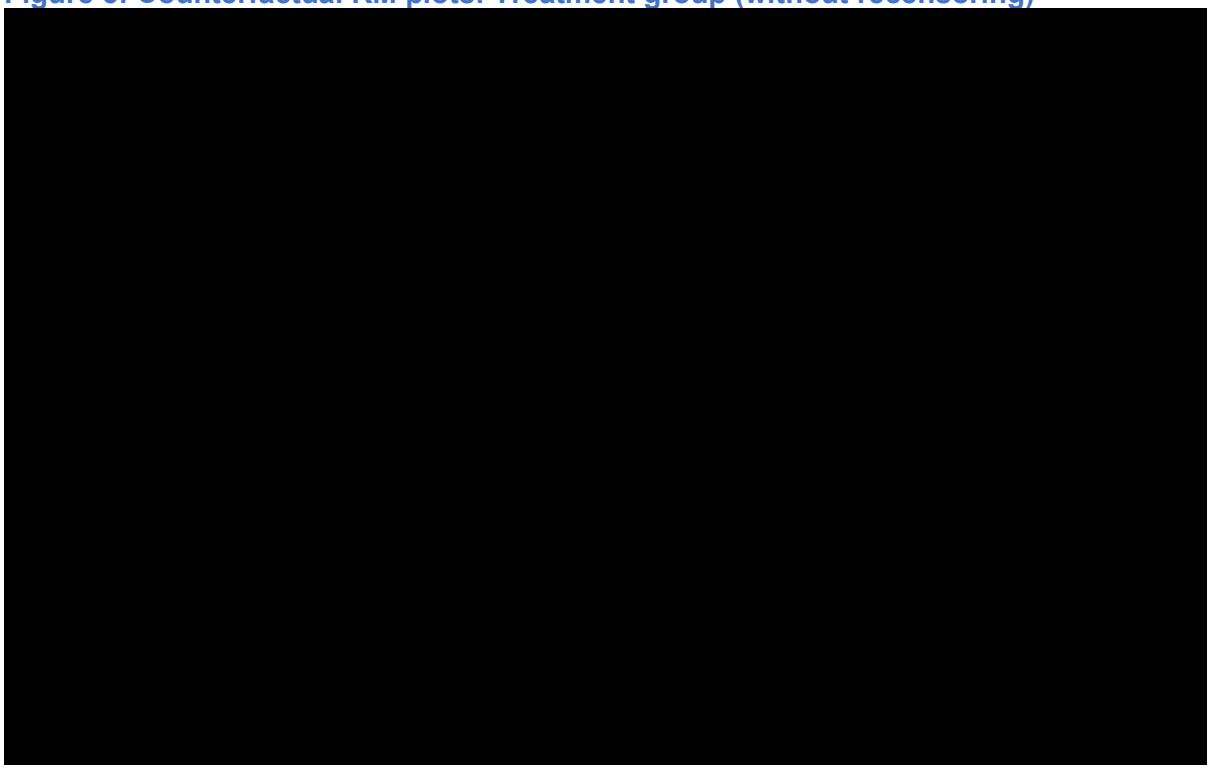


Figure 4: Counterfactual KM plots: Treatment group (with recensoring)

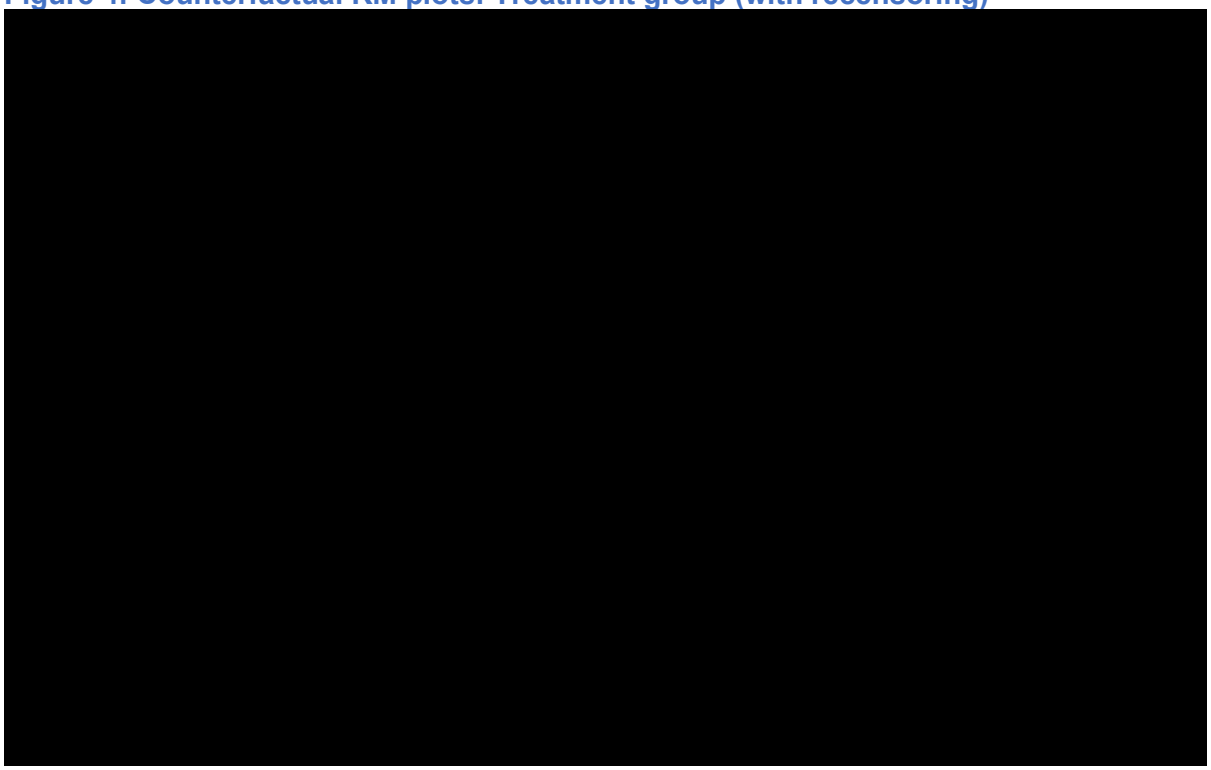


Table 1: Results of updated RPSFTm analysis, alongside ITT and RPSFT for crossover and subsequent anti-MCL therapies

Approach to treatment effect	Re-censoring	Hazard ratio estimate	Lower 95% CI	Upper 95% CI	Exponential of Psi (95% Confidence intervals)
Intention to treat results		[redacted]	[redacted]	[redacted]	[redacted]
'as treated' (on treatment)	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
'ever treated' (treatment group)	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]

Across all scenarios, the treatment effect after crossover adjustment ranged from [redacted]. Crossover adjustment resulted in numerical improvements to the hazard ratio for ABR versus PBR. The application of re-censoring led to an improved treatment effect for ABR. In all RPSFT analyses, ABR was associated with improved OS versus PBR.

A2. Document B, Section B.2.6.1.1.1 p44, Table 16. Please explain why the percentage of deaths prior to progression is higher in the ABR group than the PBR group?

Table 16 (Analysis of PFS by IRC assessment [FAS: censoring COVID-19 death]; Company submission) reports 26 deaths in the ABR arm and 18 deaths in PBR arm as events for the COVID-19 censored PFS analysis. A summary of deaths in this population, alongside primary causes of death, is presented in Table 2. There were no meaningful differences in primary causes of death, including "disease progression", "AE" and "other" (<1% difference), other than those with "unknown" cause where 5 patients in the ABR arm died versus none in the ABR arm.

Table 2 Summary of deaths (COVID-19 censored population, including crossover period)

	No. (%) of patients	
	ABR (N=299)	PBR (N=299)
Deaths	[redacted]	[redacted]
Primary cause of death		
Adverse event	[redacted]	[redacted]
Disease progression†	[redacted]	[redacted]
Other‡	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

† The subjects died without PD assessed by IRC, but the site entered the primary cause as "Disease Progression".
‡ 'Other' represents AEs that occurred beyond the treatment period that were considered unrelated to any of the study drugs (in line with AE reporting guidelines).
All deaths included both treatment-emergent and nontreatment-emergent deaths.
Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; FAS, full analysis set; PBR, placebo, bendamustine, rituximab.

Baseline characteristics of the ECHO study

A3. Document B, Section B.2.3.7, p.33, Table 8. For the baseline characteristics of the participants of the ECHO study, please provide data indicating the presence of TP53 mutation/deletion in the intervention and control groups if these are available.

Among the 598 patients randomised to ABR or PBR (299 in each arm), known TP53 mutation at baseline was found in 7.4% and 9.7% of patients, respectively. These are available from the updated analysis of the Phase 3 ECHO trial, presented at the ASH Annual meeting in December 2024 (1).

Outcome Assessment

A4. Document B, Section B.2.3.5.1 p30. The EAG notes that progression and all the secondary efficacy outcomes were assessed by an Independent Review Committee (IRC). Please specify the number of participants in the IRC and clarify whether they were blinded.

The Independent Review Committee (IRC) comprised of 4 independent reviewers. These were 3 independent radiologists and 1 independent oncologist. All 4 reviewers were blinded to the randomised treatment. Each radiographic scan (imaging timepoint) for a subject was assessed by 2 independent radiologists, who are dual board certified in radiology and nuclear medicine or have equivalent. A third radiologist, who did not participate in the subject's timepoint imaging review, provided a radiology adjudication review in the event of disagreement by the two independent radiologists. The independent oncologist provided the final overall tumour assessment of a patient's response to therapy in the trial.

Adjustment for COVID-19 deaths

A5. Document B, Section B.2.6.1.1.1 p44, Table 16. Please clarify how participants with death related to COVID-19 and without disease progression prior to death were treated in the analyses. The text suggests that these participants were excluded; however, the table suggests that these participants were censored at their date of death. The EAG believes that censoring is more appropriate.

The text in Document B is incorrect; in the sensitivity analysis, patients with death related to COVID-19 and without PD prior to death were censored, not excluded.

Literature searches

A6. Document B, Section B.2.10. For the indirect treatment comparison (ITC), searches were performed in Medline and Embase, but not in the Cochrane Library (CENTRAL and CDSR), clinical trial registries, or HTA sources. This approach could have resulted in missing relevant peer-reviewed literature. Please justify your decision to limit the ITC searches to Medline and Embase. The EAG notes that

additional sources were searched for the SLR assessing the clinical effectiveness of acalabrutinib in combination with bendamustine and rituximab.

The feasibility of ITC was conducted based on the list of studies identified from a targeted literature review (TLR), which searched Medline, Embase, and conference proceedings. Later, a systematic literature review (SLR) was conducted, in which Medline, Embase, the Cochrane library, conference proceedings, clinical trial registries, and additional grey literature sources were searched. Relative to the TLR, the SLR did not identify any additional studies of relevance for inclusion in the ITC, despite the additional sources searched.

Adverse events

A7. Document B, Section B.2.10. Please provide adverse event data on major bleeding and atrial fibrillation in the ECHO trial.

Adverse event data for major haemorrhage and atrial fibrillation are provided in Table 3. Please note that these are also available in Appendix M.3.3.2, page 110, Table 62.

Table 3: Treatment-emergent adverse events of clinical interest (SAS)

	ABR (N=297)			PBR (N=297)		
	Any grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Atrial fibrillation	20 (6.7%)	12 (4.0%)	0	13 (4.4%)	5 (1.7%)	0
Major haemorrhage	7 (2.4%)	6 (2.0%)	0	16 (5.4%)	9 (3.0%)	1 (0.3%)

MedDRA version 26.1.
Patients were only counted once for each preferred term using the highest grade.
Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAS, safety analysis set.

Section B: Clarification on cost-effectiveness data

Economic model structure

B1. PRIORITY. Document B, Section B.3.3.2.2, P.85-86.

The EAG acknowledges the company's description of the benefits of partitioned survival modelling, and generally agrees with all the points raised. However, Table

30 of the company submission shows that most previous models in this space, including those developed for NICE TA370 and TA502 have used Markov cohort models. The EAG notes that partitioned survival models are often used in cancer appraisals. However, they have substantial limitations when considering the assessment of early-phase treatments where several lines of subsequent treatment are considered before the OS endpoint. Relying on one OS curve, with relatively immature data underestimates the OS benefits of future subsequent treatment lines. For example, the model underestimates the OS benefits of 2nd and 3rd line treatments like ibrutinib and CAR-T therapy. It also fails to capture any progression-free survival benefit for these treatments. The EAG would appreciate the following additional points of clarification:

A. Did the company conduct any structural scenario analyses or develop a Markov model? If so, the EAG would appreciate it if this could be provided.

Both partitioned survival model (PSM) and state transition model (STM) structures were considered during the model conceptualisation phase, and it was determined that the STM introduced considerable complexity and uncertainty when compared to a PSM. Firstly, it was not feasible to expand the three-state structure to allow for second, or later lines of progression, as there was insufficient evidence across trials in MCL for the modelling of second progression events (i.e. no PFS2 endpoints for ECHO, or for the BRIGHT and Stil-NHL studies for R-CHOP). The introduction of external data also adds uncertainty to the model as it requires the integration of disparate data sources. While data limitations impact both the PSM and STM model structures, the additional uncertainties introduced by the STM approach made the PSM the more parsimonious choice.

When scrutinising the modelling precedent in MCL, the Company noted that in the most recent NICE assessment that used a Markov state transition model (TA502), concerns were raised regarding structural assumptions imposed by the model, as well as its ability to predict OS in the manufacturer's clinical trial. To predict OS, the state transition model relies on the accurate modelling of transitions between intermediary states and death. Ultimately, the ERG in TA502 believed that this approach introduced an additional layer of uncertainty and concluded that the observed OS KM curves (with appropriate extrapolation) from the pivotal clinical trial

would provide the best estimate of OS, and using this data directly to inform a PSM would be preferable over the assumptions required for a STM.

As detailed in Section B.3.3.2.2 of Document B, a key strength of the PSM is that it allows for both PFS and OS, which are key endpoints collected in the ECHO trial, to be utilised directly to determine the proportion of patients occupying each health state at each model cycle. This was one of the key reasons for why the PSM was chosen over other methods and a STM was not developed, and structural scenario analyses were not explored.

B. Please provide a commentary on the limitations of partitioned survival modelling in this setting and provide details of how the impact of these limitations has been minimised within the company submission.

The Company acknowledges that there are limitations of the PSM in this setting, and these limitations were described in Section B.3.8 of Document B. Namely, the independent modelling of OS and PFS curves within a PSM framework only implicitly accounts for the transition from the progressed disease state to death, limiting the possibility to model multiple subsequent lines of treatment. Although, as noted above, external data to ECHO could have been used to inform post-progression outcomes in the model, but this would have required strong assumptions on the generalisability of data between trials, introducing uncertainties in the model akin to those highlighted by the ERG for TA502.

It should be noted that the second PFS benefit of subsequent treatment lines would partially cancel out as it impacts all treatment arms in the model, albeit with a greater impact on the control arms (BR and R-CHOP), given access to more effective treatments such as BTKis in the 2nd line setting. Furthermore, the survival benefits of subsequent treatment lines are captured in the OS data from ECHO, including subsequent BTKIs. In addition, the post-progression benefit of subsequent treatment lines would manifest as improvements in quality of life, impacting on the utility score of patients in the PD state. Due to discounting, and the limited duration of survival after progression, the utility score assigned to PD was not identified as a key driver of model results in the DSA. Hence, the omission of modelled second or later progression states from the model is unlikely to materially impact on results.

C. Please consider whether any further scenario analyses could be conducted within the partitioned survival analysis model to address the limitations identified above.

Within the current model framework, it is not possible to explore further scenarios that address the limitations highlighted above. It is noted that a limitation of the PSM structure is its inability to explicitly model health states for subsequent lines of therapy. However, as discussed in B1 (A) and B1 (B) the model maximises its use of the ECHO trial data by assuming the observed OS data accurately captures the outcomes post-progression for patients with subsequent treatments, rather than introducing uncertainties from external data sources. The model also makes use of ECHO trial data to inform the proportion of patients receiving 2nd and 3rd line treatments.

Furthermore, the proportions of patients receiving subsequent treatments have been validated by UK clinical experts to more accurately align the cost of subsequent treatments with UK clinical practice. It is acknowledged that that this includes a proportion of patients receiving CAR-T at 3rd line. However, it is anticipated that this proportion is fairly small, so it is unlikely to have a large impact on the OS projections extrapolated from the trial data.

So, while the limitations of the PSM structure are acknowledged, the Company consider the employed model structure as a robust representation of both the available ECHO trial data and UK clinical practice.

Clinical parameters

B2. Document B, Section B.3.4.4. TTD for ABR and PBR, P. 112.

Please provide a table with full details of all reasons for treatment discontinuation, reported as n/N (%).

Details of primary reason for treatment discontinuation are provided in Table 4. Please note that these are also available in Table 10 of the CSR.

Table 4: Study treatment status and discontinuation (Full Analysis Set)

	ABR (N = 299)	PBR (N = 299)
Patients randomised (Full Analysis Set), n (%)	[redacted]	[redacted]
Treated with ≥ 1 dose of study drug (Safety Analysis Set), n (%)	[redacted]	[redacted]
Randomised but not treated[a], n (%)	[redacted]	[redacted]
Disposition status on study treatment, n (%)		
Patients ongoing[b]	[redacted]	[redacted]
Patients who discontinued study treatment	[redacted]	[redacted]
Primary reason for study treatment discontinuation[c]		
Adverse event	[redacted]	[redacted]
Objective evidence of PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patient's withdrawal of consent	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]
Clinical PD	[redacted]	[redacted]
Patient lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Acalabrutinib/placebo, n (%)		
Patients treated with study drug	[redacted]	[redacted]
Patients on treatment	[redacted]	[redacted]
Patients who discontinued study drug	[redacted]	[redacted]
Primary reason for study drug discontinuation		
Adverse event	[redacted]	[redacted]
Objective evidence of PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patient's withdrawal of consent from study	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]
Clinical PD	[redacted]	[redacted]
Patient lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Bendamustine, n (%)		
Patients treated with study drug[d]	[redacted]	[redacted]
Patients on treatment	[redacted]	[redacted]
Patients completed per protocol	[redacted]	[redacted]
Patients who discontinued study drug	[redacted]	[redacted]
Primary reason for study drug discontinuation		
Adverse event	[redacted]	[redacted]
Objective evidence of PD	[redacted]	[redacted]

	ABR (N = 299)	PBR (N = 299)
Investigator's decision	[redacted]	[redacted]
Patient's withdrawal of consent from study	[redacted]	[redacted]
Clinical PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patient lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Rituximab, n (%)		
Patients treated with study drug	[redacted]	[redacted]
Patients on treatment	[redacted]	[redacted]
Patients completed per protocol[e]	[redacted]	[redacted]
Patients who discontinued study drug	[redacted]	[redacted]
Primary reason for study drug discontinuation		
Adverse event	[redacted]	[redacted]
Objective evidence of PD	[redacted]	[redacted]
Death	[redacted]	[redacted]
Investigator's decision	[redacted]	[redacted]
Patient's withdrawal of consent from study	[redacted]	[redacted]
Clinical PD	[redacted]	[redacted]
Patient lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Patients who discontinued all study treatment[c], n (%)	[redacted]	[redacted]
Patients who discontinued B and/or R only, n (%)	[redacted]	[redacted]
Patients who exited study, n (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Patient's withdrawal of consent from study	[redacted]	[redacted]
Patient lost to follow-up	[redacted]	[redacted]
Other	[redacted]	[redacted]
Time on study (months)[f]		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

a Patients 0100-30393, 0100-30674, 0907-30373, and 1503-30012 were randomised by without exposure data.
b At least one of the study drugs was ongoing (acalabrutinib, placebo, bendamustine, or rituximab).
c Based on the earlier drug of the regimen that were discontinued under each arm. Discontinued all study treatment based on randomised treatment assignment.
d Patient 0933-30563 in the PBR arm had 1 dose of rituximab and then discontinued without receiving placebo or bendamustine.
e Patients who were reported by the investigator to have completed rituximab treatment per protocol.
f Time on study = study exit date – date of randomisation + 1 day..
Reference: ECHO Interim CSR, Table 10, Page 82.

B3. PRIORITY. Document B, Section B.3. – clinical expert opinion

For all economic model parameters (e.g., validation of OS and PFS extrapolations, 2nd and 3rd line treatment distributions) informed by clinical expert opinion, please provide full details of the number of responding experts, their expertise, and where possible the specific values for each parameter provided by each expert. Please integrate variation in the clinical expert opinion into the PSA.

Interviews were conducted with four currently practicing consultant haematologists – three from the UK and one from Scotland. These interviews were used to validate the extrapolation of OS and PFS, and to gain insight on subsequent treatment distributions for patients who have progressed from 1L MCL. High level details of each clinical expert are provided in the submitted reference pack, in the file labelled "*AZ Data on File. REF-255537_ECHO NICE clinician interviews*".

The clinicians were asked to validate the OS and PFS extrapolations from the ECHO trial data. While there was no consensus on curve selections for OS and PFS, it was generally agreed that long-term projections should be approached conservatively, with a clinical benefit for OS and PFS in favour of ABR. Therefore, the model's base case uses the gamma curve as a conservative extrapolation of OS and PFS.

The clinicians were also asked to provide the distribution of patients across treatments at 2nd and 3rd line. Participant responses for 2nd line distributions are detailed in Table 5, and 3rd line distributions are detailed in Table 6. The average values across the four participants were used to inform the 2nd and 3rd line subsequent treatment distributions used in the economic model.

Table 5: Clinician responses for 2L subsequent treatment distributions

	ABR					BR					R-CHOP				
Clinician	1	2	3	4	Average (model base case values)	1	2	3	4	Average (model base case values)	1	2	3	4	Average (model base case values)
Ibrutinib	0%	NR	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
R-CHOP	90%	NR	33.33%	100%	74%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
VR-CAP	10%	NR	33.33%	0%	14%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
R-BAC	0%	NR	33.33%	0%	11%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-BAC, rituximab, bendamustine, cytarabine; NR, not reported; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

Table 6: Clinician responses for 3L subsequent treatment distributions

	ABR					BR					R-CHOP				
Clinician	1	2	3	4	Average (model base case values)	1	2	3	4	Average (model base case values)	1	2	3	4	Average (model base case values)
Ibrutinib or chemotherapies (R-CHOP, R-BAC, VR-CAP)	50%	NR	NR	NR	50%†	50%	25%	NR	NR	62.50%†	50%	10%	20%	60%	65.00%†
CAR-T	50%	NR	NR	NR	50%	50%	75%	NR	NR	37.50%	50%	90%	80%	40%	35.00%

†ABR patients receiving chemotherapies are equally split across R-CHOP, R-BAC and VR-CAP in the economic model. BR and R-CHOP patients receiving chemotherapies are equally split across R-CHOP, R-BAC, VR-CAP and ibrutinib in the economic model

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-BAC, rituximab, bendamustine, cytarabine; NR, not reported; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone

In the 3rd line setting, to inform the proportion of patients receiving R-CHOP, R-BAC, VR-CAP and ibrutinib, the percentage of patients that would receive chemotherapies/ibrutinib were equally split across these treatments for the BR and R-CHOP arm. For the ABR arm, the percentage that would receive chemotherapies was split between R-CHOP, R-BAC and VR-CAP, as these patients were assumed not to receive ibrutinib following 1L treatment with ABR, as per clinical practice.

As it is not possible to integrate the results of these interviews into the PSA, an additional scenario analysis has instead been provided to explore the range of results using alternative subsequent treatment proportions estimated by each of the four clinical experts. Where clinicians did not report results, the averages used in the model are instead assumed. The results of these scenarios are presented in Table 7.

Table 7: Deterministic pairwise results of scenarios using individual clinicians' estimations of subsequent treatment proportions

ICER versus:	Scenario pairwise ICERs, £/QALY				Original submitted pairwise ICER, £/QALY
	Clinician 1	Clinician 2	Clinician 3	Clinician 4	
BR	£228	-£8,494	£15,955	£5,986	10,153
R-CHOP	-£5,848	-£27,908	-£19,310	-£2,485	2,486

Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

B4. PRIORITY. Document B, Section B.3.4.5., P.115.

The EAG notes that HRs from the NMA are included in the economic model to estimate the OS and PFS benefit of R-CHOP vs. BR only.

A. Please clarify whether the HRs provided in Table 42 are derived from the COVID-censored analysis set or the ITT analysis set from the ECHO trial. Please provide data from both analyses.

The HRs presented in Table 42 of Document B are derived from the COVID-19 censored analysis set, as described in the text immediately above Table 42. The HRs presented in Table 22 (PFS) and Table 24 (OS) of Document B are derived from the ITT dataset. Table 8 below presents the OS and PFS HRs derived from both the COVID-19-censored analysis set and the ITT analysis set.

Table 8: Hazard ratios of clinical outcomes for R-CHOP versus BR (fixed effects): COVID-19-censored and ITT analysis sets

Parameter	COVID-19-censored analysis set	ITT analysis set
OS	[redacted]	[redacted]
PFS	[redacted]	[redacted]

Abbreviations: COVID, coronavirus disease; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival

B. Please provide a sensitivity analysis for PFS and OS data using HRs for all treatment comparisons derived from the NMA. This may be of interest if the Committee is satisfied that the PH assumption holds across all comparisons.

A scenario has been conducted in which clinical efficacy data for R-CHOP is estimated using HRs applied to the ABR arm of the ECHO trial rather than the BR arm. In this scenario, clinical efficacy data for ABR and BR are both independently extrapolated from ECHO trial data, as per the submitted base case analysis. As the ITC results report HRs for ABR against R-CHOP, the HRs for R-CHOP versus ABR are calculated as 1/HR for use in the model scenario.

The HRs used in the scenario are presented in Table 9, while Table 10 presents the deterministic results under this model scenario.

Table 9: Hazard ratios, upper and lower bounds for R-CHOP versus ABR

Parameter	COVID-19-censored analysis set		ITT analysis set	
	Hazard ratio (ABR versus R-CHOP)	Hazard ratio (R-CHOP versus ABR)	Hazard ratio (ABR versus R-CHOP)	Hazard ratio (R-CHOP versus ABR)
OS	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: COVID, coronavirus disease; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

Table 10: Deterministic pairwise results using hazard ratios for R-CHOP versus BR

Technologies	Total costs, £	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Scenario pairwise ICER, £/QALY	Original submitted pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,153	10,153
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5,747	2,486

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; NHB, net health benefit; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

C. To further assess the appropriateness of the PH assumption, please provide additional analysis, exploring log-time interactions for each treatment as this may help to reduce the uncertainty about the validity of the PH assumption for OS and PFS.

The assessment of PHs in ECHO, BRIGHT and Stil-NHL1 followed guidance from NICE TSD14 and included assessment of Schoenfeld residual and inspection of the log-cumulative hazards plot. The assessment was performed for each trial and time to event endpoint that reported a Kaplan-Meier plot alongside the treatment effect estimate from Flinn 2019 and Rummel 2013, the two trials comparing R-CHOP against BR included in the ITC. The results of these tests are presented below for Flinn 2019, assessing PFS and OS for R-CHOP and BR, and Rummel 2013, assessing PFS for R-CHOP and BR.

Figure 5 and Figure 6 present the log-cumulative hazard and Schoenfeld residual plots, respectively, for PFS data in Flinn 2019. It is seen that the log-cumulative hazard plots are generally parallel over time. The Schoenfeld residual plots report a

p-value > 0.05, suggesting no statistically significant evidence to reject the null hypothesis of proportional hazards. Finally, visual inspection of the Schoenfeld residual plots indicate that the proportional hazards assumption holds as the plots are approximately horizontal.

Figure 7 and Figure 8 present the same diagnostic tests for PFS data from Rummel 2013. It is noted that the log-cumulative hazard plots cross, however overall they are parallel. Furthermore, visual inspection of the Schoenfeld plots do not indicate a violation of the proportional hazards assumption, as the plots are approximately horizontal. Similarly, while the log-cumulative hazard plots for OS data from Flinn 2019 cross, they are generally parallel over time and the Schoenfeld residual plots do not indicate a violation of the proportional hazards assumption (Figure 9 and Figure 10). Therefore, it is arguable that the proportional hazards assumption holds for the trials used to inform the ITC assessing R-CHOP against BR.

Figure 5: Log-cumulative hazard plot for PFS data (Flinn 2019)

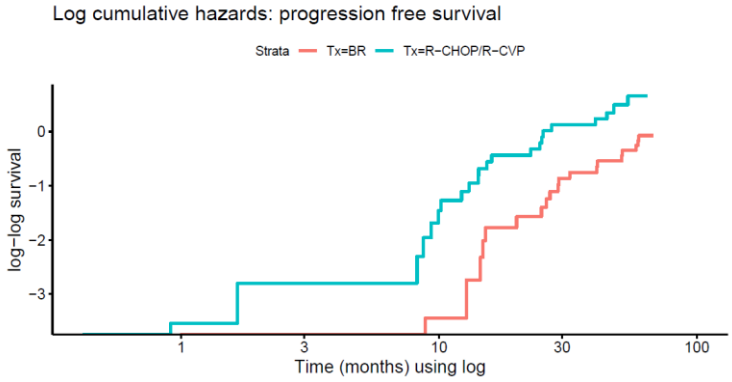


Figure 6: Schoenfeld residual plots for PFS data (Flinn 2019)

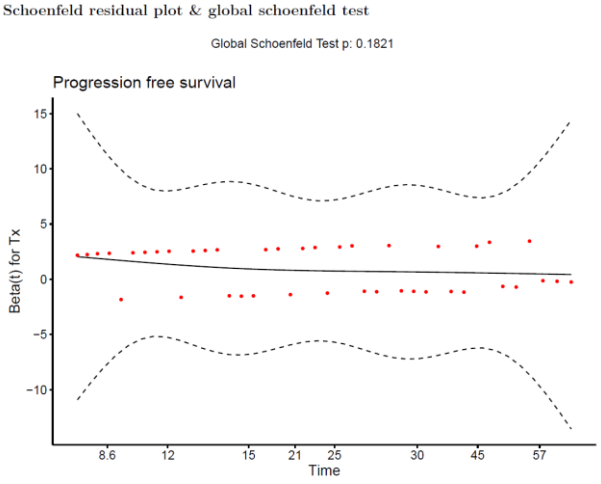


Figure 7: Log-cumulative hazard plots of PFS data (Rummel 2013)

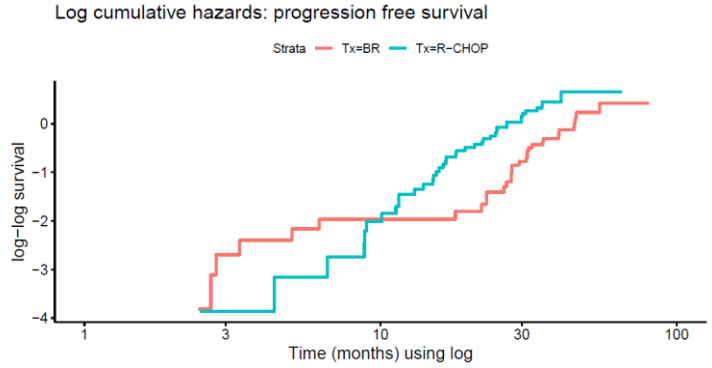


Figure 8: Schoenfeld residual plots of PFS data (Rummel 2013)

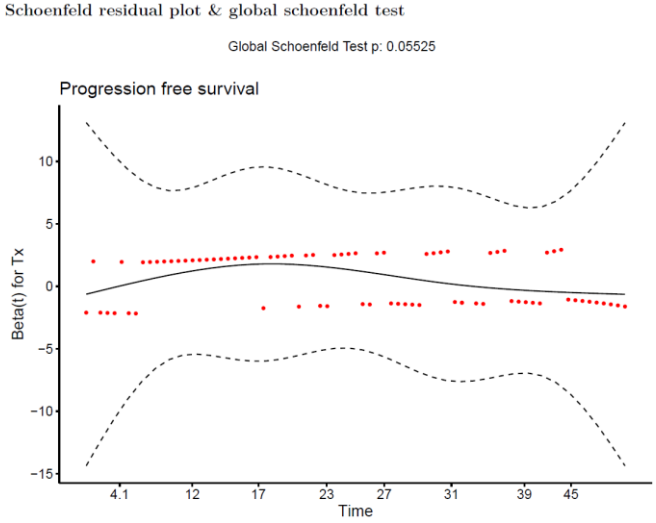


Figure 9: Log-cumulative hazards of OS data (Flinn 2019)

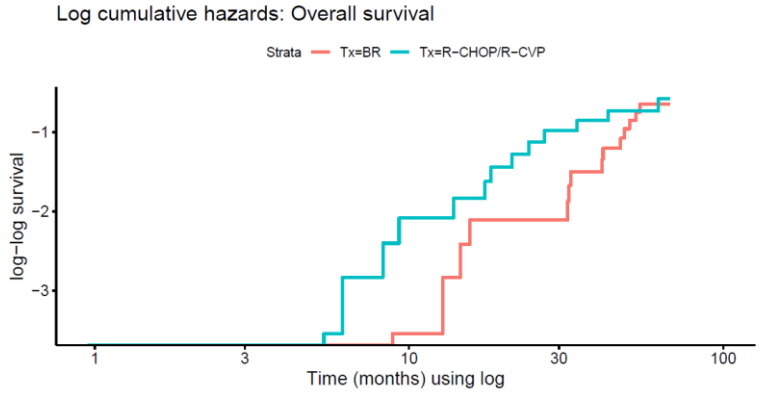
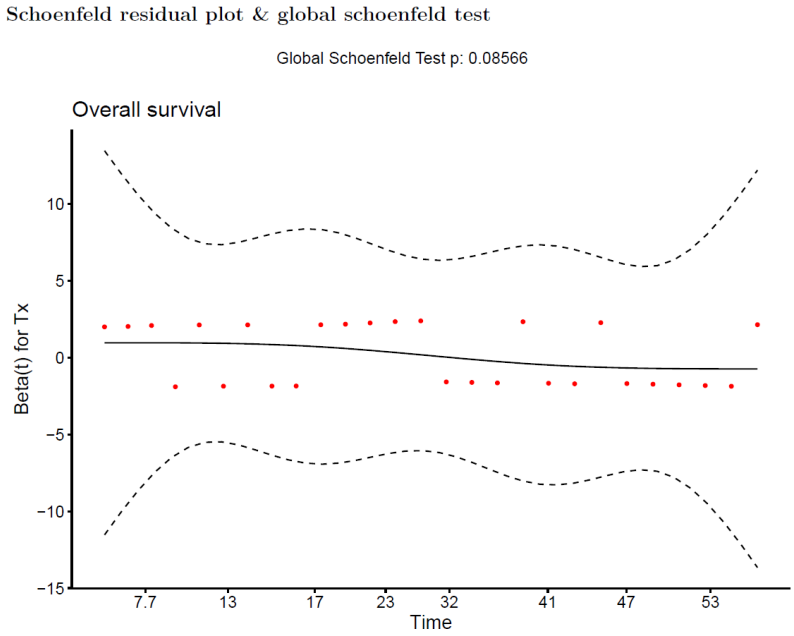


Figure 10: Schoenfeld residual plots OS data (Flinn 2019)



In each study, the Schoenfeld GT test was applied to a Cox regression model with a single covariate for treatment (e.g., ABR vs PBR). The resulting global test is therefore not dependent on other covariates. In general, however, the manufacturer agrees with the EAG that the GT test (and by extension, other tests) provides a high bar for assessing PH given that the test is likely underpowered to detect non-PH (2). This lack of statistical power is further hampered by the small sample sizes of the R-CHOP studies. As a result, visual inspection of the trends in the log-cumulative hazard plot was also performed. Whilst subject to limitations, the NMA of log-hazard ratios provides a reasonable estimate of treatment effect for R-CHOP given the available evidence.

The Company acknowledges that the Schoenfeld test is likely underpowered to detect violation of proportional hazards, given the small sample sizes of the studies of R-CHOP. However, the network meta-analysis provides a reasonable estimate of treatment effect of R-CHOP given the available evidence, and a visual inspection of the log-cumulative hazard plots would suggest it is reasonable to assume the proportional hazards assumption is not violated.

D. If the PH assumption is not deemed appropriate, please consider more flexible piecewise models that could be used to relax the PH assumption but maintain the use of the HRs from the NMA.

Flexible models were not explored given the standard parametric models were found to fit the observed data well and aligned with clinical expectations. The use of HRs from the NMA to inform the R-CHOP arm was deemed appropriate as our testing revealed it is reasonable to assume the proportional hazards assumption is not violated.

B5. Document B, Section B.3.5.3., P.121.

The EAG notes some minor discrepancies between the TEAE incidence rates for COVID-19 pneumonia, COVID-19 and Rash maculo-papular in table 46 (page 45) versus table 28 (page 69). Please:

A. Align the rates used in the model for COVID-19 pneumonia, COVID-19 and Rash maculo-papular with that reported in the clinical effectiveness section.

The corrected TEAE incidence rates (Grade ≥3) are presented in presented in Table 11.

Table 11: Updated TEAE incidence rates (Grade ≥3)

AE	ABR, %	BR, %	R-CHOP, %
Anaemia	9.4	10.1	13.6
Febrile neutropenia	5.1	2.4	13.6
Leukopenia	5.7	6.1	29.3
Lymphopenia	2.7	5.4	8.7
Neutropenia	35.4	37.0	66.9
Pneumonia	8.8	6.4	4.5
Thrombocytopenia	6.1	5.4	5.8
COVID-19 pneumonia	13.5	10.4	0.0
COVID-19	8.8	7.1	0.0
Rash maculo-papular	7.1	0.7	0.0
Neutrophil count decreased	15.5	10.1	0.0
White blood cell count decreased	10.1	3.7	0.0
Lymphocyte count decreased	6.4	9.8	0.0
Hypertension	5.4	8.4	0.0
Source	ECHO trial (3)	ECHO trial (3)	LYM-3002 (4)

Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; AE, adverse event; BR, bendamustine + rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

On aligning the adverse events incidence rates with Table 11 (and consistent with Table 28 of Document B), the following results are generated by the model:

Table 12: Deterministic pairwise results following correction of TEAEs

Technologies	Total costs, £	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Updated base case pairwise ICER, £/QALY	Original submitted pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	10,003	10,153
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,340	2,486

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; NHB, net health benefit; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

B. Update the company base case and economic model to reflect the preferred TEAE incidence rates.

These changes are now reflected in the updated company base case, on the "Safety" sheet. The inputs for incidence of COVID-19 pneumonia, COVID-19 and

Rash maculo-papular, for ABR and BR, have been updated to reflect the values presented in the above table. These are cells D20:D22 and E20:E22 of the “Safety” sheet. The default values for these parameters have also been updated in the “data_parameters” sheet, in cells L112-L114 and L126-L128.

C. Adverse events are applied as a one-off cost and disutility in the model. Please comment on whether it is reasonable to assume that these events are not recurrent, using ECHO trial data where possible.

The application of adverse event costs and disutility values as a one-off adjustment is consistent with standard practice in modelling for oncology, and was a simplifying assumption. As adverse event incidence rates, costs and disutility values are not highlighted in the DSA as influential parameters, it is unlikely that modelling adverse events on a recurrent basis rather than as a one-off event would alter decision-making.

B6. Document B, Section B.3.5.3.1., P.122.

Table 46 (page 122) presents the disutility and duration of the TEAEs included in the model. The EAG was able to source the duration (days) with LYM-3002 trial data for the R-CHOP treatment arm presented in table 45, page 139, document B of TA370. However, the EAG has not been able to source the disutilities presented in table 46, page 122 of document B (of this submission). Please clarify where the disutility values used in the model for this submission were sourced from.

Disutility values for all adverse events excluding COVID-19, COVID-19 pneumonia, hypertension, rash maculo-papular, decreased neutrophil, white blood cell and lymphocyte count are sourced from TA370, in Table 47 of Document B.

The disutility of hypertension is taken from TA931 (Zanubrutinib for the treatment of CLL), as reported in Table 80 of Document B.

In the base case analysis, it is assumed that the disutility values associated with decreased counts of neutrophils, white blood cells and lymphocytes are equal to the disutility values used for neutropenia, leukopenia and lymphopenia respectively, in the absence of other data.

Similarly, in the base case it is assumed that the disutility values associated with COVID-19 and COVID-19 pneumonia are equal to an average of the disutility values of all other adverse events, in the absence of other relevant data.

Health state utility values

B7. PRIORITY. Document B, Section B.3.5.1.1., P.119.

This section details the analysis of the EQ-5D-5L data sourced from the ECHO trial. Please provide:

A. the full output of the MMRM model which contained only the covariate for progression status. In particular, the coefficient and standard error for progression.

The parameter estimates for the MMRM model, which contained only the covariate for progression status are reported in Table 13 below. Progression is associated with [redacted] with a standard error of [redacted].

Table 13: MMRM model parameter estimates (progression status as covariate)

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B. Only AIC statistics appear to have been used to inform model selection. Please provide further details of how the best fitting model was selected.

The progression status model was selected as it produced the lowest AIC statistics. It is also the case that this model produces the lowest BIC statistics, therefore both goodness-of-fit statistics indicate the progression model as the best fitting model. The AIC and BIC statistics of all models are displayed in Table 14.

Table 14: Goodness of fit statistics for MMRM utility models

Description	AIC	BIC
Treatment	-6323.5	-6223.1
Progression status	-6324.7	-6224.3
Treatment + progression status	-6317.4	-6217.0

Description	AIC	BIC
Treatment * progression status	-6313.1	-6212.7

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterionfurth

Further to this, there was no significant evidence of a difference in utility across treatment arms. Therefore, a MMRM using progression as the only covariate was considered most relevant to inform the model.

C. Please clarify whether the explored models included adjustment for baseline EQ-5D utility score, age and gender. If not, please explore the addition of these adjustments or provide a rationale for their exclusion.

To provide health state utility inputs to the cost-effectiveness model, a series of MMRM analyses were conducted using all completed EQ-5D-5L questionnaires in ECHO.

As presented in Table 14, a total of four MMRM analyses were performed, incorporating the following covariates: treatment arm only, progression state only, treatment plus progression, and an interaction model (i.e., treatment, progression, and treatment by progression). Model selection was guided by the AIC statistic and confirmed by the BIC statistic.

Baseline EQ-5D-5L, age and sex, were excluded from the original MMRM analysis as randomisation in ECHO was expected to balance these characteristics across treatment arms. When extrapolating results over a lifetime horizon, the impact of aging on health state utility was captured using age-related utility data from the UK general population.

The results of the MMRMs informed structural assumptions in the cost-effectiveness model, for example, by determining whether utilities should vary based on treatment arm, as well as progression-state. Marginal means estimates from the MMRMs provided health state utility inputs to the cost-effectiveness model.

As requested by the EAG, an updated MMRM analysis was conducted, including baseline covariates of EQ-5D-5L utility score, age and gender. This analysis included only patients with baseline EQ-5D-5L (548 patients reporting 4741 EQ-5D-5L utility scores), representing a subset of the original analysis cohort (585 patients

reporting 5,225 EQ-5D-5L utility scores). Additionally, in the updated MMRM, the dependent variable was post-baseline EQ-5D-5L utility score to avoid correlation with the independent variable of baseline EQ-5D-5L. The corresponding dependent variable in the original MMRM was EQ-5D-5L utility score, including baseline and post-baseline measures. Finally, to improve model fit, the baseline age covariable was centred on the mean baseline age of the ECHO trial (i.e., baseline age was equal to subject age minus 71 years). A summary of the fitted parameters for the MMRM with baseline covariables is presented in Table 15, alongside the values from the original MMRM.

The addition of baseline EQ-5D-5L utility score, age and gender to the original MMRM analysis had only minimal impact on results and did not impact on the interpretation of results. In both the updated and original MMRMs, there were no significant difference ($p<0.05$) in utility score when comparing across treatment arms and between pre- and post-progression phases of ECHO. In both analyses, there was insufficient EQ-5D-5L data available after progression to reliably estimate the effect of progression on health state utility. The utility weight of patients with progressed disease was therefore based on external data, as described in Section B.3.5.4 of the submission document.

The marginal mean estimate of health state utility for the progression-free period of ECHO was [redacted] (95% CI [redacted]) in both the updated and original MMRM analyses. Therefore, the base case ICER would remain the same, irrespective of whether the progression-free health state utility was taken from the original or updated MMRM analyses.

Table 15: Summary of the fitted parameters for the MMRM with baseline covariates

Parameter	Treatment		Progression status		Treatment + Progression status		Treatment * Progression status	
	Original UK IRC	Updated UK IRC	Original UK IRC	Updated UK IRC	Original UK IRC	Updated UK IRC	Original UK IRC	Updated UK IRC
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
Post-progression			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR: Post-progression							[redacted]	[redacted]
Age (centred on 71.2 years)		[redacted]		[redacted]		[redacted]		[redacted]
Sex (Male vs Female)		[redacted]		[redacted]		[redacted]		[redacted]
Baseline EQ-5D-5L utility score		[redacted]		[redacted]		[redacted]		[redacted]

B8. PRIORITY. Document B, Section B.3.5.4., P.123.

The utility value for progressed disease is sourced from TA502 (which is informed using pooled data for the ibrutinib arms of the RAY and SPARK studies). The EAG notes that that the justification for using TA502 utilities is [redacted]. However, the sourced EQ-5D value from TA502 is based on only N=36 observations. Please provide:

A. further clarification on why the EQ-5D observations from ECHO are not suitable to inform the utility value of the progressed disease state.

The ECHO trial EQ-5D observations produce a progressed disease health state utility value of [redacted]. The general population utility value for patients at the start of the model is 0.787. The use of the ECHO trial-derived utility value for progressed disease would lack face validity, as it implies a [redacted] for patients with progressed disease than the general population utility.

The Company conducted three additional, informal interviews with UK clinicians to gain further insight on quality of life for progressed disease, versus progression-free patients. According to these experts, the quality of life of patients with progressed disease would be considerably worse than progression-free patients. Patients who have progressed will decline quickly compared to progression-free patients. Therefore, the [redacted] observed in the ECHO trial is not clinically plausible.

Furthermore, on reviewing previous submissions in MCL and CLL, it is seen that the ratio of progression-free and progressed disease utility is much lower than that observed in the ECHO trial. Table 16 reports the utility values for progression-free and progressed disease, and the absolute and relative differences, for previous submissions.

Table 16: Overview of health state utility values used in previous submissions

Technology appraisal	Progression-free health state utility	Progressed disease health state utility	Absolute difference	Ratio of progression free to progressed disease utility
ECHO trial with TA502 decrease (base case analysis)	[redacted]	[redacted]	[redacted]	[redacted]
ECHO trial	[redacted]	[redacted]	[redacted]	[redacted]
TA370: 1L MCL, 2015	0.764	0.693	0.07	0.91
TA502: RR MCL, 2018	0.780	0.680	0.10	0.87
TA931: CLL, 2023	0.783	0.600	0.18	0.77
TA891: 1L CLL, 2023	Health state utilities redacted			
TA663: 1L CLL, 2020	0.670	0.600	0.07	0.90
TA119: 1L CLL, 2007	0.80	0.60	0.20	0.75
TA796: CLL, 2022	Progressed disease health state utility value unavailable			
TA689: 1L CLL, 2021	Utility values censored			

Abbreviations: 1l, first-line; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; RR, relapsed or refractory.

While the ratio between progression-free and progressed disease is as low as 0.87 in TA502, the most recent submission in MCL, [redacted].

Overall, when comparing the ECHO trial utility values to both the general population utility and previously used health state utility values, the ECHO trial produces a progressed disease value that lacks face validity and does not reflect precedent. It is also not reflective of clinical reality, according to UK clinical experts' understanding of quality of life in progression-free and progressed disease MCL patients. So, it has been deemed unsuitable to inform the utility value of the progressed disease state.

B. justification for why the use of TA502 progressed disease utility is considered more appropriate for this assessment. The EAG accepts that there is little data to inform the utility value within MCL; however, EQ-5D estimates could potentially have been obtained for other forms of lymphoma.

As previously described, it was considered that the utility value for progressed disease from the ECHO trial was considered unsuitable, [redacted].

Therefore, an adjustment to the ECHO trial's progression-free utility value, using the absolute difference between health state utility values from TA502, was selected to

inform the progressed-disease utility value. In this way, ECHO trial data was used where possible and adjusted by the most appropriate precedent values.

TA502 was considered the most appropriate submission to inform this adjustment as the most recent appraisal in MCL. TA370 was also considered, however this submission is outdated as it has been reported anecdotally amongst clinicians that clinical outcomes have generally improved since the time of this submission. Furthermore, the EAG for TA370 criticised that the impact of progression on utility was likely underestimated, as utility was only assessed whilst patients were on treatment. So, TA502 was considered a more suitable precedent in MCL.

TA931, the most recent submission in CLL with publicly available utility values, has also been considered to inform the utility value for the progressed disease health state. However, these values are sourced from TA689, which cites Holzner et al 2004 as a source for progressed disease utility in first-line CLL. This is a considerably dated source, which uses the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy (FACIT) to measure quality of life, as opposed to the EQ-5D.

Therefore, TA502 was selected as the most suitable source to adjust the utility values produced from the ECHO trial, as it is the most recent submission in the relevant disease area.

Table 17: Deterministic pairwise results for alternative utility sources

Technology appraisal	ICER versus BR	ICER versus R-CHOP
ECHO trial with TA502 decrease (updated base case)	£10,003	£2,340
ECHO trial	£11,673	£3,024
TA502: RR MCL	£9,998	£2,327
TA370: 1L MCL	£10,679	£2,552
TA931: CLL	£8,799	£1,919
TA663: 1L CLL	£11,996	£2,841
TA119: 1L CLL	£8,596	£1,860

Abbreviations: 1l, first-line; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukaemia; ICER, incremental cost-effectiveness ratio; MCL, mantle cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RR, relapsed or refractory.
These scenario results are produced using the updated base case with TEAEs corrected, as per B5.

Subsequent treatment costs

B9. PRIORITY. Document B, Section B.3.6.1.3. Subsequent treatment costs, P. 141.

The EAG notes that the costs of acalabrutinib have been removed from second-line treatment in the comparator arm of the model. This is appropriate as the NICE appraisal will assess a world with, versus a world without acalabrutinib. However, related to query A1 above, this assumes that there is no incremental OS benefit of acalabrutinib at 2nd line compared to ibrutinib, which is costed for 100% of patients receiving post-progression treatment in the control group. Please comment on the validity of this assumption. If a scenario analysis is provided in response to A1 above, please also integrate this into the economic model.

In the ECHO trial, patients on the comparator arm were permitted to cross over to receive acalabrutinib monotherapy following disease progression. This is consistent with BSH guidelines, which state that patients relapsing after 1st line immunochemotherapy would go on to receive a BTKi. However, given acalabrutinib is not currently reimbursed in the UK for use in the 2nd line setting, from a costing standpoint, the model assumes that patients instead move on to ibrutinib, which is currently the only reimbursed BTKi option in RR MCL in England. Although these adjustments were made to the costing to reflect UK clinical practice, adjustments were not made to the efficacy inputs; the assumption is that OS is equivalent for patients treated with ibrutinib or acalabrutinib in the 2nd line setting.

In the absence of head-to-head clinical trial data comparing OS of acalabrutinib and ibrutinib in 2nd line, a matched-adjusted indirect comparison of these treatments is cited to validate the assumption of their equivalence at 2nd line. Gaitonde et al. 2022 (5) used individual data from 124 patients treated with acalabrutinib in a Phase II trial (ACE-LY-004) in R/R MCL, adjusted to match the average baseline characteristics reported for the three identified clinical trials of ibrutinib in R/R MCL. After matching, it was found that, although OS and PFS were numerically increased for acalabrutinib versus ibrutinib, a statistically significant difference was not observed. This is demonstrated by the hazard ratios for acalabrutinib against ibrutinib for OS (0.87, 95% CI: 0.64–1.17, p=0.35) and PFS (0.92, 95% CI: 0.74–1.15, p=0.48). Therefore,

it is valid to assume that there is no incremental OS benefit of acalabrutinib in 2nd line compared to ibrutinib in the base case analysis of the economic model. Furthermore, if we were to account for the numerical increase in efficacy for acalabrutinib versus ibrutinib, as the economic model assumes that 100% of patients receive ibrutinib following BR, it may overestimate OS for the BR arm, given efficacy was based on patients who had received subsequent acalabrutinib in the ECHO trial. The base case analysis is therefore likely conservative in this regard.

B10. PRIORITY. Document B, Section B.3.6.1.3. Subsequent treatment costs, P. 141.

Please provide a table comparing the distribution of second and third-line treatments from the ECHO study with those used in the economic model based on clinical expert opinion. Please provide a scenario analysis using the ECHO study's subsequent treatment distributions.

Table 18 presents the 2nd line subsequent treatment distributions taken from the ECHO trial and the clinical validation proportions (per the base case analysis) presented in the model. Table 19 presents the same for 3rd line subsequent treatment distributions.

Table 18: 2nd line subsequent treatment distributions

Treatment	ECHO trial distribution		Clinical expert opinion distribution	
	ABR	BR	ABR	BR
Ibrutinib	[redacted]	[redacted]	0.00%	100.00%
R-CHOP	[redacted]	[redacted]	74.44%	0.00%
Lenalidomide + rituximab	[redacted]	[redacted]	0.00%	0.00%
Rituximab	[redacted]	[redacted]	0.00%	0.00%
RBAC	[redacted]	[redacted]	11.11%	0.00%
VR-CAP	[redacted]	[redacted]	14.44%	0.00%

Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; BR, bendamustine + rituximab; CSR, clinical study report; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Table 19: 3rd line subsequent treatment distributions

Treatment	ECHO trial distribution		Clinical expert opinion distribution	
	ABR	BR	ABR	BR
R-CHOP	[redacted]	[redacted]	16.67%	15.63%
Ibrutinib	[redacted]	[redacted]	0.00%	15.63%
Lenalidomide + Rituximab	[redacted]	[redacted]	0.00%	0.00%
Lenalidomide	[redacted]	[redacted]	0.00%	0.00%
Venetoclax	[redacted]	[redacted]	0.00%	0.00%
CAR-T	[redacted]	[redacted]	50.00%	37.50%
R-BAC	[redacted]	[redacted]	16.67%	15.63%
VR-CAP	[redacted]	[redacted]	16.67%	15.63%

Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; BR, bendamustine + rituximab; CSR, clinical study report; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

The results using the ECHO trial subsequent treatment distributions compared to the base case analysis (using distributions based on expert clinical opinion) are presented in Table 20.

Table 20: Deterministic pairwise results using ECHO CSR subsequent treatment proportions

Technologies	Total costs, £	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Scenario pairwise ICER, £/QALY	Updated base case pairwise ICER, £/QALY
ABR	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	83,239	10,003
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,592	2,340

Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; BR, bendamustine + rituximab; CSR, clinical study report; ICER, incremental cost-effectiveness ratio; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.
These scenario results are produced using the updated base case with TEAEs corrected, as per B5

Subsequent treatment distributions based on clinical expert opinion were used in the base case analysis given the ECHO trial was conducted internationally and includes treatment options not available to clinicians in the UK. Consequently, the treatment pathways observed in the trial are not fully reflective of UK clinical practice. For example, lenalidomide + rituximab and rituximab monotherapy are not reimbursed for the treatment of RR MCL in the UK and therefore would not represent a 2nd line

treatment option for patients progressing following ABR or BR. Another example is that some patients in the ABR arm of the ECHO trial went on to receive ibrutinib in the 2nd line, which is not considered to be reflective of UK clinical practice; patients given a BTKi as a 1L treatment for MCL would not then be treated with another BTKi. As explained in Section B.3.6.1.3 of Document B, this is because patients who progress following treatment with a BTKi may develop resistance to this mechanism of action, meaning that subsequent treatment with the same mechanism of action would be ineffective. Therefore, the distribution of subsequent treatments applied in the model are representative of UK clinical practice and treatment guidelines in MCL and a scenario using the ECHO trial distributions is not considered to be an appropriate alternative analysis given the clear deviation from clinical reality in the UK.

B11. <u>PRIORITY</u>. Document B, Section B.3.6.1.3.1 Subsequent treatment distribution, P. 144, Tables 63.

Please provide further information about the reasons why patients in the ECHO study were ineligible for subsequent treatment and full details of the reasons, including n/N (%) for each reason, by study arm, as to why patients with non-fatal progression events in the ECHO trial were not deemed eligible for further treatment. Please clarify how such patients would be managed in UK clinical practice.

In the economic model, the proportion of patients receiving 2nd line treatment is calculated as the number of patients with at least one subsequent therapy, divided by the number of patients with disease progression. The proportion of patients receiving 3rd line treatment is calculated as the number of patients receiving two, three or four subsequent treatments, divided by the number of patients with disease progression. So, [redacted]% ([redacted]) patients on the ABR arm receive 2nd line treatment, and [redacted]% ([redacted]) receive 3rd line treatment. On the BR arm, [redacted]% ([redacted]) receive 2nd line treatment and [redacted]% ([redacted]) receive 3rd line treatment.

The company is unable to provide further information on the reasons why patients in the ECHO study were ineligible for subsequent treatment from the trial data. Therefore, clinical opinion from three UK clinical experts was sought on this. It was considered by UK clinical experts that a proportion of progressed disease patients are likely to be ineligible for subsequent treatment owing to an accumulation of

comorbidities during their first-line MCL treatment. Furthermore, patients' elderly age in the ECHO trial may mean they are not healthy enough to receive further treatment after disease progression especially chemotherapy and CAR-T therapies as these may not be well tolerated particularly in an elderly patient population.

Patients with progressed disease who are considered ineligible for subsequent treatment would be managed with best supportive care.

B12. PRIORITY. Document B, Section B.3.6.1.3.1 Subsequent treatment distribution, P. 144 - 145, Tables 64 & 66.

Please provide further justification for the subsequent treatment proportions used in the economic model at 2L and 3L respectively. The EAG notes that the ECHO trial data show a substantial difference in the proportion receiving subsequent treatment between Acalabrutinib + BR (2L: [redacted]; 3L: [redacted]) and BR (2L: [redacted]; 3L: [redacted]). For both tables, please:

A. Explain why a substantial proportion of patients would not be eligible for subsequent treatment post-progression.

The ECHO trial does not capture detailed data on reasons for ineligibility for subsequent treatment. Therefore, clinical expert opinion was sought to determine this.

According to UK clinical experts, it is reasonable that a substantial proportion of patients would not be eligible for treatment post-progression – particularly in the 3rd line setting. Firstly, patients may have accumulated comorbidities during their time on first-line treatment. Secondly, the trial's patient population is elderly, meaning that by the time they progress, their age may preclude them from being healthy enough to receive further treatment. Finally, UK clinical experts noted that such an elderly patient population may not want further treatment post-progression. Thus, according to these experts, the small proportion of patients receiving subsequent treatment post-progression is reasonable.

B. Provide full details of the calculation as n/N (%).

The proportion of patients receiving 2nd line treatment was calculated as the number of patients with at least one subsequent anticancer therapy (Table 14.1.3.3) divided by the number of patients with disease progression (Table 17 of CSR). The proportion of these patients who receive a 3rd line treatment was calculated as the number of patients with 2, 3 or more than 4 subsequent regimens (Table 14.1.3.3) divided by the number of patients with disease progression (Table 17 of CSR).

Therefore, on the ABR arm, [redacted] of patients receive 2nd line treatment and [redacted] receive 3rd line treatment. Similarly, on the BR arm, [redacted] received 2nd line treatment and [redacted] received 3rd line treatment.

These proportions are reported in Table 64 and Table 66 of Document B, showing patients receiving subsequent treatments in the 2nd and 3rd line settings, respectively.

C. Use the observed data for subsequent treatment proportions to inform a standard error for use in the probabilistic analysis. Please update the PSA using this information.

Standard deviation for the proportion of patients receiving subsequent treatments is informed in the model using the number of progressed disease patients on each treatment arm from the ECHO trial, using the formula:

$$\sqrt{\frac{(x*N)*(N-(x*N))}{N^2*(N+1)}},$$

where x represents the subsequent treatment proportion and N represents the number of progressed disease patients on the treatment arm. Therefore, the Company feels that observed data for subsequent treatment proportions has been correctly implemented in the model to inform the PSA.

D. Provide details of the time (in days) between observation of a progression event, and the initiation of the next line of treatment using data from the ECHO trial. Please provide the mean, SD, median, IQR, minimum and maximum.

Table 21 presents details on the time between observation of a progression event and initiation of the next line of treatment from the ECHO trial. It should be noted that only patients who experienced a progression event by BICR and received a first subsequent therapy are included in this analysis.

Table 21: Time between progression event and initiation of the next line of treatment

Treatment	n	Mean	Median	Minimum	Maximum	IQR	SD
ABR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PBR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; IQR, interquartile range; PBR, placebo, bendamustine + rituximab; SD, standard deviation

E. Provide real-world evidence to support the difference in subsequent treatment proportions between the ECHO study arms.

The Company were unable to source real-world evidence on subsequent treatment proportions following 1st line ABR, BR and R-CHOP. Therefore, clinical opinion was sought to justify why differences in subsequent treatment use might differ between treatment arms. This clinical input is detailed in the response below (B12 (F)).

F. Provide clinical justification as to why a difference might exist between the arms. Please provide responses from a range of clinical experts to assess the generalisability of these data to UK clinical practice.

According to interviews conducted with three UK clinicians during the clarification questions stage, it is reasonable that the proportion of patients receiving subsequent treatments post-progression would differ between treatment arms as with better disease control on first-line treatment, there is less need for further lines of therapy. Given the likelihood of overall survival being higher on ABR compared to BR and R-CHOP, it is reasonable to assume that fewer patients who progress would require subsequent treatment.

G. Comment on any methodological or trial protocol reasons why a difference has been observed. For example, one reason might be that progression events were observed later in the ABR arm of the ECHO trial, which might mean that subsequent lines of treatment had not yet commenced in the ABR

at the last data cut-off. Please comment on the robustness and validity of such an assumption.

As noted in B12 (F), it is in line with UK clinical expert opinion that there would be a difference in subsequent treatment proportions between patients initiated on ABR and BR, owing to the better disease control associated with ABR. Additionally, the differences in subsequent treatment proportions observed between treatment arms in the ECHO trial may be attributed to the difference in methodology of assessing progressed disease and subsequent treatment use. The PFS events for progressed disease patients were evaluated by IRC assessment. However, the subsequent therapy rate was based on PD assessments made by the Investigator, and a decision by the Principle Investigator to start subsequent therapy, without requiring IRC confirmation.

For patients in the ABR arm, nine were declared to have progressed disease by IRC, but did not start subsequent therapy and remained on their frontline treatment, as the investigator did not report them as having progressed disease. However, in the PBR arm, all patients who were considered by the IRC as being progressed were reported by investigators as such, and therefore received subsequent treatments.

In summary, the difference in the approach to PD assessment and in the approach to initiate subsequent treatment explains the difference in the proportion of progressed disease patients receiving subsequent treatments across ABR and BR in the economic model.

H. Provide details of a scenario analysis that equalises the proportion of patients receiving subsequent treatments at 2L and 3L in the economic model.

Table 22 presents the results when equalising the proportions of patients receiving 2nd and 3rd line treatments on the BR arm for all treatment arms in the model.

In this scenario, [redacted] of patients with progressed disease receive 2nd line treatment, and [redacted] of these receive a 3rd line treatment, across all treatment arms in the model. It is emphasised that this scenario is not considered clinically realistic. As described in B12 (F), UK clinicians would expect that patients initiated with ABR experience better disease control, with less need for subsequent lines of therapy.

So, the proportion of patients requiring subsequent treatments would be lower than for those initiated on BR.

Table 22: Deterministic pairwise results when using 2nd and 3rd line treatment proportions for BR across all treatment arms

Technologies	Total costs, £	Total LYs	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	Scenario pairwise ICER, £/QALY	Updated base case pairwise ICER £/QALY
ABR	[redacted]	[redacted]	[redacted]					
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,839	10,003
R-CHOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,024	2,340

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; NHB, net health benefit; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

These scenario results are produced using the updated base case with TEAEs corrected, as per B5.

I. Provide further justification for the assumption that the proportion receiving subsequent treatment following R-CHOP would be equal to BR. Please provide information from any real-world evidence to support this assumption. If real-world evidence does not exist, please provide further details of clinical expert validation.

As real-world evidence is not available for subsequent treatment use, clinical validation was sought to validate this assumption. UK clinical experts suggested that it is reasonable to assume that the proportion of patients initiated on R-CHOP requiring subsequent treatment is equal to that of patients initiated on BR, in the absence of real-world data.

Section C: Textual clarification and additional points

Interviews with clinicians

C1. Appendix N. Page 112 of Document B Appendices.

Please provide the report titled "*AZ Data on File. REF-251322_ECHO NICE clinician interviews*" which summarises findings from the 1:1 interviews with consultant haematologists in the UK.

The report titled "*AZ Data on File. REF-255537_ECHO NICE clinician interviews*" has been provided in the NICE Docs response.

References

1. Dreyling M, Mayer J, Belada D, Song Y, Jurczak W, Paludo J, et al., editors. 1626 High-Risk Subgroups and MRD: An Updated Analysis of the Phase 3 ECHO Trial of Acalabrutinib with Bendamustine/Rituximab in Previously Untreated Mantle Cell Lymphoma. Abstract presented at 66th ASH meeting San Diego, California December 7-10 2024.
2. Austin PC. Statistical power to detect violation of the proportional hazards assumption when using the Cox regression model. J Stat Comput Simul. 2018;88(3):533-52.
3. Acerta Pharma/AstraZeneca. Phase 3, randomized, double-blind, placebo-controlled, multicenter study of bendamustine and rituximab (BR) alone versus in combination with acalabrutinib (ACP-196) in subjects with previously untreated mantle cell lymphoma (ECHO). Interim Clinical Study Report. Data on file. 2024.
4. Robak T, Jin J, Pylypenko H, Verhoef G, Siritanaratkul N, Drach J, et al. Frontline bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) versus rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in transplantation-ineligible patients with newly diagnosed mantle cell lymphoma: final overall survival results of a randomised, open-label, phase 3 study. The Lancet Oncology. 2018;19(11):1449-58.
5. Gaitonde P, Cai L, Miranda PAP, Roos J, Rule S, Wang M, editors. 1583 Matching-Adjusted Indirect Comparisons of the Efficacy and Safety of Acalabrutinib Versus Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma. Poster presented at 64th ASH meeting New Orleans, Louisiana December 10-13; 2022.

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Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

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].

Information on completing this submission

- 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.

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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 5th most common 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 only 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 a financial cap of £50,000 of 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.**	None
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 spoke to 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 a type of blood cancer, where white blood cells known as lymphocytes grow out of control. It is the 5th most common type of cancer in the UK. There are two main types of lymphoma: 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 around 60 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 they developed 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 nHL which develops from 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. However as it often relapses multiple times it causes a significant burden. It tends to be a cancer of later years, with most people diagnosed being middle-aged or older. MCL often grows very quickly, which means symptoms can develop fast. Symptoms 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 is 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 and can be particularly burdensome as one of patient's described, *"I also had to accept the tiredness and the limitations that imposed".* The psychological impact of a diagnosis of lymphoma is enormous. Patients have described insomnia, anxiety and a constant fear of dying to us. MCL usually responds well to treatment, but unfortunately is likely to relapse after treatment. Patients and those close to them live with this fear which obviously adds to this impact. It can have a significant impact on their mental health as described by this patient,

	"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". 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 feel powerless to help, especially as MCL is a cancer which is likely to come back despite responding to treatment. One of our patients summed this up, "*I think it is worse for carers. The patient is taken care of but the carers can feel a bit helpless to do anything"*. This sentiment was echoed by another, "*It is very hard for my wife as we always have the fact it will come back hanging over us"*. One patient who was unfortunately diagnosed and treated during the pandemic described how this feeling of helplessness was heightened, "*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 which include the stage, prognostic score or symptoms of the lymphoma, along with the patient's age and overall health. In some cases, for example when patients have very few symptoms as the lymphoma is growing slowly, no active treatment is 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 symptoms, they do have to endure the constant worry that their lymphoma may return, "*Getting the diagnosis and understanding that it was treatable but not curable – therefore being placed on Watch and Wait was challenging!".* If treatment is required, in most cases 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 effective and helps to prevent the MCL from spreading, but it can be incredibly difficult to endure. If patients are less fit 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 would be dead now without it"*. However the treatments can be very difficult to endure, even the more gentler regimens with numerous side effects: *"The side-effects (of chemotherapy) were insomnia and extreme tiredness plus hair loss".* *"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".*

	As well as the short-term side effects our patients described longer term effects that still impact them. This can be fatigue, peripheral neuropathy or mental health problems: *"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".* *"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".* *"Long term effects are lowered immunity to infections".* If patient's respond to chemotherapy they may be offered an autologous stem cell transplant (SCT). However this requires intensive chemotherapy and patients have to be fit enough. As MCL primarily affects older people many patients sadly do not meet the criteria*, "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".* .

8. Is there an unmet need for patients with this condition?	MCL is a very difficult cancer to live with. It 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 requiring various treatment regimens, "*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".* With this in mind patients 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, which adds to the fear that the treatment options that they are offered will either not provide a long term remission, or will cause intolerable side effects: *"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".* *"Obviously we'd all hope for a cure with a treatment that did not endanger life and had fewer side effect"".* *"Yes there is an unmet need. The perfect treatment would be something with relatively little side effects".* These views were confirmed with the recent 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. They feel that acalabrutinib may provide an option which is more tolerable: *"The drug appears to have a better side effect profile than other BTK inhibitors".* *"It has a low risk of discontinuation due to adverse events. This is a huge point for me as to start down a treatment path and then you have to stop due to adverse events is absolutely devastating for the patient and their families, and takes its toll mentally".* *"I was keen to continue life after my treatment. If there are treatments that have limited side effects, and also less chance of discontinuation then this also contributes to better mental health".* Another advantage is that acalabrutinib offers another oral option. Some current treatment options can only be given intravenously which require recurrent, often daily, hospital appointments. This can be incredibly disruptive for both the patient, and those around them. It can also be financially difficult for example if time needs to be taken off work: *"The fact that it is oral and doesn't need a hospital attendance is a big plus for both the patient and the carer".* *"Using a less invasive treatment makes a huge difference to the patient".*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients felt that any side effects may be a disadvantage of this treatment. However our patients felt that if these side effects were not worse than the disease itself it was worth it, *"There are some disadvantages, but the advantages outweigh these in my opinion".*

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.	Our patients felt that patients who were not fit enough for other treatments were more likely to benefit from acalabrutinib: *"MCL occurs mainly in the older patient group and I suspect that older less fit patients will benefit from it".* *"When a lymphoma is aggressive or particularly life limiting there needs to be more treatment options available to prolong life".*

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Our patients could not think of any equality issues but felt that all patients should be able to access all the best treatment options available, "*I think it's important that all patients get access to experts in this particular field. I appreciated the multidisciplinary approach of a large teaching hospital".*

Other issues

13. Are there any other issues that you would like the committee to consider?	One of our patients wanted to make the following point, "*Nice should consider benefits against risks of side effects and see what is best for the patients".*

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 that can be taken orally, and therefore limit the trips to hospital would be welcomed by patients • Patients would welcome a treatment which prolongs time between relapses, but also does not have intolerable side effects •

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Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Professional 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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	The Royal College of Pathologist and University Hospitals Plymouth NHS Trust
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of treatment is to attain a remission and maintain remission for as long as possible, achieving a good quality of life.
7. 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.)	Radiological response and the achievement of remission is a clinically significant endpoint. Most trials use the measure of progression-free survival (ie time from treatment to disease progression or death) as a primary endpoint and this is a well accepted clinical endpoint Ultimately a prolongation of overall survival is the most clinically significant outcome
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Mantle cell lymphoma is an incurable blood cancer with an inevitable pattern of relapse. Most patients with MCL will die from the disease. It is recognised that the best response to treatment is the the first line setting, so optimising first line treatment is key to improving outcomes from this disease.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients >60yo who are not suitable for high dose containing chemotherapy are most commonly given Rituximab-bendamustine (approximately 2/3 of patients) or RCHOP (approx 1/3) followed by maintenance rituximab. VRCAP is NICE appoved but is rarely prescribed in the UK.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The BCSH MCL guideline is frequently referenced by UK clinicians. Eyre TA, Bishton MJ, McCulloch R, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. Br J Haematol 2024;204:108-26.
9b. 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.)	There is some variation in clinician choice of RCHOP versus R-bendamustine as initial induction chemotherapy. This is based on a lack of randomised evidence comparing the two with rituximab maintenance. However emerging evidence suggests RCHOP is inferior to Rbendamustine, and R bendamustine is likely to become more widely used in the UK in the future as standard of care.
9c. What impact would the technology have on the current pathway of care?	There is currently no way for patients to access BTK inhibitors in the 1st line setting in the UK. The triplet combination of bendamustine, acalabrutinib and rituximab could become a standard of care 1st line treatment option for this group of patients
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This technology could replace standard 1st line treatment options in the UK. It could also replace standard 2nd line treatment options, as current guidelines and commissioning criteria recommend mono therapy with BTK inhibitor (ibrutinib) as 2nd line treatment.

10a. How does healthcare resource use differ between the technology and current care?	Current treatment - usually 6 cycles of R-bendamustine (6*4 weekly cycles) followed by 12 8weekly cycles of maintenance rituximab, The technology under assessment is identical, but with the addition of acalabrutinib daily as an oral medication until disease progression or toxicity. This will require ongoing prescriptions (in practice every 3-4 months) post maintenance. Most paitents are usually followed up every few months as standard of care.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care, prescribed by haematology or oncology consultants
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Oral BTK inhibitors are widely used in a number of haematological indications including CLL, MCL as second line, Waldenstroms, and marginal zone lymphoma so I don't think additional training will be required.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Current standard of care would be to give induction chemotherapy and maintenance rituximab, then to give ibrutinib mono therapy at relapse. Ibrutinib has toxicities including cardiac toxicity which is much rarer with acalabrutinib. Most UK physicians would prefer to have an alternative with a less toxic, better tolerated BTKi which this treatment would offer.
11a. Do you expect the technology to increase length of life more than current care?	The trial data suggests a slight overall survival advantage for the ABR versus BR (med 73.8 mo versus 72.1mo). The trial was significantly affected by the COVID-19 pandemic and the authors of the study suggest that if it were not for the COVID- associated deaths, the OS advantage for ABR versus BR would be greater (censoring for COVID deaths widens the difference in the OS curves).
11b. Do you expect the technology to increase health-related quality of life more than current care?	Acalabrutinib has a more favourable toxicity profille compared to ibrutinib which is the only currently available BTKi in the UK for MCL (as 2nd line). Furthermore patients are likely to feel better and have an improved quality of life when in remission from MCL for longer compared to standard of care.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Only a very small number of patients (eg those with metallic heart valves on warfarin) would be difficult to give acalabrutinib to. Patients who are eligible for an autologous stem cell transplant were not included in the trial and will continue to receive high dose chemotherapy regimens.

The use of the technology

13. 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.)	This is not likely to be more challenging to deliver than current standard of care treatments. Physicians are already very familiar with BTK inhibitor treatment and acalabrutinib has a more favourable adverse event profile than ibrutinib, which is the currently available BTKi for MCL (in 2nd line)

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment will be stopped at progression or if unacceptable toxicity is experienced. Patients with MCL are routinely followed up in clinic to monitor for signs of progression even with current SOC regimens. Median treatment exposure in the ECHO trial was 29 months
15. 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?	The currently available BTKi in second line, ibrutinib, is associated with significant toxicity including serious cardiac toxicity and sudden cardiac death, which appears to be less common with acalabrutinib.
16. 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. Prolongation of remission after 1st line therapy is a key endpoint in mantle cell lymphoma, as it is well recognised that responses to subsequent lines of therapy tend to decrease as patients become more heavily treated.
16a. Is the technology a 'step-change' in the management of the condition?	Yes. This would be the first indication in the UK for the first line treatment of MCL with a BTKi
16b. Does the use of the technology address any particular unmet need of the patient population?	We currently do not have any access to first-line BTK inhibitors in the UK for MCL and this technology would allow this

17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The Adverse event profile from this combination published thus far does not appear significantly different to BR chemotherapy plus rituximab maintenance. There were slightly more infections in the ABR arm, including COVID-19 (the trial was conducted at the peak of the COVID pandemic) but no significant excess cardiac toxicity.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the trial inclusion criteria were reflective of UK clinical practice, and the control arm of the study reflects UK standard practice.
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Yes. Progression-free survival, overall survival and toxicity are the most important outcomes to measure.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/a

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA370]?	No
21. How do data on real-world experience compare with the trial data?	There is currently no real-world evidence for using ABR as it has only been accessed in a trial context. However, in 2nd line use, outcomes with BTKi are comparable to trial data.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Topic-specific questions

23a Approximately what proportion of people with untreated mantle cell lymphoma would eligible or ineligible for haematopoietic stem cell transplantation (HSCT)? How is eligibility for HSCT determined?	Most trials including HSCT include patients <65yo. Some centres will offer HSCT to patients up to around 70 yo if they are fit and have no comorbidities. In practice it is an individualised assessment of overall fitness and patient choice taking into account other treatment options. Median age of MCL diagnosis in UK is 72, so in practice only approximately 1/3 of patients with MCL are eligible for HSCT.
23b Do you expect the technology to be suitable for use by people who may be ineligible or eligible for HSCT?	It is possible that a small number of patients on the borderline for HSCT eligibility will choose this technology over HSCT containing treatment.

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Mantle cell lymphoma is an incurable blood cancer and duration of response to first line therapy is an important determinant of outcome • The ECHO study demonstrates a clinically meaningful improvement in progression-free survival for the addition of acalabrutinib to the Bendamstine-rituximab chemotherapy combination • High dose chemotherapy with HSCT is not a good option for the majority of patients with MCL • This technology would allow access to BTK inhibitors to patients with MCL in the first line setting. • The addition of acalabrutinib to Bendamustine based chemotherapy does not appear to lead to excess toxicity.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Clinical expert statement

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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.

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.

The deadline for your response is **5pm** on **Wednesday, 21 January 2026.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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 previously untreated mantle cell lymphoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Aim to achieve a sustained remission (prevent progression) that prolongs life. Aim to maintain a good quality of life for patients whilst on therapy.

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 per Lugano Classification criteria, 2014.
10. In your view, is there an unmet need for patients and healthcare professionals in mantle cell lymphoma?	Yes.
11. How is previously untreated mantle cell lymphoma currently treated in the NHS? • 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?	Current clinical guidelines: Eyre TA, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. *Br J Haematol.* 2024; 204(1):108-126. Pathway for older patients with MCL (unfit for transplant) is well defined: • In patients unsuitable for high dose cytarabine-based induction and autologous stem cell transplant (ASCT), offer R-chemotherapy combinations as current standard of care (1A). • Offer R-CHOP, R-bendamustine, R-BAC and VR-CAP as options for previously untreated patients unsuitable for ASCT (1A). *(most commonly with rituximab maintenance)* Practice has recently evolved following publication of the ENRICH study (Lewis D, et al *Lancet.* 2025) and R-CHOP is no longer recommended. Anticipated impact: clinicians will offer Acalabrutinib + BR as a treatment option to this patient cohort. Given the clinical trial data, it is likely this will be generally adopted.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	R-Bendamustine with rituximab maintenance is currently the most used regimen for this patient cohort. Approval of the new technology would mean patients will generally receive current standard of care alongside additional acalabrutinib oral

• 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)	therapy, which is continuous therapy until clinical progression, or intolerable side effects. Treatment will be delivered by specialists in secondary care. Impact: The frequency of MCL patients suitable for this therapy will be low and therefore introduction of technology would not expect to require additional facilities. Acalabrutinib is already commonly used in CLL, so clinicians are familiar with management and additional training is not likely to be required.
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?	The clinical trial full analysis population OS data did not demonstrate survival advantage (HR 0.86 (0.65 to 1.13), P=0.274). However, the Covid19 deaths censored data signalled a trend to improved survival (HR 0.75 (0.53 to 1.04); P=0.0797). The data suggests that overall survival may be improved with this treatment. Clinical trial data indicated adverse events were more common with acalabrutinib + BR, which is expected with the addition of therapy. Discontinuation rate for adverse events was higher than placebo (42.8% vs 31%). It is likely that frequency of adverse events would increase with the new technology. However, it is possible that improved progression free survival will have psychological benefits. The anticipated additional toxicity will depend on how clinicians adopt the new technology. The ENRICH study (Lewis DJ, et al *Lancet.* 2025, 406;1953-1968) compared current standard of care with ibrutinib plus rituximab (chemotherapy free regimen). Data showed that the chemo free regimen had equivalent PFS and OS data to R-Benda. This data indicates that in suitable cases, clinicians using acala-BR should be comfortable making bendamustine dose reductions to minimise impact of treatment toxicity.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Treatment should only be used in patient group considered unfit for autologous stem cell transplant, as per trial design. In frail patients the regimen is likely to be poorly tolerated.
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)	Impact: as patients will be on continuous therapy, overall, it is likely they will require more frequent clinic follow up (but only after completion of maintenance rituximab). Acalabrutinib is already commonly used in CLL so clinicians are familiar with management. Patients generally receive treatment every 12 weeks with telephone assessment and repeat blood tests are often performed in the community. Patients are recommended to monitor blood pressure and annual ECG is normally performed due to recognised potential side effects. As MCL represents only 6% of non-Hodgkin lymphoma, and not all MCL patients will be suitable for this therapy, the total additional workload on the specialist clinic will be modest and should be easily absorbed.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required compared to current standard of care.
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	No.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	There is an anticipated trend towards first-line chemotherapy-free regimens in MCL. This technology does not avoid chemotherapy but provides access to a

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?	well-tolerated oral non-chemo tablet that may allow clinicians to safely reduce chemotherapy intensity without loss of treatment efficacy.
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?	Clinical trial data indicates increased risk of grade 3-4 infection during the maintenance phase of therapy (20.8% vs 14.9%), and skin and subcutaneous tissue disorders were more common during the chemotherapy phase (grade 3-4 12.8% vs 2.7%). The study took place at the height of the Covid19 pandemic and acala-BR was associated with a higher Covid19 mortality rate (9.4% vs 6.7%). Data suggests patients receiving acala-BR are more likely to have infections, which may require antibiotics and potentially hospital admissions.
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?	The clinical trial reflects current UK standard of care clinical practice. The patient population had a lower proportion of MIPI high risk patients than would be expected in a real-world population of similar age-profile. The most important outcomes are progression free survival and overall survival, which were measured.
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?	No real-world data available for Acala-BR.
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. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	Not applicable.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The new technology offers improved progression free survival for older patients with mantle cell lymphoma

The new technology may improve overall survival for older patients with mantle cell lymphoma, but clinical trial data is inconclusive.

As the new technology adds extra therapy to current standard of care, it is likely to be associated with increased adverse events.

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Clinical expert statement

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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.

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NICE National Institute for Health and Care Excellence

The deadline for your response is **5pm** on **Monday 5 January 2026.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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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	[redacted]
2. Name of organisation	The Royal College of Pathologist and University Hospitals Plymouth NHS Trust
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? X A specialist in the treatment of people with mantle cell lymphoma? X 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)	☐x 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)	☐x Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

8. What is the main aim of treatment for previously untreated mantle cell lymphoma? (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)	
10. In your view, is there an unmet need for patients and healthcare professionals in mantle cell lymphoma?	
11. How is previously untreated mantle cell lymphoma currently treated in the NHS? • 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?	

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • 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)	
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22. How do data on real-world experience compare with the trial data?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

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.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

NICE National Institute for Health and Care Excellence

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. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 18 April.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

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	[redacted]
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 been following social media and online meetings with other patients who have experienced mantle cell lymphoma and other lymphomas. I am also a retired surgeon!

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the 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 receurrent 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.
7a. What do you think of the current treatments and care available for previously untreated 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 heterogenous condition with a huge variation in presentation and course of the disease. 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 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 'choice' there is sometimes anxiety about what the best route might be.
8. If there are disadvantages for patients of current NHS treatments for previously untreated 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 Being able to carry on a reasonable quality of life is important. Minimising side effects and complications is valuable

9a. If there are advantages of acalabrutinib with bendamustine and rituximab 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 acalabrutinib with bendamustine and rituximab 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) Prolonging the 1st remission as well as maintaining a reasonable quality of life 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 acalabrutinib are much more easily tolerable than the chemotherapy drugs
10. If there are disadvantages of acalabrutinib with bendamustine and rituximab over current treatments on the NHS please describe these. For example, are there any risks with acalabrutinib with bendamustine and rituximab? 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 acalabrutinib but I also understand that acalabrutinib has a better side effect profile than ibrutinib. Having been through problems with the 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
11. Are there any groups of patients who might benefit more from acalabrutinib with bendamustine and rituximab 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 would find stem cell transplants and/or 'harsher' treatments more difficult to tolerate

ios	We are all dependent on the quality of the specialist team and their ability to help with the understanding of a wide range of individuals presenting with this condition and each individual's way of coping with this difficult situation. Printed information is very valuable to patients and so leaflets etc. need to be published in different languages Many patients presenting with mantle cell lymphoma are in the older age group and it is very difficult for some to understand the complexities of managing this disease. They need time and support from family and health care professionals….
13. 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.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Because mantle cell lymphoma is a 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 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 team
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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Age, Gender and Overall Survival for Bendamustine + Rituximab

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents patient demographic characteristics and overall survival among patients who have received a first line treatment of Bendamustine + Rituximab for mantle cell lymphoma (MCL).

Method

A snapshot of SACT data was taken on 4th January 2025 and made available for analysis on 20th January 2025. SACT is only considered complete when 90% of trusts have submitted data. As a result, SACT is considered complete up to 31st March 2024. Patients were traced for their vital status on 5th October 2024.

Descriptive statistics of age and gender were computed, as well as overall survival (OS) Kaplan-Meier graphs and parametric fits.

Linkages to HES and cancer registration data were made in order to identify whether a patient had an autologous stem cell transplant and obtain relevant ICD-O-3 morphology codes.

Cohort inclusions / exclusions

Patients were included in this cohort where :

- Country code was 'England'
- Age at start of treatment (using start date of regimen) was 18 or over
- Gender field was known (male or female)
- Diagnosis occurred between 2017 and 2022
- ICD-O-3 morphology code was 9673
- First systemic treatment was Bendamustine + Rituximab (first regimen on or after diagnosis date was Bendamustine + Rituximab)

and excluded where:

- the patient received an autologous stem cell transplant

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

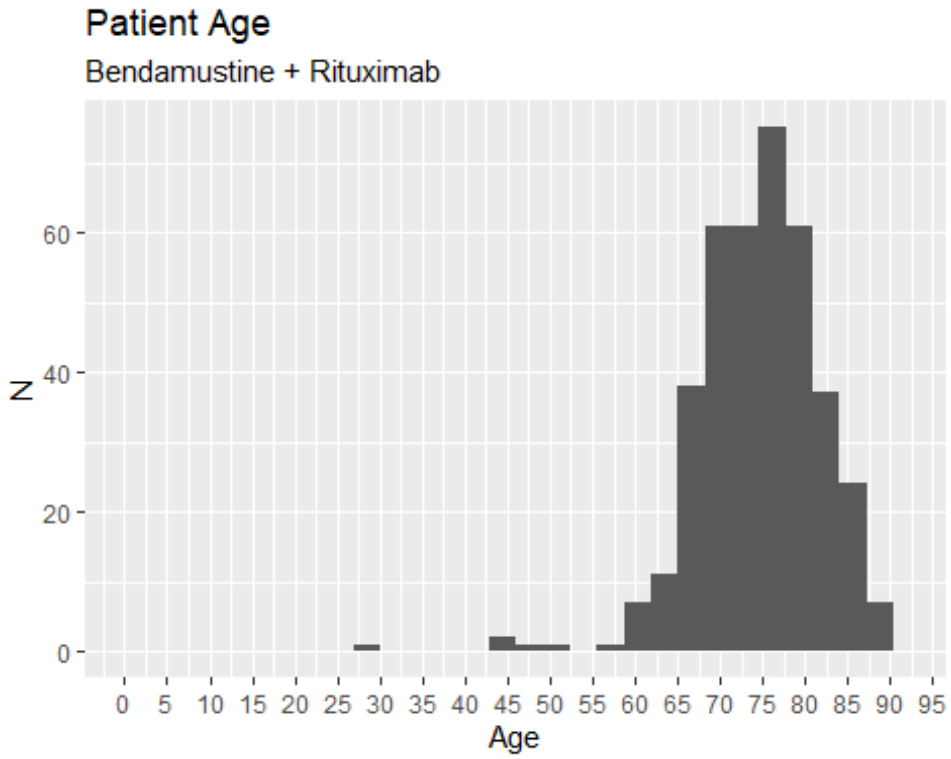
Results

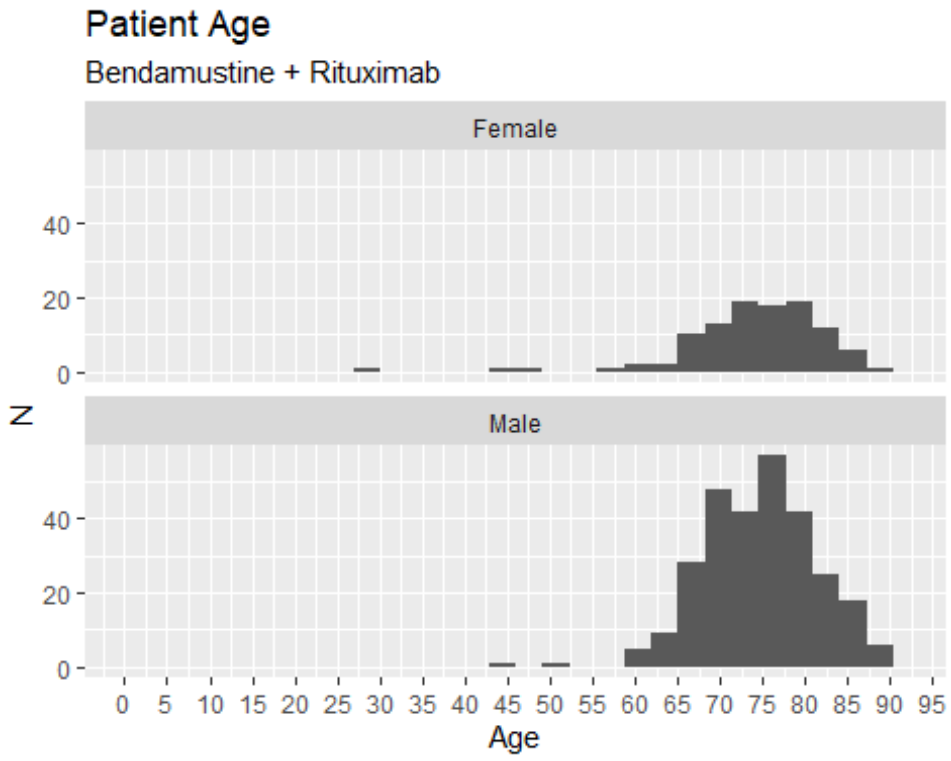
Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received bendamustine + rituximab. Age is measured at the commencement of the first treatment regimen containing bendamustine + rituximab.

Characteristic	**Female** N = 106[1]	**Male** N = 283[1]
Age at start of regimen	74, (8) : 75 (70, 79)	75, (7) : 75 (70, 79)

[1]Mean, (SD) : Median (Q1, Q3)

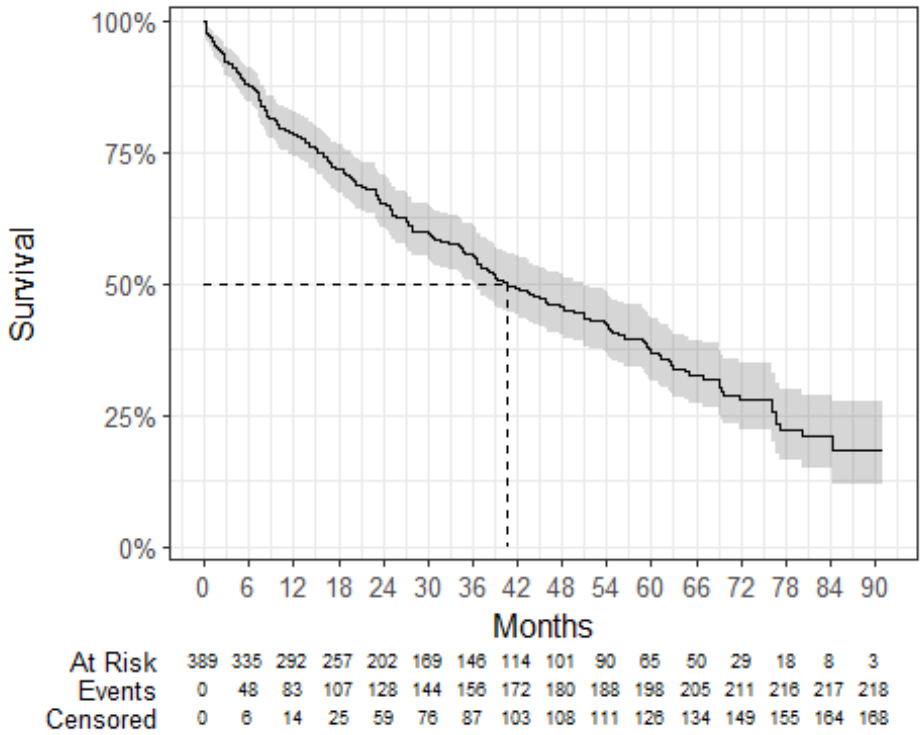



Patient Age
Bendamustine + Rituximab
Female
Male
N
40
20
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95
Age

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of bendamustine + rituximab.



Median survival was 40.51 months, and restricted mean survival (over the whole curve) was 45.4 months. The minimum follow-up time was 0.1 months, median 25.1 months, and maximum follow-up time of 91.1 months.

Exponential

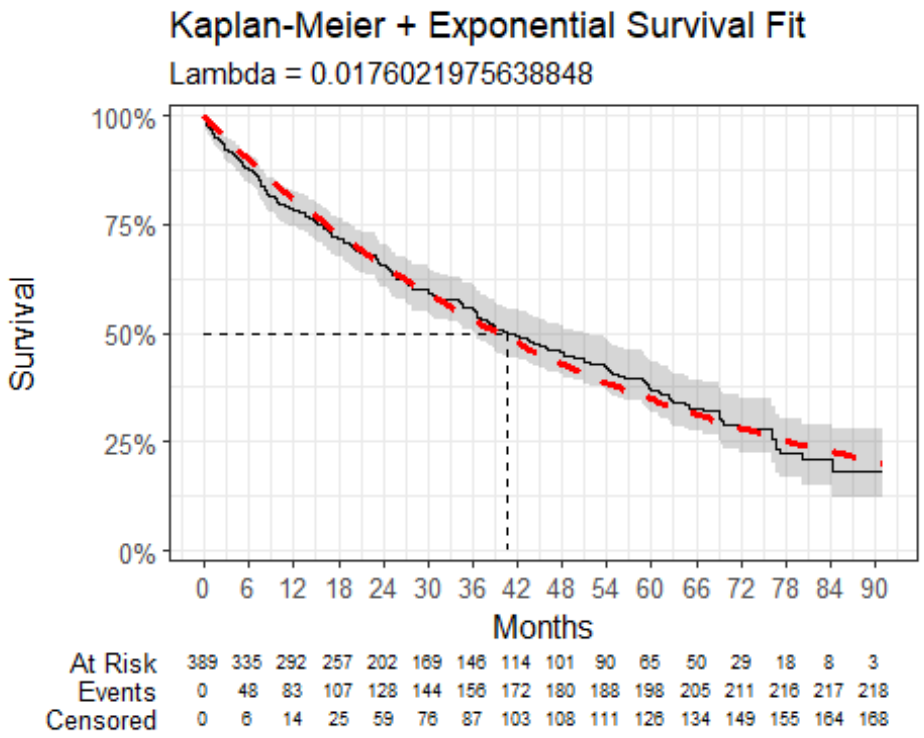


Table 1: Survival Model Fit Summary (Exponential distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	4.040	0.068	59.64592	0

log-likelihood = -1098.66147204631

AIC = 2199.32294409263

BIC = 2203.28652343625

Weibull

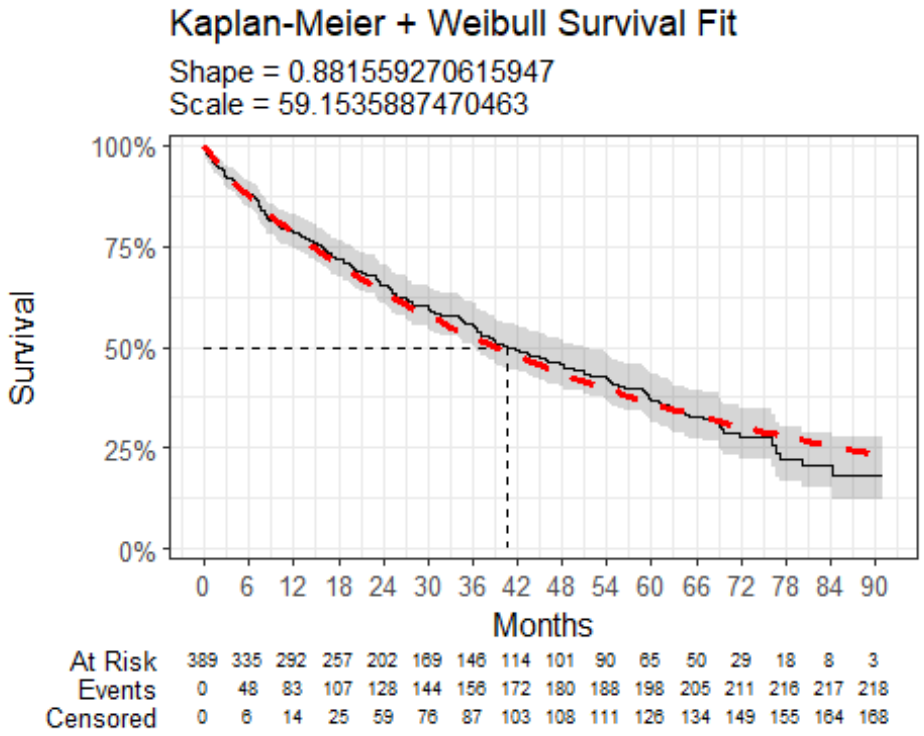


Table 2: Survival Model Fit Summary (Weibull distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	4.080	0.080	51.157663	0.00000000
Log(scale)	0.126	0.058	2.156261	0.03106328

log-likelihood = -1096.20604966639

AIC = 2196.41209933277

BIC = 2204.33925802001

Log-Normal

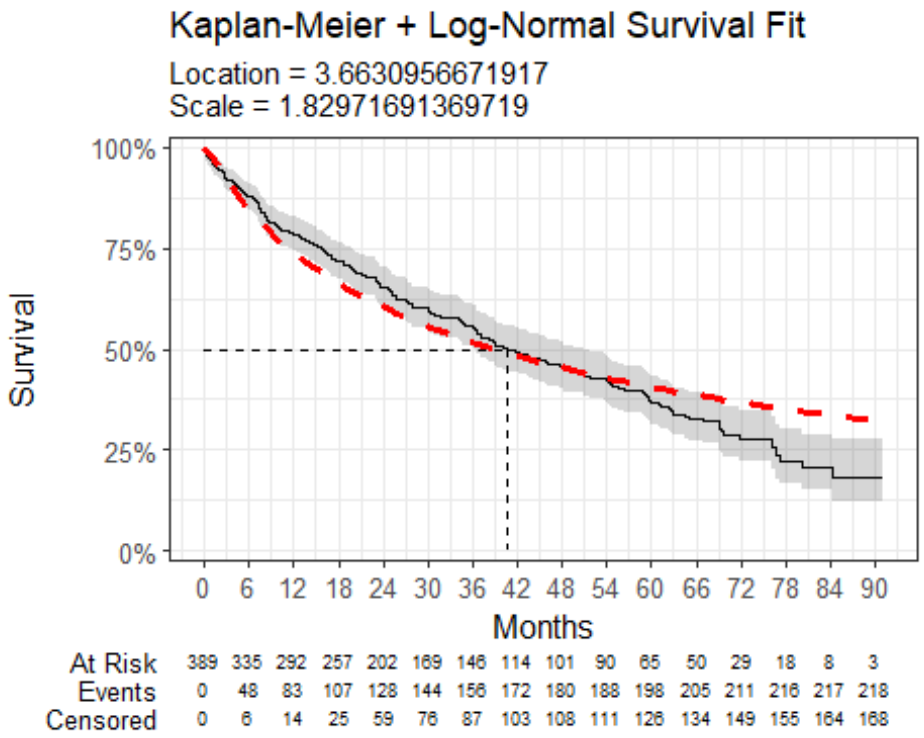


Table 3: Survival Model Fit Summary (Log-Normal distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.663	0.109	33.63792	4.682534e-248
Log(scale)	0.604	0.051	11.94987	6.502479e-33

log-likelihood = -1115.24883067187

AIC = 2234.49766134374

BIC = 2242.42482003098

Log-Logistic

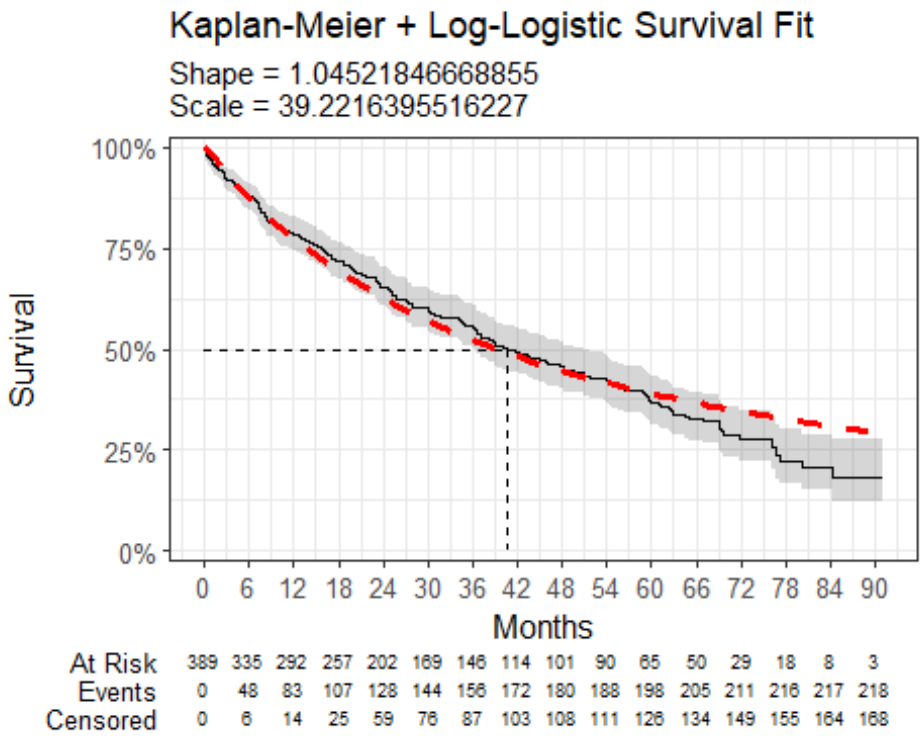


Table 4: Survival Model Fit Summary (Log-Logistic distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.669	0.092	39.9977729	0.0000000
Log(scale)	-0.044	0.058	-0.7603991	0.4470161

log-likelihood = -1104.35520146403

AIC = 2212.71040292806

BIC = 2220.6375616153

Gaussian

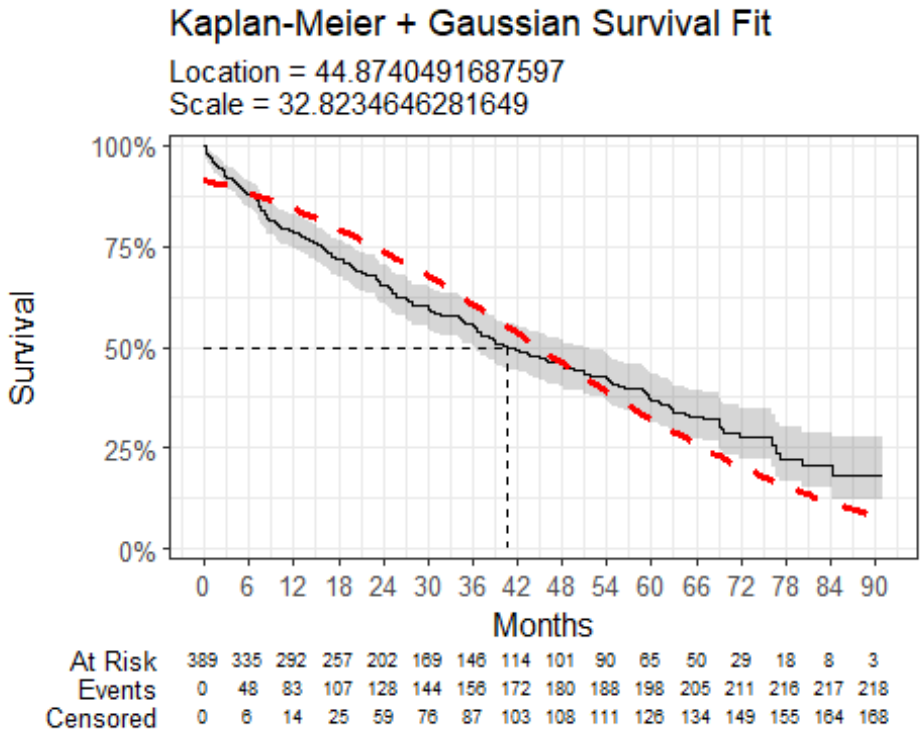


Table 5: Survival Model Fit Summary (Gaussian distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	44.874	1.954	22.96212	1.115076e-116
Log(scale)	3.491	0.050	69.71482	0.000000e+00

log-likelihood = -1181.20083376518

AIC = 2366.40166753035

BIC = 2374.32882621759

Gamma

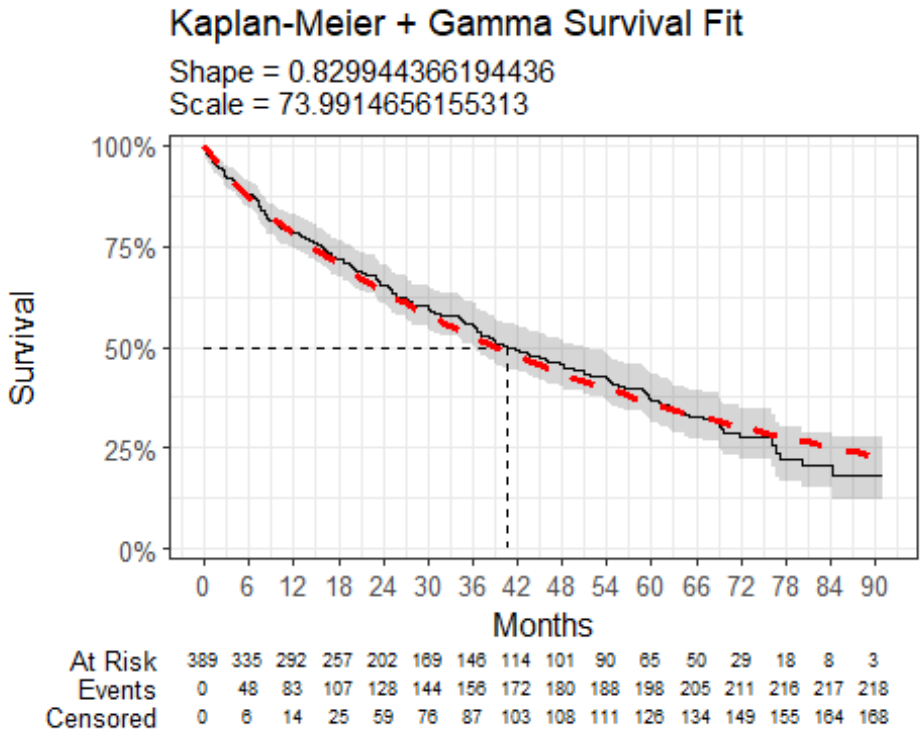


Table 6: Survival Model Fit Summary (Gamma distribution)

Parameter	Estimate	Std. Error	L95.	U95.
shape	0.830	0.063	0.71535526	0.96288892
rate	0.014	0.002	0.01039736	0.01756766

log-likelihood = -1095.49548535397

AIC = 2194.99097070795

BIC = 2202.91812939518

Generalised Gamma

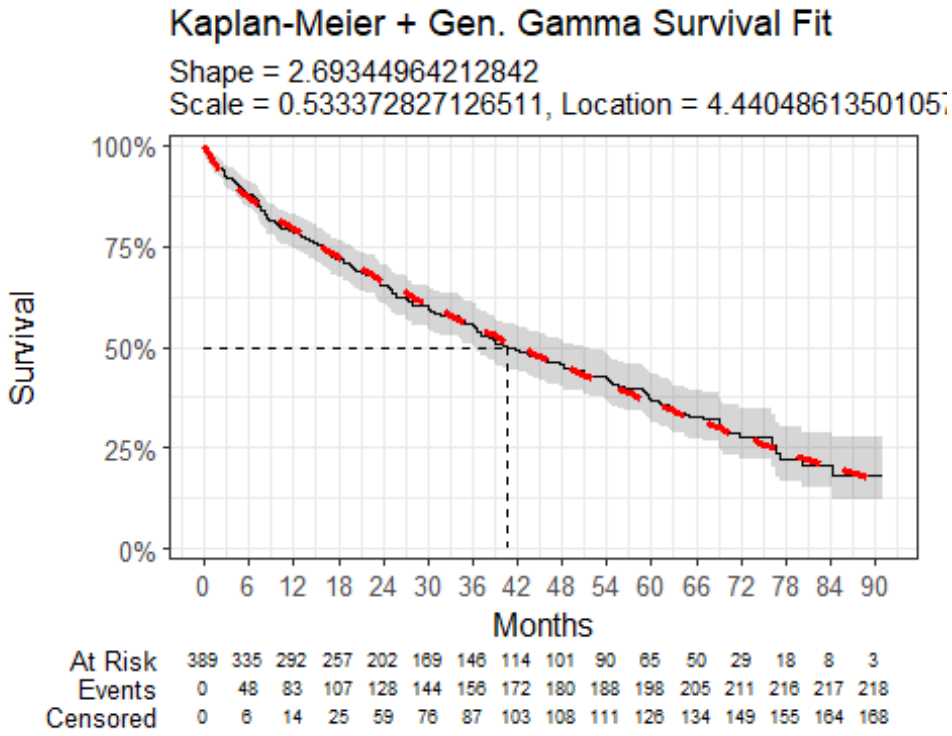


Table 7: Survival Model Fit Summary (gengamma distribution)

Parameter	Estimate	Std. Error	L95.	U95.
mu	4.440	0.290	3.8714051	5.009567
sigma	0.533	0.443	0.1046456	2.718573
Q	2.693	2.338	-1.8895017	7.276401

log-likelihood = -1093.0319307162

AIC = 2192.0638614324

BIC = 2203.95459946325

Gompertz

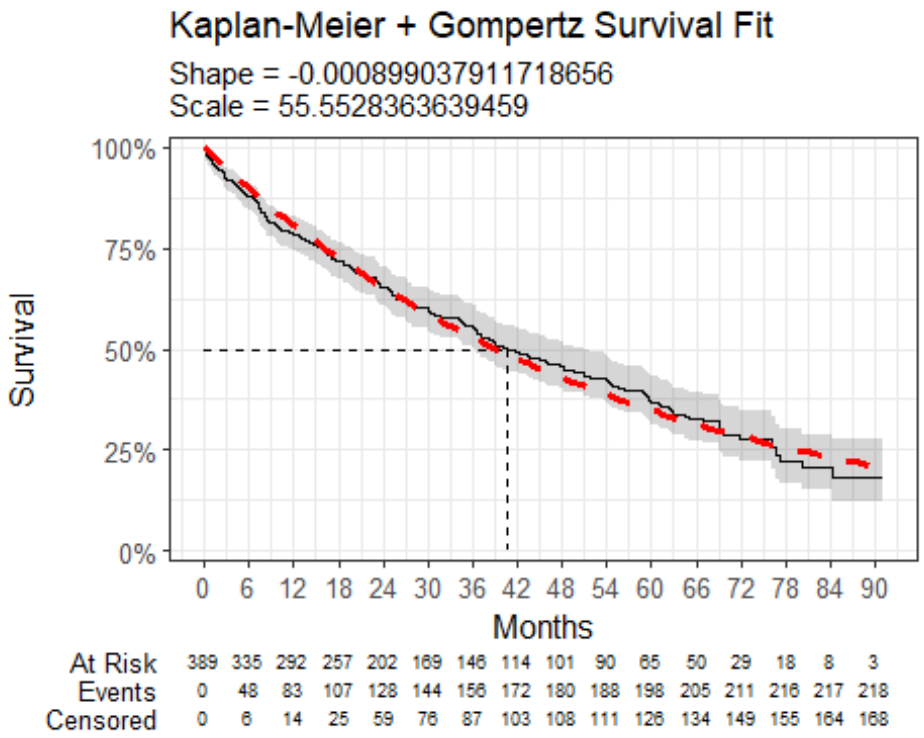


Table 8: Survival Model Fit Summary (Gompertz distribution)

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.001	0.003	-0.007703898	0.005905822
rate	0.018	0.002	0.014528267	0.022303536

log-likelihood = -1098.62763667123

AIC = 2201.25527334246

BIC = 2209.18243202969

Age, Gender and Overall Survival for R-CHOP

Introduction

This report was produced in partnership by the National Disease and Registration Service (NDRS) and National Institute for Health and Care Excellence (NICE). It presents patient demographic characteristics and overall survival among patients who have received a first line treatment of R-CHOP for mantle cell lymphoma (MCL).

Method

A snapshot of SACT data was taken on 4th January 2025 and made available for analysis on 20th January 2025. SACT is only considered complete when 90% of trusts have submitted data. As a result, SACT is considered complete up to 31st March 2024. Patients were traced for their vital status on 5th October 2024.

Descriptive statistics of age and gender were computed, as well as overall survival (OS) Kaplan-Meier graphs and parametric fits.

Linkages to HES and cancer registration data were made in order to identify whether a patient had an autologous stem cell transplant and obtain relevant ICD-O-3 morphology codes.

Cohort inclusions / exclusions

Patients were included in this cohort where :

- Country code was 'England'
- Age at start of treatment (using start date of regimen) was 18 or over
- Gender field was known (male or female)
- Diagnosis occurred between 2017 and 2022
- ICD-O-3 morphology code was 9673
- First systemic treatment was R-CHOP (first regimen on or after diagnosis date was Cyclophosphamide + Doxorubicin + Rituximab + Vincristine)

and excluded where:

- the patient received an autologous stem cell transplant, identified via linkage with HES and the presence of OPCS codes indicative of this procedure

Patient Acknowledgement

This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data is collated, maintained and quality assured by the National Cancer Registration and Analysis Service, which is part of NHS England.

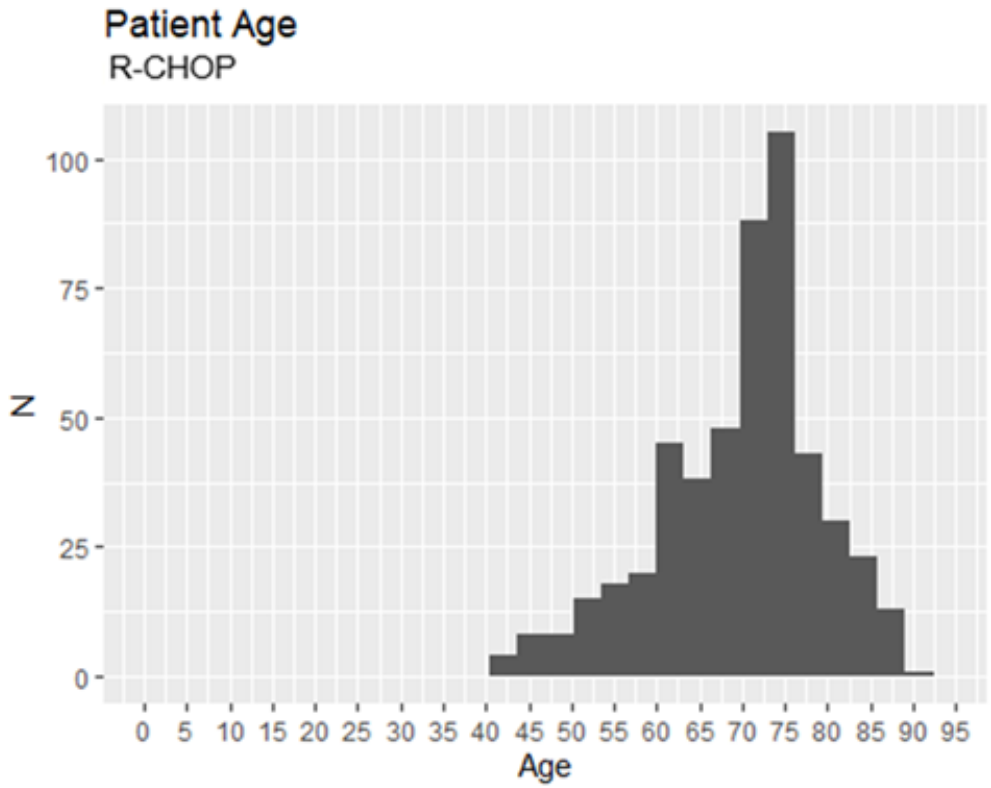
Results

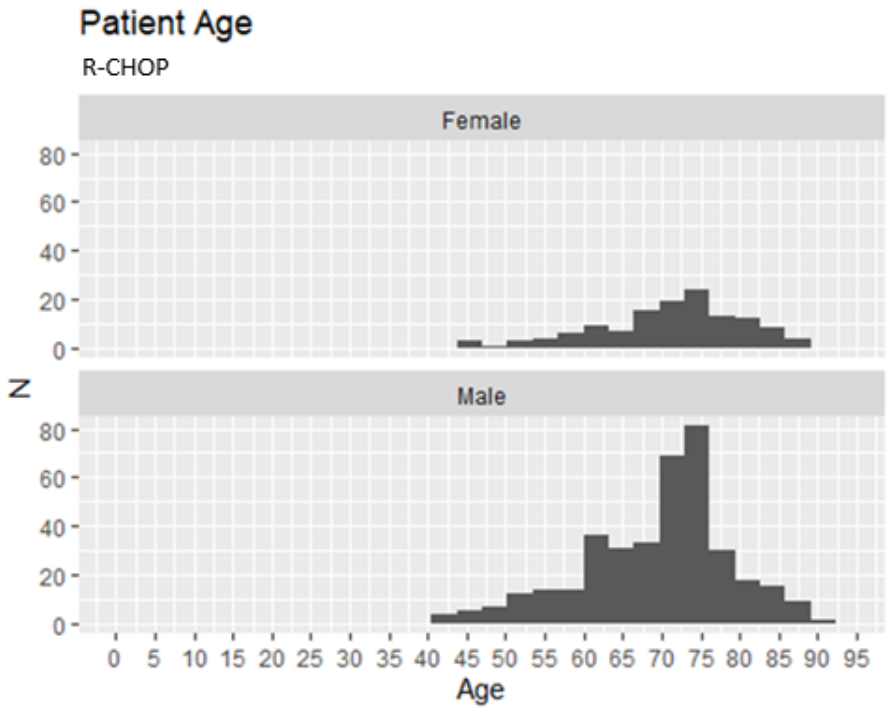
Age at start of treatment

The table below sets out the mean age, std. deviation, median age and IQR of patients who have received R-CHOP. Age is measured at the commencement of the first treatment regimen containing R-CHOP.

Characteristic	**Female** N = 129[1]	**Male** N = 379[1]
Age at start of regimen	71, (10) : 72 (66, 77)	69, (9) : 71 (64, 75)

[1]Mean, (SD) : Median (Q1, Q3)

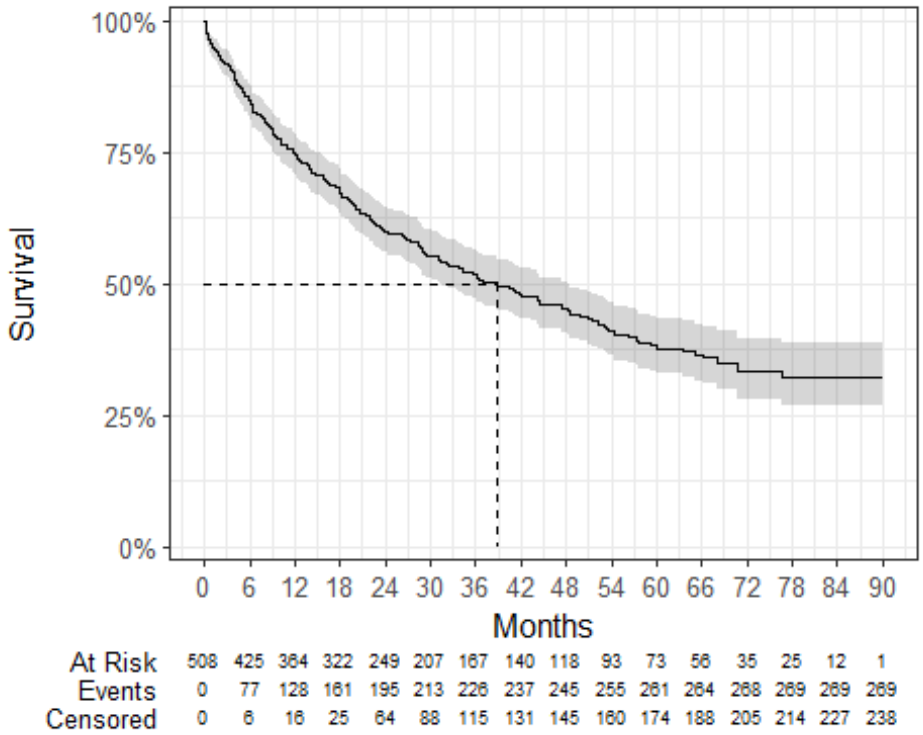



Patient Age
R-CHOP
Female
Male
N
0
20
40
60
80
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95
Age

Overall Survival

Base K-M plot

The Kaplan-Meier plot below shows survival over time for those receiving a treatment regimen of R-CHOP.



Median survival was 38.8 months, and restricted mean survival (over the whole curve) was 45.98 months. The minimum follow-up time was 0.1 months, median 23.4 months, and maximum follow-up time of 90.1 months.

Exponential

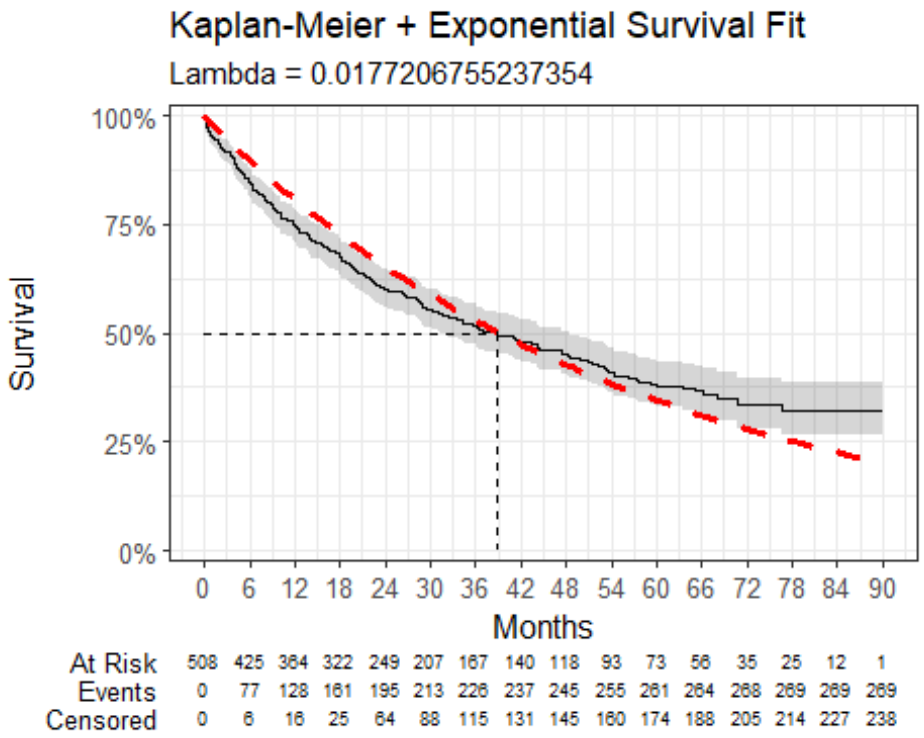


Table 1: Survival Model Fit Summary (Exponential distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	4.033	0.061	66.1465	0

log-likelihood = -1353.88324414229

AIC = 2709.76648828458

BIC = 2713.99696973216

Weibull

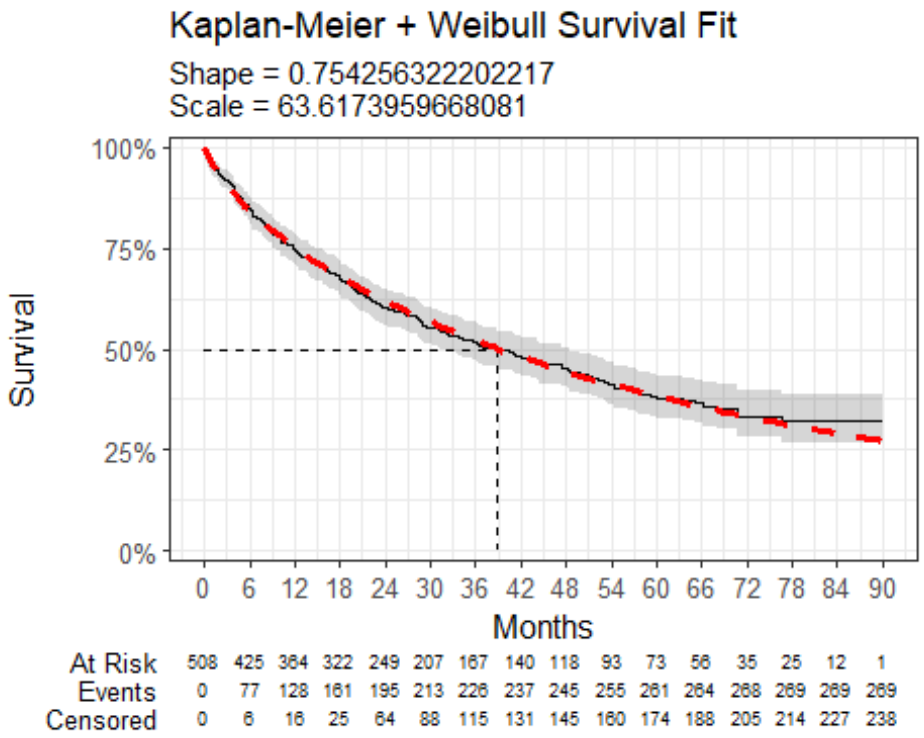


Table 2: Survival Model Fit Summary (Weibull distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	4.153	0.086	48.30689	0.000000e+00
Log(scale)	0.282	0.053	5.28702	1.243253e-07

log-likelihood = -1338.08681008253

AIC = 2680.17362016506

BIC = 2688.63458306022

Log-Normal

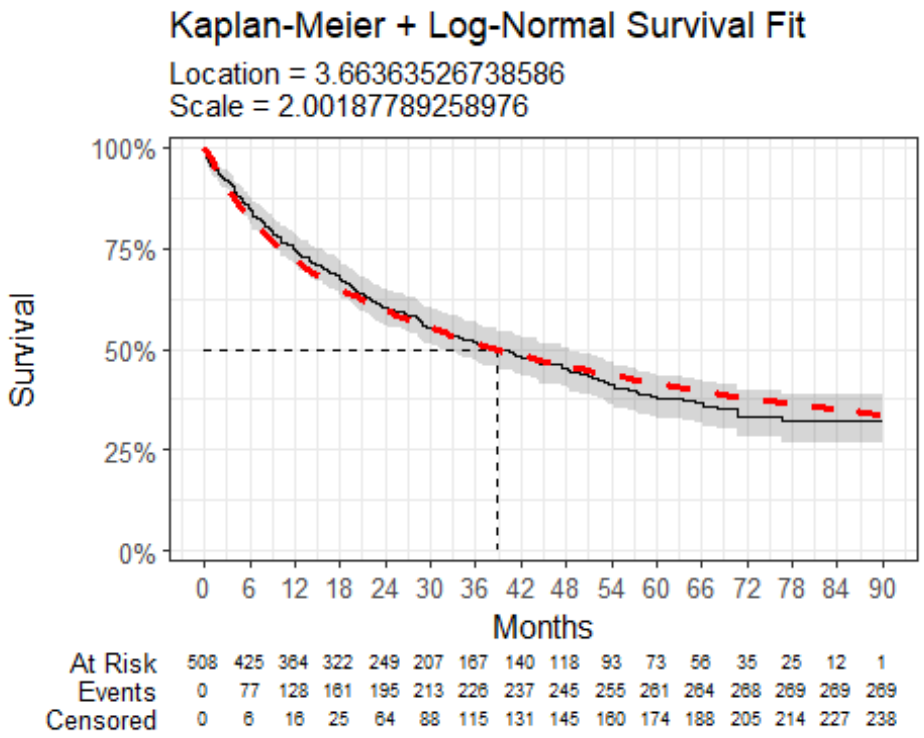


Table 3: Survival Model Fit Summary (Log-Normal distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.664	0.107	34.37983	5.048189e-259
Log(scale)	0.694	0.047	14.90981	2.845451e-50

log-likelihood = -1342.02409622722

AIC = 2688.04819245444

BIC = 2696.5091553496

Log-Logistic

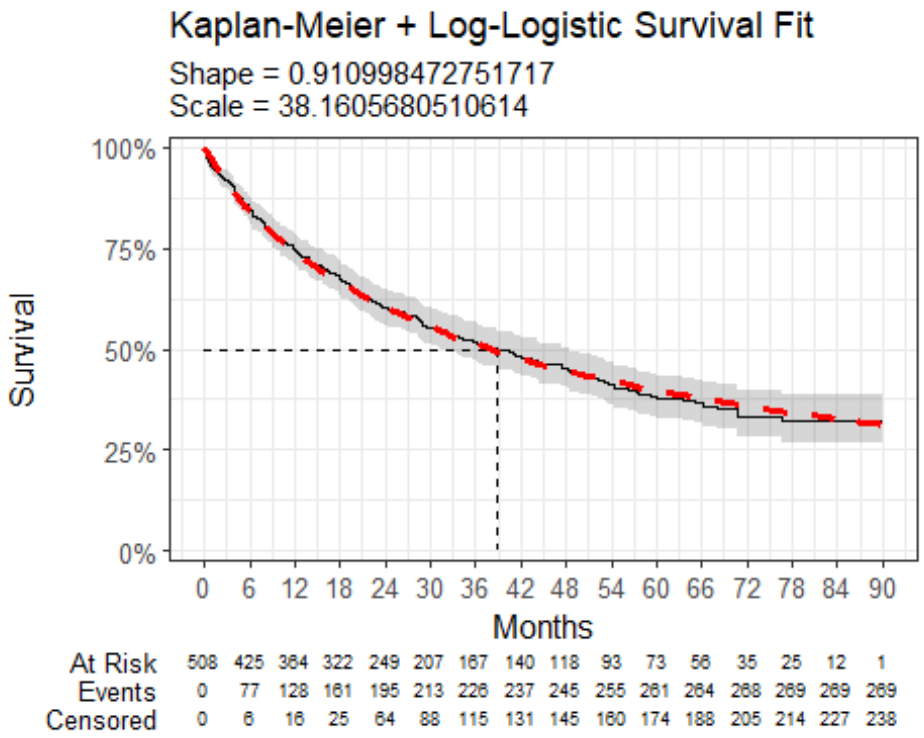


Table 4: Survival Model Fit Summary (Log-Logistic distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	3.642	0.094	38.789047	0.00000000
Log(scale)	0.093	0.053	1.770747	0.07660284

log-likelihood = -1337.69732052872

AIC = 2679.39464105745

BIC = 2687.8556039526

Gaussian

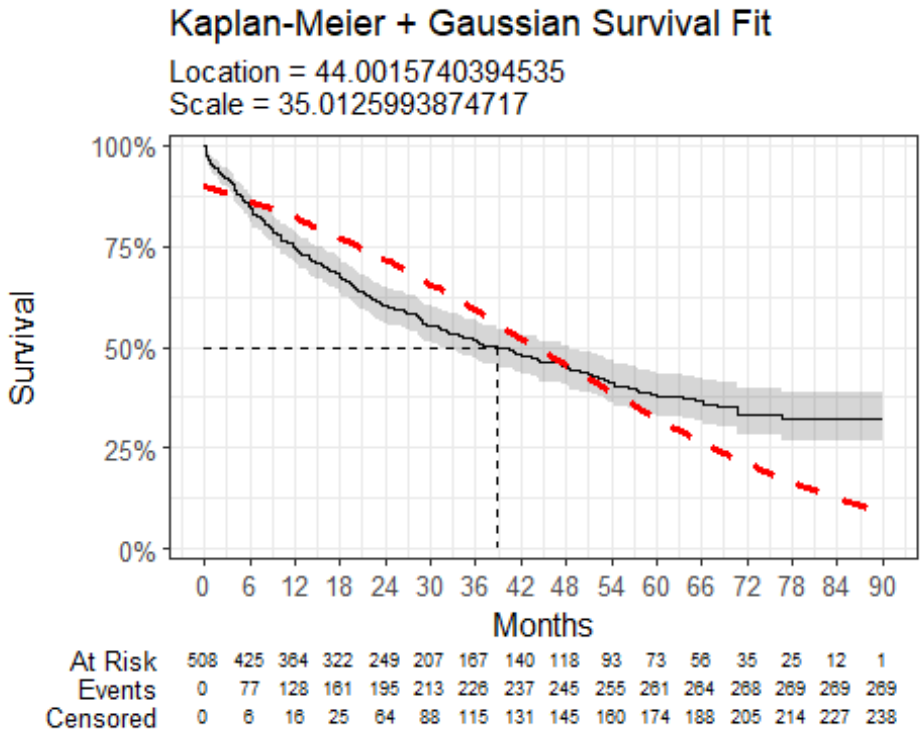


Table 5: Survival Model Fit Summary (Gaussian distribution)

Parameter	Estimate	Std. Error	z	p-value
(Intercept)	44.002	1.860	23.65661	1.009285e-123
Log(scale)	3.556	0.046	76.64452	0.000000e+00

log-likelihood = -1500.82946335829

AIC = 3005.65892671658

BIC = 3014.11988961174

Gamma

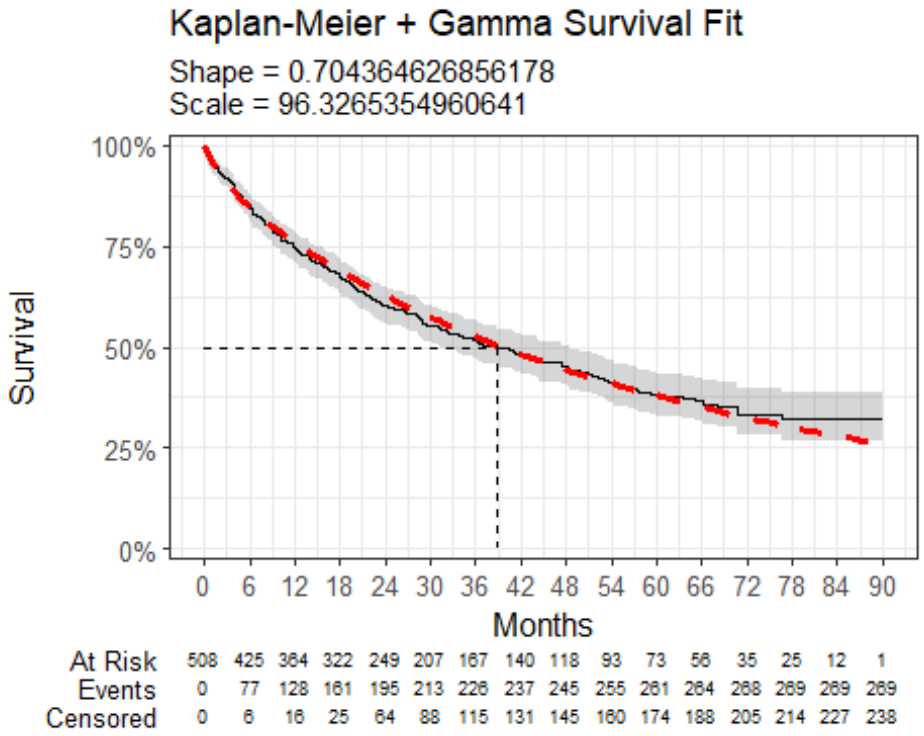


Table 6: Survival Model Fit Summary (Gamma distribution)

Parameter	Estimate	Std. Error	L95.	U95.
shape	0.704	0.048	0.616989655	0.8041132
rate	0.010	0.001	0.007995648	0.0134789

log-likelihood = -1339.21374125672

AIC = 2682.42748251343

BIC = 2690.88844540859

Generalised Gamma

Table 7: Survival Model Fit Summary (gengamma distribution)

Parameter	Estimate	Std. Error	L95.	U95.
mu	4.023	0.137	3.754747	4.290976
sigma	1.532	0.174	1.226072	1.915233
Q	0.689	0.227	0.244845	1.133310

log-likelihood = -1337.25866696758

AIC = 2680.51733393517

BIC = 2693.2087782779

Gompertz

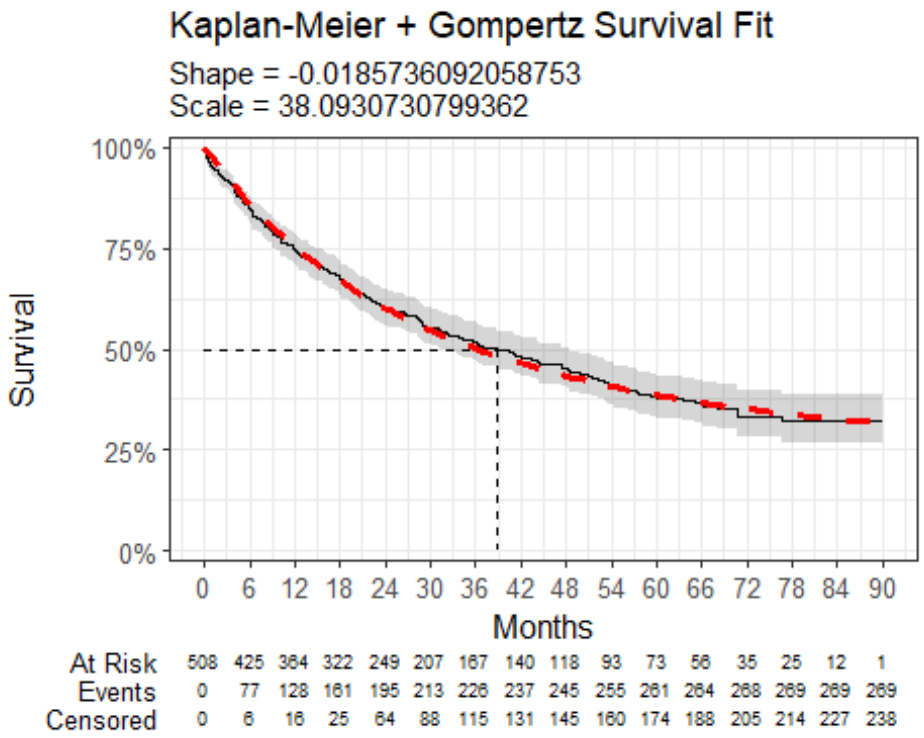


Table 8: Survival Model Fit Summary (Gompertz distribution)

Parameter	Estimate	Std. Error	L95.	U95.
shape	-0.019	0.004	-0.02594659	-0.01120063
rate	0.026	0.002	0.02191287	0.03144914

log-likelihood = -1339.99998215606

AIC = 2683.99996431212

BIC = 2692.46092720728

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

Produced by Aberdeen HTA Group

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Rider on responsibility for report

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Contribution of authors

MI and MC reviewed and critiqued the clinical effectiveness evidence presented in the company submission with support from MB; DC and TV checked and critiqued the statistical analyses presented in the company submission; CK and DB reviewed and critiqued the cost-effectiveness evidence and economic model presented in the company submission; PM checked and critiqued the company's search strategies; GP provided clinical guidance and comments on the draft report. DB coordinated all aspects of this appraisal and is the guarantor of this report. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

1L	First-line
2L	Second-line
3L	Third-line
ABR	Acalabrutinib, bendamustine, rituximab
Acala	Acalabrutinib
AE	Adverse event
AIC	Akaike information criteria
AIHA	Autoimmune haemolytic anaemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
BR	Bendamustine + rituximab

BSA	Body surface area
BSH	British Society for Haematology
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CAR-T	Chimeric antigen receptor T-cell
cBTKi	Covalent Bruton's tyrosine kinase inhibitor
CC	Critical care
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CMU	Commercial Medicines Unit
CNS	Central nervous system
CMV	Cytomegalovirus
CPI	Consumer price index
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAPS	Directly accessed pathology services
DCO	Data cut-off
DIC	Deviance information criterion
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Drugs and pharmaceutical electronic market information tool
EORTC	European Organization for Research and Treatment of Cancer
ERG	Evidence Review Group
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma

FAS	Full analysis set
FCR	Fludarabine, cyclophosphamide, rituximab
HCP	Healthcare Professional
HCRU	Healthcare resource use
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplant
HSUV	Health state utility value
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
INR	International normalised ratio
IRC	Independent Review Committee
ITC	Indirect treatment comparison
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
IXRS	Interactive voice/web response system
KM	Kaplan–Meier
LDH	Lactate dehydrogenase
LY	Life year
LYMS	Lymphoma-specific subscale
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
MIPI	Mantle Cell Lymphoma International Prognostic Index
MMRM	Mixed model for repeated measures
N/A	Not applicable
NE	Not estimable
NHB	Net health benefit

NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NMA	Network meta-analysis
ONS	Office for National Statistics
ORR	Overall response rate
OS	Overall survival
PAS	Patient access scheme
PBR	Placebo, bendamustine, rituximab
PCR	Polymerase chain reaction
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazards
PO	Orally
PPAS	Per protocol analysis population
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QD	Once daily
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	Quality of life
QTc	Corrected QT interval
R	Rituximab
R-BAC	Rituximab, bendamustine, cytarabine
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

R-CVP	Rituximab, cyclophosphamide, vincristine, prednisolone
R/R	Relapsed/refractory
RCT	Randomised controlled trial
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCT	Stem cell transplant
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care
STM	State transition model
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TECH-VER	Technical verification
TLR	Targeted literature review
TOI	Trial outcome index
TP53	Tumour protein 53
TSD	Technical support document
TTD	Time to treatment discontinuation
TTR	Time to response
ULN	Upper limit of normal
VR-CAP	Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone

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. 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 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Section 1.6 summarises the impact of the EAG's preferred assumptions on cost-effectiveness results. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

The focus of the submission received from AstraZeneca is acalabrutinib in combination with bendamustine and rituximab (BR) for the treatment of adults with previously untreated mantle cell lymphoma (MCL). The company proposed acalabrutinib + BR as first-line treatment in the care pathway for those with advanced MCL who are unsuitable for autologous stem cell transplant (ASCT) and would otherwise be considered for BR or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone).

The company's main clinical effectiveness evidence for acalabrutinib is obtained from an ongoing, Phase 3, randomised, double-blind, placebo-controlled multicentre study, ECHO (NCT 2023-505707-23-00).

Table 1 Summary of key issues

ID 6155	Summary of issue	Report sections
1	Economic model structure.	4.2.2
2	Extrapolation of OS and PFS data (covid-19 censored or ITT analysis set).	4.2.6
3	Health State Utility Value for progressed disease.	4.2.7
4	Subsequent treatment durations and distributions for 2nd and 3rd line treatment.	4.2.8

Key: ITT, intention to treat; OS, overall survival; PFS, progression free survival

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company prefers to use a partitioned survival analysis model to estimate cost-effectiveness, but the EAG would have preferred the company to use a Markov state transition model that more accurately captures the benefits of subsequent lines of treatment. The EAG consider the partitioned survival modelling approach to under-estimate OS benefits of subsequent treatments and does not model any of their PFS benefit.

- The company prefers to estimate ABR and BR OS and PFS using independently fitted parametric survival curves to the respective arms of the ECHO trial, based on an analysis set where covid-19 deaths are censored. The EAG prefers to use dependent survival extrapolations and to assume that the proportional hazards assumption holds. The EAG also prefers to base extrapolations on the intention to treat analysis set.

- The company prefers gamma parametric extrapolations for OS and PFS in both the ABR and PBR arms of the model. The EAG prefers the exponential extrapolations because they more closely align with expert opinion and are aligned with the EAG's view that the PH assumption is likely to hold.

- The company prefers progressed disease utilities that are fixed over time, where as the EAG prefers PD utilities that reduce over time, given that the modelled cohort progress through several lines of treatment with an expectation that each progression

event would reduce quality of life. The EAG consider a reducing utility to reduce the magnitude of bias associated with not fully modelling the treatment benefits of subsequent treatment lines in the partitioned survival model.

- The company prefers to include 3rd line progression subsequent treatment costs, but the EAG prefers not to include these costs given that there is limited evidence to support the impact of acalabrutinib on subsequent need for 3rd line treatment. The EAG also prefers to use different assumptions to the company about relative dose intensities, treatment distributions and vial sharing.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life 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 QALYs by:

- Increasing progression free survival and reducing the proportion of the cohort in the progressed disease at any given point in time.

Overall, the technology is modelled to affect costs by:

- Increasing the treatment acquisition costs of first line treatment
- Reducing the treatment acquisition and administration costs of 2nd and 3rd line treatments compared to BR alone or R-CHOP.

The modelling assumptions that have the greatest effect on the ICER are:

- The decision to use a partitioned survival model instead of a Markov state transition model.
- Decisions about the most appropriate progressed disease health state utility value
- Assumptions underpinning the calculation of 2nd and 3rd line subsequent treatment costs.

1.3 The decision problem: summary of the EAG's key issues

Overall, the company's decision problem aligns with the NICE final scope. However, the EAG notes that the company defined a narrower population than the NICE scope, which includes all adults with previously untreated MCL. The company focused specifically on patients with advanced disease who are unsuitable candidates for ASCT. The ECHO study further narrowed this focus to an older population (aged 65 and above). Consequently, the company excluded comparator treatments that are infrequently used for this population in the UK, such as VR-CAP (bortezomib-based therapy), R-BAC (cytarabine-based immunochemotherapy), and radiotherapy. The EAG's clinical expert considers the company's decision problem to be reasonable.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG found no major concerns regarding the design or conduct of the ECHO study. The impact of the decision to estimate PFS, OS and TTD using an analysis set with covid-19 deaths censored, or an intention to treat (ITT) analysis is described in Issue 2, Section 1.5.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Issue 1 Economic model structure.

Report section	4.2.2
Description of issue and why the EAG has identified it as important	The company preferred partitioned survival model structure does not incorporate PFS benefits, and likely underestimates the OS benefits of subsequent treatment lines following progression after treatment with ABR and BR.
What alternative approach has the EAG suggested?	The EAG would have preferred a Markov state transition model that explicitly models the treatment costs and benefits of subsequent treatment lines.
What is the expected effect on the cost-effectiveness estimates?	All else held equal, the direction of bias would be expected to favour the initial line of treatment with a longer time to progression (ABR). This would mean that the ICER for ABR vs. BR is underestimated. The magnitude of bias is uncertain.
What additional evidence or analyses might help to resolve this key issue?	The EAG believe that a Markov state transition model should be developed. A Markov modelling approach would align closely with other NICE appraisals of MCL, especially those conducted early in the treatment pathway. The EAG has attempted to implement scenario analyses in the partitioned survival model with a view to minimising the bias of modelling costs but incompletely modelling the benefits of subsequent treatment lines. However, these are exploratory and should be interpreted cautiously.

Key: ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression free survival.

Issue 2 Extrapolation of OS and PFS data (covid-19 censored or ITT analysis set).

Report section	4.2.6
Description of issue and why the EAG has identified it as important	The company model OS and PFS using an analysis set where covid-19 deaths are censored. OS and PFS are modelled by fitting individual parametric extrapolation curves to ABR and BR data from the ECHO trial. The company has not provided sufficient evidence that covid-19 deaths from the trial are not generalisable to UK clinical practice. Choices about the most appropriate analysis set have important implications for treatment acquisition costs and QALYs in the model.
What alternative approach has the EAG suggested?	The EAG prefers the use of OS and PFS extrapolations based on the ITT analysis set, assuming PH assumptions hold and applying a HR for ABR vs. BR to an exponential parametric distribution for both OS and PFS.
What is the expected effect on the cost-effectiveness estimates?	As there were more covid-19 deaths in the ABR arm of the ECHO study, the company's approach may over-estimate QALY gains and treatment acquisition costs for ABR. The net impact on the ICER depends on other assumptions in the model, but using the ITT analysis set reduces the EAG corrected, company preferred base case ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG would appreciate full details of parametric curve selection for the ITT analysis set, for joint models, including AIC and BIC criterion, which were not available to the EAG.

Key: ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression free survival.

Issue 3 Health State Utility Value for progressed disease.

Report section	4.2.7
Description of issue and why the EAG has identified it as important	The company has applied a fixed PD utility across all subsequent lines of treatment. This is important because it likely under-estimates PD utilities early in the model trace, but over-estimates them later. This issue is related to Issue 1 above and has a potentially large impact on the ICER.
What alternative approach has the EAG suggested?	The EAG would have preferred each line of treatment to be modelled independently in a Markov state transition model with decreasing utilities at each subsequent stage of progression.
What is the expected effect on the cost-effectiveness estimates?	The company's approach likely over-estimates the utility of progressed disease. The impact could potentially lead to a substantial over-estimation of the ICER, given that ABR delays disease progression compared to BR.
What additional evidence or analyses might help to resolve this key issue?	As per issue 1 above.

Key: ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EAG, external assessment group; HSUV, health state utility value; ICER, incremental cost-effectiveness ratio; PD, progressed disease.

Issue 4 Subsequent treatment durations and distributions for 2nd and 3rd line treatment.

Report section	4.2.8
Description of issue and why the EAG has identified it as important	Subsequent treatment durations and distributions of subsequent treatments at both 2nd line and 3rd line are uncertain. The company's economic model uses ECHO trial data to derive the proportion of patients receiving subsequent treatment lines, with a substantially greater proportion in the PBR arm receiving subsequent treatment. Durations are sourced from a range of literature and treatment distribution is based on clinical expert opinion, with only one expert providing model inputs for 3rd line in both the ABR and BR arms of the model.
What alternative approach has the EAG suggested?	The EAG explores a range of scenarios to illustrate uncertainty. Given the model structure concern, the EAG prefers to remove 3rd line subsequent treatment costs.
What is the expected effect on the cost-effectiveness estimates?	Any under-estimation of the proportion requiring subsequent treatment in the ABR arm, compared to UK clinical practice (longer-term) would lead to over-estimation of subsequent treatment cost savings for ABR.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers the proportion of patients requiring subsequent treatments, the duration of subsequent treatments and the distribution of treatments across available therapies to be an unresolved area of uncertainty. A range of evidence could help reduce the uncertainty. For example, longer follow-up data from the ECHO trial may help better understand proportions requiring 2nd and in particular 3rd line treatments. Real-world data, eg. SACT data would help better understand subsequent treatment distributions, and potentially treatment durations in UK clinical practice, especially for the BR arm of the model.

Key: ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EAG, external assessment group; SACT, systemic anti-cancer therapy dataset.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG identified two calculation errors, 1) with respect to the calculation of subsequent treatment administration costs in the model and 2) with respect to a typographical error in the selection of pack sizes for treatment acquisition costs. The EAG have applied all preferred assumptions to the corrected version of the company's preferred modelling assumptions and settings. For all analyses in the EAG preferred base case, R-CHOP is more costly and less effective, therefore is dominated by BR. Table 2 therefore reports ICERs for ABR vs. BR only. Full incremental analyses results can be found in Chapter 6.

Table 2 Summary of EAG's preferred assumptions and ICERs (ABR vs. BR)

Scenario	Incremental cost	Incremental QALYs	ICER (ABR vs. BR)
EAG corrected base case analysis post clarification queries	[redacted]	[redacted]	[redacted]
Clinical parameters (OS, PFS, TTD) derived from the ITT analysis set	[redacted]	[redacted]	[redacted]
OS and PFS curves derived from joint (dependent) models	[redacted]	[redacted]	[redacted]
OS and PFS curves based on exponential parametric extrapolation curves	[redacted]	[redacted]	[redacted]
HSUVs and event duration for covid-19 pneumonia AEs assumed equal to pneumonia	[redacted]	[redacted]	[redacted]
Decreasing utility value of progressed disease based upon exponential function where utility equals 0.45 at 2.06 years	[redacted]	[redacted]	[redacted]
Remove vial sharing assumption for IV treatments	[redacted]	[redacted]	[redacted]
Assume subsequent treatment RDIs = first line, or TA370 values	[redacted]	[redacted]	[redacted]
EAG preferred subsequent treatment durations (2nd and 3rd line treatments)	[redacted]	[redacted]	[redacted]
Remove 3rd line treatments	[redacted]	[redacted]	[redacted]
EAG's preferred base case (All scenarios above combined)	[redacted]	[redacted]	[redacted]

Key: ABR, Acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EAG, external assessment group**;** ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years.

Modelling errors identified and corrected by the EAG are described in Section 4.2.8 and Section 5.1 of the EAG report. For further details of the exploratory and sensitivity analyses done by the EAG, see Chapter 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from AstraZeneca is untreated mantle cell lymphoma. The company's description of the health condition in terms of prevalence, symptoms and complications appears accurate and in line with the decision problem. The relevant intervention for the submission is acalabrutinib (Calquence©) in combination with bendamustine and rituximab.

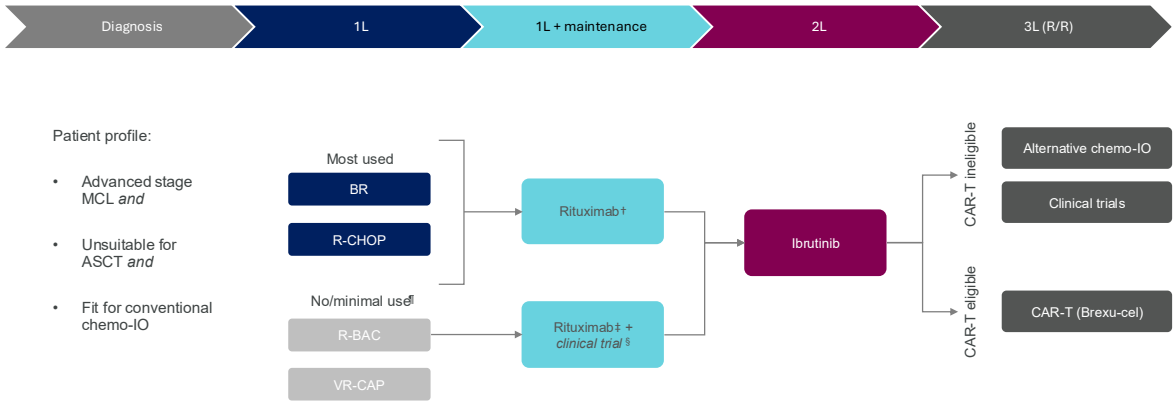
2.2 Background

The company submission (CS) describes mantle cell lymphoma (MCL) as a rare subtype of non-Hodgkin lymphoma, characterised by the production of abnormal B-cells in the mantle zone (i.e. outer edge) of the lymph nodes. In the UK, around 600 people are diagnosed with MCL every year.[1-3] More males than females are diagnosed with MCL, with a ratio of 2.4:1.[2, 3] The Hospital Admitted Patient Care Activity data for MCL (code C83.1) for the year 2023-2024 reports 8,615 finished consultant episodes involving patients of mean age of 68 years and a mean length of stay in hospital of 9.3 days.[4] The cause of MCL is unknown but most cases show overexpression of cyclin D1 which is an important event in its pathogenesis.[3, 5]

The most common symptoms of MCL are painless swellings of the lymph nodes in the neck, armpit and/or groin. General symptoms (known as B symptoms; namely heavy night sweats, unexplained weight loss and fever) are also experienced by some patients.[1, 3] Around 10-15% of patients are diagnosed with clinically and pathologically indolent MCL and can be asymptomatic.[6]

The Lugano Classification is used for staging in lymphoma, ranging from Stage I (localized lymphoma) to Stage IV (spread to distant extranodal sites).[7] MCL is an aggressive type of lymphoma and most patients present with stage IV disease.[1, 3, 8] Median duration of remission is 1.5 to 3 years and median overall survival is 3 to 6 years with standard chemotherapy. Five-year net survival is 47.4% overall.[2, 9] Treatment of MCL has improved greatly in recent years but relapses remain common and MCL is largely incurable.[5]

The CS cites the NICE guideline NG52 and British Society for Haematology (BSH) guideline for the management of MCL.[6, 10] For early stage asymptomatic MCL, a 'watch and wait' approach until disease progression or radiotherapy are recommended. Management of advanced MCL is based on suitability for autologous stem cell transplant (ASCT) which is, in turn, based on individual patient factors including age and fitness for transplantation. Treatment of patients who are candidates for ASCT generally involves intensive cytarabine-containing chemoimmunotherapy, consolidation ASCT (in those with objective response) and maintenance rituximab.[6, 10] The company provides a description of the current clinical pathway in Section B.1.3.2 of the CS. An overview of the treatment pathway for patients who are not candidates for ASCT is presented as Figure 1, Document B of the CS, reproduced as Figure 1 below.

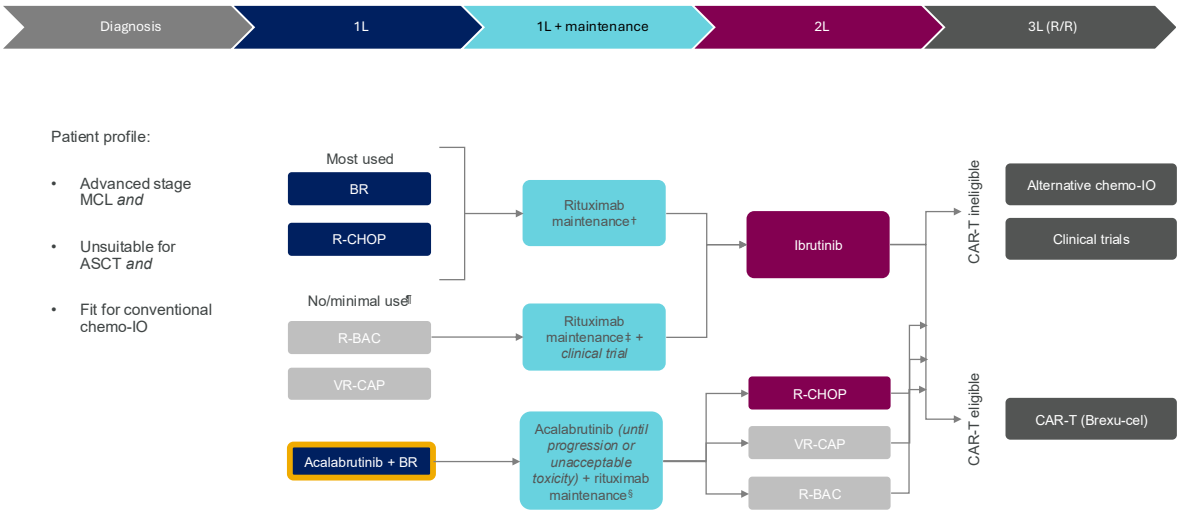


Abbreviations: 1/2/3L, first-/second-/third-line; ASCT, autologous stem cell transplant; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor T-cell; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-The BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
† For patients with newly diagnosed MCL who are not fit enough for high-dose chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy, rituximab maintenance may be given every 2 months until disease progression.
‡ For patients with newly diagnosed MCL who are in remission after cytarabine-based induction and high-dose chemotherapy, rituximab maintenance may be given every 2 months for 3 years.
§ BSH guidelines suggest that rituximab maintenance following R-BAC should not be offered outside of a clinical trial.
¶ Used in less than 3% of patients.
References: Eyre T et al. 2024;[6] NICE NG52;[10] AstraZeneca Data on File REF-251322, 2024.[11]

Figure 1 Current treatment pathway for advanced MCL unsuitable for ASCT [reproduced from Figure 1, Document B of the CS]

The company notes that bendamustine + rituximab (BR), and rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) are currently the principal treatment

options for first-line treatment in this population. The EAG clinical expert is in agreement. The company anticipates that acalabrutinib + BR will be used in first-line treatment of patients with advanced MCL who are unsuitable for ASCT and would otherwise be considered for BR or R-CHOP. The anticipated place for acalabrutinib + BR is presented in Figure 2, Document B of the CS and is reproduced as Figure 2. The EAG clinical expert agrees with the positioning of ABR but notes that VR-CAP is used rarely and is unlikely to be second line. In addition, R-BAC is very unlikely to be second line if bendamustine has been used first-line.



Abbreviations: 1/2/3L, first-/second-/third-line; ABR, acalabrutinib, bendamustine, rituximab; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; brexu-cel, brexucabtagene autoleucel; CAR-T, chimeric antigen receptor T-cell; chemo-IO, immunochemotherapy; MCL, mantle cell lymphoma; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.
† For patients with newly diagnosed MCL who are not fit enough for high-dose chemotherapy and where there has been a response to R-CHOP-based immunochemotherapy, rituximab maintenance may be given every 2 months until disease progression.
‡ For patients with newly diagnosed MCL who are in remission after cytarabine-based induction and high-dose chemotherapy, rituximab maintenance may be given every 2 months for 3 years.
§ For patients treated with ABR, acalabrutinib may be given until progression or unacceptable toxicity. Rituximab maintenance may be given every 2 months for 2 years.
¶ Used in less than 3% of patients.
References: Eyre T et al. 2024;[6] NICE NG52;[10] AstraZeneca Data on File REF-251322, 2024.[11]

Figure 2 Anticipated place in therapy for ABR [reproduced from Figure 2, Document B of the CS]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of the adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with previously untreated MCL	Adults with previously untreated MCL who are considered unsuitable candidates for ASCT	Until now, 1L treatment for MCL has required dichotomising patients based on ASCT suitability based on a range of factors, including patient choice, the timing of relapse, age, previous treatment, and general health and fitness.[12] Patients deemed suitable for a transplant typically receive aggressive chemoimmunotherapy, consolidative ASCT in first remission, and rituximab maintenance.[6] For the older, less fit population who are unsuitable for aggressive induction therapy, BR and R-CHOP are recommended, with BR considered SoC for the majority of patients.[6] The evidence from the Phase 3 ECHO trial focuses on patients with untreated MCL who are considered unsuitable candidates for ASCT.[6, 11]	The EAG clinical expert agrees that the company's target population is reasonable. Patients fit for ASCT will continue to get an intensive chemotherapy approach with ASCT.
Intervention	Acalabrutinib with bendamustine and rituximab	As per NICE scope	-	The intervention described in the CS matches that described in the NICE final scope. Acalabrutinib is a selective inhibitor of BTK which is an important element of B cell receptor signalling that regulates B cell proliferation and survival. Acalabrutinib and its active metabolite (ACP-5862) form a

				covalent bond with a cysteine residue in the BTK active site leading to irreversible inactivation of BTK.[13, 14] Acalabrutinib as monotherapy or in combination with Obinutuzumab is indicated for adults with previously untreated chronic lymphocytic leukaemia (CLL). Acalabrutinib as monotherapy is indicated for adults with CLL who had received at least one prior therapy.[14] The anticipated indication covered in the CS is acalabrutinib in combination with bendamustine and rituximab the treatment of adults with previously untreated MCL. A marketing authorisation application was submitted to the MHRA in September 2024. The anticipated date of UK regulatory approval is [redacted]
Comparator(s)	Established clinical management without acalabrutinib, including: • Chemotherapy in combination with rituximab, including bendamustine with rituximab (BR) • Cytarabine-based immunochemotherapy • Radiotherapy • Bortezomib	• Chemotherapy in combination with rituximab: – BR – R-CHOP	To understand the standard treatments currently used in the NHS for this population and to identify appropriate comparators, AstraZeneca conducted one-to-one interviews with several haematology-oncology consultants in the UK who treat MCL (see **Error! Reference source not found.**). All clinicians independently agreed that the treatments used in the UK for patients with untreated MCL who are considered unsuitable candidates for ASCT are **BR** and **R-CHOP**, with BR considered as the SoC .	The EAG clinical expert is satisfied with the comparators addressed in the company's decision problem. Radiotherapy is not applicable, as true stage 1 disease is very rare. High dose cytarabine is also not given first line in this unfit for ASCT population

			Although **VR-CAP** (**V = bortezomib**) is recommended in the guidelines for patients with 1L MCL who are unsuitable for ASCT, all clinicians stated that this therapy is rarely used in the UK due to increased toxicity versus R-CHOP and the need for frequent monitoring.[6, 11] Similarly, with **R-BAC (cytarabine-based immunochemotherapy)**, this regimen is associated with significant infective and haematological toxicity[6] and is therefore not frequently used.[11] Finally, **radiotherapy** is reserved for patients with early-stage MCL and therefore falls outside the remit of the population in this submission which includes patients with advanced disease who are unsuitable for ASCT.[6, 10] The insights gathered from the UK clinicians on the appropriate comparators align with the BSH guidelines for treating 1L MCL patients unsuitable for transplant, which describe the toxicity of both R-BAC and VR-CAP.[6]	
Outcomes	The outcome measures to be considered include: • PFS • OS • Response rates • Adverse effects of treatment • HRQoL	As per NICE scope	-	The EAG considers the outcomes addressed by the company to be appropriate

Economic analysis	cost effectiveness expressed as incremental cost per quality-adjusted life year; time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies; costs will be considered from an NHS and Personal Social Services perspective.	As per scope	As per scope	See detailed critique of economic modelling methods in chapter 4.
Subgroups	-	-	-	Subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms. These included: • Sex • Age category • Race • Geographic region • Baseline ECOG PS • Tumour bulk • Ann Arbor staging for lymphoma • Histologically documented MCL

				• MCL type (classic type versus blastoid variant and pleomorphic variant versus other) • Ki-67 • Bone marrow involvement • Extranodal disease • Gastrointestinal disease • Simplified MIPI score • Lactate dehydrogenase (LDH) > upper limit of normal (ULN) • COVID-19 vaccine status
Special considerations including issues related to equity or equality	-	-	-	The CS states that the use of ABR is not expected to raise any equality issues. The EAG is in agreement.

Abbreviations: 1L, first-line; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; BSH, British Society for Haematology; CAR-T, chimeric antigen receptor T-cell; HRQoL, health-related quality of life; MCL, mantle cell lymphoma; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The EAG's appraisal of the company's systematic literature review (SLR) methodology is summarised in Table 4.

Table 4 EAG's appraisal of the literature review methods presented in the CS

Review process EAG	EAG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D.1 of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, and CDSR for evidence syntheses. Relevant conference proceedings and trial registers were also searched. Full details are provided in Appendix D.1.1 of the CS. Searches were not restricted by any eligibility criteria so all results were discovered and only those relevant to the scope were selected.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	The eligibility criteria outlined in Appendix D, Section D.1.2.2.1.3, Table 10 are consistent with the decision problem outlined in the NICE final scope.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, section D.1.2.2.1.1 *"The titles and abstracts for articles identified by the electronic searches were screened by two independent reviewers (double-blind) […]. Both*

Review process EAG	EAG response	Comments
		reviewers determined whether the article met the pre-defined eligibility criteria […] with any uncertainties or discrepancies resolved by reviewer discussion and/or escalation to a third independent reviewer (project lead or a senior team member). All decisions, including the rationales, were documented." Appendix D, section D.1.2.2.1.2 *"Full-text review was carried out by two reviewers (double-blind), with any uncertainties resolved by reviewer discussion and/or escalation to a third senior reviewer. As described above, the studies were selected according to the eligibility criteria in* ***Error! R eference source not found.*** *and rationales for exclusion were documented."*
Was data extraction conducted by two or more reviewers independently?	Partially	Appendix D, section D.1.2.3 *"Data were extracted by one researcher and checked for accuracy by an independent researcher."*
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Appendix D, section D.1.2.4 *"Quality and risk of bias assessment was performed in a double-blind manner on the included full publications using one of the following tools depending on the study design:* *• Cochrane risk-of-bias (ROB) 2 tool for RCT studies* *• Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized interventional studies and single-arm studies* *•Newcastle-Ottawa Scale (NOS) series for all non-interventional clinical evidence".*

Review process EAG	EAG response	Comments
Was the risk of bias assessment conducted by two or more reviewers independently?	Probably yes	Appendix D, section D.1.2.4 *"Quality and risk of bias assessment was performed in a double-blind manner on the included full publications …"*
Was identified evidence synthesised using appropriate methods?		The network meta-analysis method used by the Company is consistent with NICE recommendations and what has been used in earlier appraisals.

The EAG conducted a quality assessment of the methods used by the company for the SLR of clinical evidence based on the Centre for Reviews and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic literature review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies that address the review question?	Yes
2. Is there evidence of a substantial effort to search for all relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

The key clinical effectiveness evidence is presented in Document B, Section B.2 of the CS. The company's main clinical evidence for acalabrutinib is obtained from the ECHO study (NCT number 2023-505707-23-00). ECHO is an ongoing, Phase 3, randomised, double-blind, placebo-controlled multicentre study, evaluating the combination of acalabrutinib + BR (ABR) versus placebo + BR (PBR) in patients

aged 65 years or older and with previously untreated MCL. *The EAG has no major concerns about the design and conduct of this trial.*

The participant flow in the ECHO study is presented in Appendix D, Section D.2, Figure 3 of the CS. An overview of the study is presented in Document B, Table 3 of the CS and reproduced as Table 6.

The ECHO study was conducted in 189 study centres in 26 countries. ECHO's target population is more specific than that of the company's decision problem for population, defined as adults with previously untreated MCL who are considered unsuitable candidates for ASCT, and includes only those who are ≥65 years of age.

A total of 635 patients were randomised in a 1:1 ratio into two arms to receive either:

- Arm 1: Acalabrutinib + six cycles of BR (ABR)
- Arm 2: Matching placebo + six cycles of BR (PBR)

Patients received acalabrutinib (100 mg twice daily orally) or matching placebo until progressed disease (PD) or unacceptable toxicity. The BR component in both the ABR and PBR regimens was administered for a fixed duration (i.e. for a maximum of 6 cycles) (each treatment cycle was 28 days). After this point, patients who achieved complete or partial response (CR or PR) received up to 12 doses of maintenance rituximab once every 8 weeks (every two cycles). Thereafter, patients continued to receive acalabrutinib monotherapy or placebo until PD or unacceptable toxicity.

Table 6 Characteristics of the ECHO study [Reproduced from Document B, Table 3, Section B.2.2 of the CS]

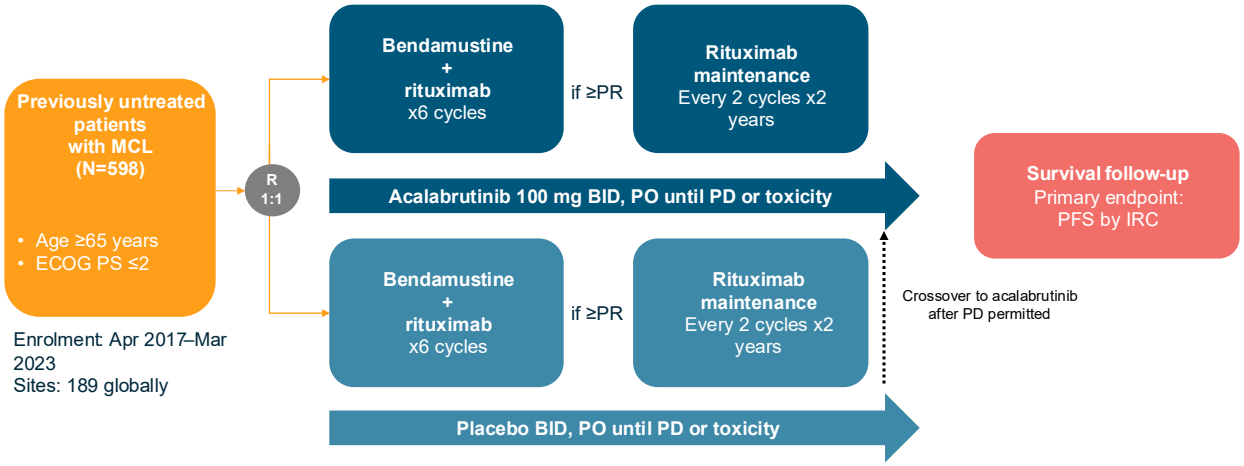
Study design	Phase 3, randomised, double-blind, placebo-controlled, multi-centre study Interim analysis DCO: 15th February 2024 Final analysis planned when approximately 268 IRC-assessed PFS events have been observed
Population	Adults with previously untreated MCL
Intervention(s)	Acalabrutinib in combination with bendamustine and rituximab
Comparator(s)	Placebo in combination with bendamustine and rituximab
Indicate if study supports application for MA	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	**PFS**, **OS**, response rates (ORR, DOR, TTR), **AEs of treatment**, **HRQoL**

Abbreviations: AE, adverse event; DCO, data cut-off; DOR, duration of response; HRQoL, health-related quality of life; IRC, Independent Review Committee; MCL, mantle cell lymphoma; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTR, time to response.

Patients randomised to the PBR arm who had PD assessed by the investigator and confirmed by an unblinded non-study team physician were permitted to cross over to receive acalabrutinib monotherapy until PD or unacceptable toxicity. In the PBR arm, 17% (n = 51/299) crossed over to acalabrutinib monotherapy during the study after experiencing PD.

A total of [redacted] patients in the ABR arm and [redacted] patients in the PBR arm received at least one subsequent anti-MCL therapy. Among these patients, [redacted] in the ABR arm and [redacted] in the PBR arm received a Bruton tyrosine kinase inhibitor (BTKi) type of subsequent anti-MCL treatment. This includes acalabrutinib for the 51 patients in the PBR arm crossed over to acalabrutinib monotherapy (counted as subsequent anti-MCL therapy) after experiencing PD. An

overview of the trial design is presented in Figure 3 of the CS and reproduced as Figure 3 below.



Abbreviations: BID, twice daily; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; MCL, mantle cell lymphoma; PD, progressed disease; PFS, progression-free survival; PO, orally; PR, partial response; PS, performance status.

Figure 3 ECHO trial design [Reproduced from Figure 3, Section B.2.3.4, Document B of the CS]

Summaries of the baseline participant and disease characteristics of the ECHO trial are presented in Table 8 of the CS and reproduced as Table 7 below. The baseline characteristics of participants are broadly similar between the study treatment groups. Across groups, most participants were males (n = 423; 70.7%), aged 70 years or older (n = 358; 59.9%), and had Ann Arbor Stage IV disease (n = 514; 86.0%). According to the simplified Mantle Cell Lymphoma International Prognostic Index (MIPI), the majority were in either intermediate (n = 253; 42.3%) or high (n = 145; 24.2%) risk groups. The company provided information regarding the presence of TP53 mutation/deletion in response to clarification queries and reported that known TP53 mutation at baseline was broadly similar between the ABR and PBR groups (299 in each group) with 7.4% and 9.7% of patients, respectively. *The EAG clinical advisor is of the opinion that the participants in the ECHO study are broadly representative of patients with MCL seen in NHS clinical practice.*

The CS describes that quality and risk of bias assessment for RCT studies was undertaken using the revised Cochrane risk-of-bias (ROB2) tool (Appendix D,

Section D.1.2.4). EAG notes that the company's quality assessment of the ECHO study presented in Table 14 of the CS (Section B.2.5) was in fact performed in line with guidance from the University of York Centre for Review and Dissemination (CRD).[15] *The EAG generally agrees with the company's quality assessment of the ECHO study and regards them as being of good methodological quality.*

Table 7 Demographics of participants in ECHO (FAS) [Reproduced from Table 8, Section B.2.3.7, Document B of the CS]

	ABR (N=299)	**PBR (N=299)**	**Total (N=598)**
Age, years			
Mean (SD)	71.6 (4.73)	71.6 (4.60)	71.6 (4.66)
Median	71.0	71.0	71.0
Min, max	65, 85	65, 86	65, 86
Age group, n (%)			
65–<70	123 (41.1)	117 (39.1)	240 (40.1)
≥70	176 (58.9)	182 (60.9)	358 (59.9)
65–<75	215 (71.9)	222 (74.2)	437 (73.1)
≥75	84 (28.1)	77 (25.8)	161 (26.9)
Sex, n (%)			
Male	214 (71.6)	209 (69.9)	423 (70.7)
Female	85 (28.4)	90 (30.1)	175 (29.3)
Race, n (%)			
White	233 (77.9)	235 (78.6)	468 (78.3)
Asian	44 (14.7)	49 (16.4)	93 (15.6)
American Indian or Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)
Black or African American	1 (0.3)	2 (0.7)	3 (0.5)
Multiple	5 (1.7)	0	5 (0.8)
Not reported	14 (4.7)	11 (3.7)	25 (4.2)
Ethnicity, n (%)			
Hispanic or Latino	34 (11.4)	33 (11.0)	67 (11.2)
Not Hispanic or Latino	245 (81.9)	252 (84.3)	497 (83.1)
Not reported	20 (6.7)	14 (4.7)	34 (5.7)
BMI, kg/m^2			

	ABR (N=299)	PBR (N=299)	Total (N=598)
Mean (SD)	27.05 (4.70)	27.01 (4.73)	27.03 (4.71)
Median	26.40	26.30	26.35
Min, max	16.2, 44.8	14.9, 41.8	14.9, 44.8
ECOG performance status, n (%)			
0	156 (52.2)	140 (46.8)	296 (49.5)
1	129 (43.1)	132 (44.1)	261 (43.6)
2	12 (4.0)	23 (7.7)	35 (5.9)
3	0 (0.0)	2 (0.7)	2 (0.3)
Missing	2 (0.7)	2 (0.7)	4 (0.7)
Tumour bulk,† n (%)			
<5 cm	187 (62.5)	186 (62.2)	373 (62.4)
≥5 cm and <10 cm	92 (30.8)	92 (30.8)	184 (30.8)
≥10 cm	20 (6.7)	21 (7.0)	41 (6.9)
Ann Arbor staging for lymphoma, n (%)			
I	2 (0.7)	1 (0.3)	3 (0.5)
II	15 (5.0)	11 (3.7)	26 (4.3)
III	31 (10.4)	24 (8.0)	55 (9.2)
IV	251 (83.9)	263 (88.0)	514 (86.0)
Patients with extranodal disease, n (%)			
1 site	155 (51.8)	155 (51.8)	310 (51.8)
2 or more sites	109 (36.5)	122 (40.8)	231 (38.6)
Simplified MIPI score, n (%)			
Low risk, i.e. 0–3	99 (33.1)	101 (33.8)	200 (33.4)
Intermediate risk, i.e. 4–5	128 (42.8)	125 (41.8)	253 (42.3)
High risk, i.e. 6–11	72 (24.1)	73 (24.4)	145 (24.2)
Time from diagnosis to randomisation, months			
Mean (SD)	3.91 (10.10)	4.27 (12.46)	4.09 (11.34)
Median	1.68	1.54	1.64
Min, max	0.0, 116.4	0.1, 142.4	0.0, 142.4

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; MIPI, Mantle Cell Lymphoma International Prognostic Index; PBR, placebo, bendamustine, rituximab; PS, performance status; SD, standard deviation.

† For target lesions at baseline, investigator assessment was used. Tumour bulk was defined as the largest diameter of a nodal or extranodal lesion.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: progression free survival (PFS), overall survival (OS), response rates, adverse effects of treatment and health-related quality of life (HRQoL).

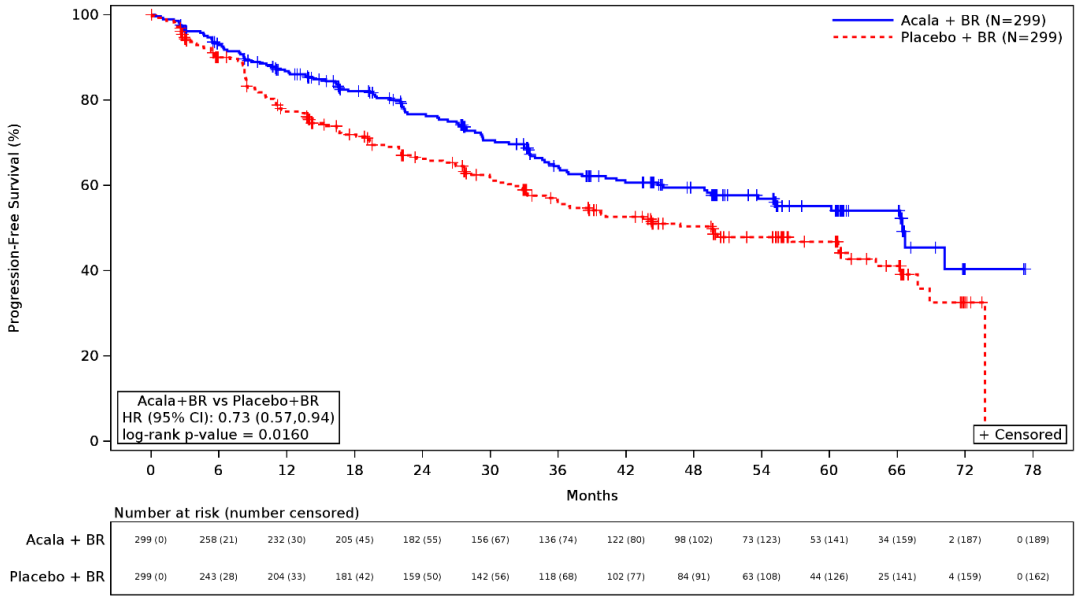
The ECHO study is ongoing and was conducted during the COVID-19 pandemic. The results of the interim analysis were based on the data cut-off date (DCO) of 15th February 2024. A final analysis is planned to occur when approximately 268 IRC-assessed PFS events (~49% data maturity) have been observed. Of the 635 patients randomised in the study, 598 were available in the full-analysis set (FAS) population (299 in the ABR arm and 299 in the PBR arm).

Primary endpoints: PFS

PFS assessed by the Independent Review Committee (IRC) was the primary endpoint of the ECHO study. With a median follow-up of 46.1 months in the ABR arm and 44.4 in the PBR arm, PFS by IRC was statistically significantly improved for ABR compared with PBR (median 66.4 months [95% CI: 55.1, not estimable [NE]] vs. 49.6 months [95% CI: 36.0, 64.1]; stratified HR 0.73 [95% CI: 0.57, 0.94]; p=0.0160) (Figure 4).

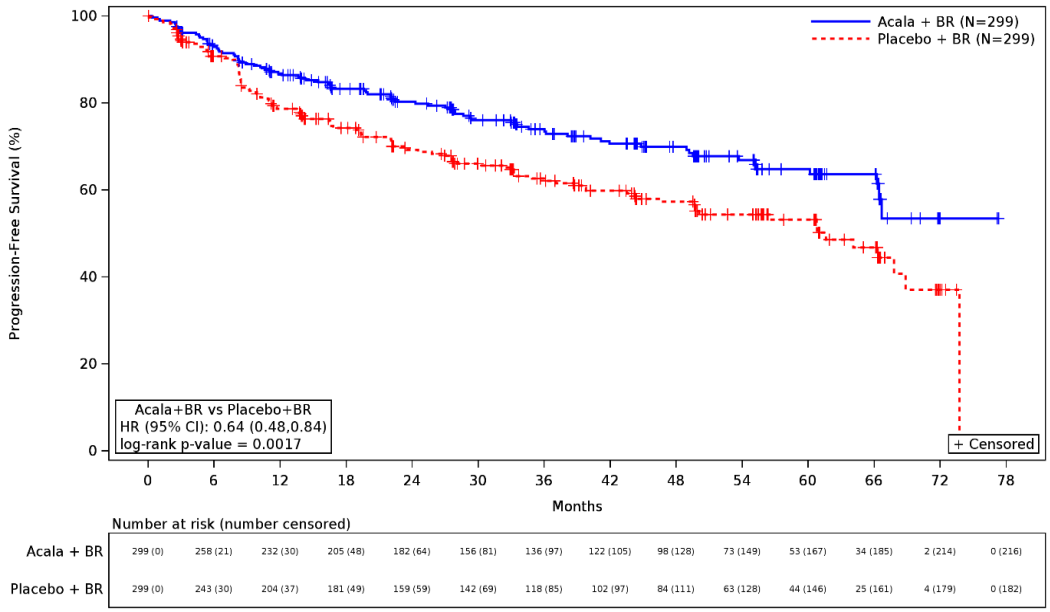
[redacted] (median [redacted] months [95% CI: [redacted]] vs. [redacted] months [95% CI: [redacted]]).

Confirmed or suspected COVID-19 deaths were included as PFS events, including those who did not experience PD prior to death. When patients with death related to COVID-19 and without PD prior to death were censored, ABR remained associated with PFS benefit compared with PBR (median PFS NE [95% CI: 66.4, NE] vs. 61.6 months [49.6, 68.9]; stratified HR 0.64 [95% CI: 0.48, 0.84], p = 0.0017) (Figure 5).



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; PFS, progression-free survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

Figure 4 KM plot for PFS by IRC assessment (FAS) [Reproduced from Figure 4, Section B.2.6.1, Document B of the CS]



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; PFS, progression-free survival.
HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

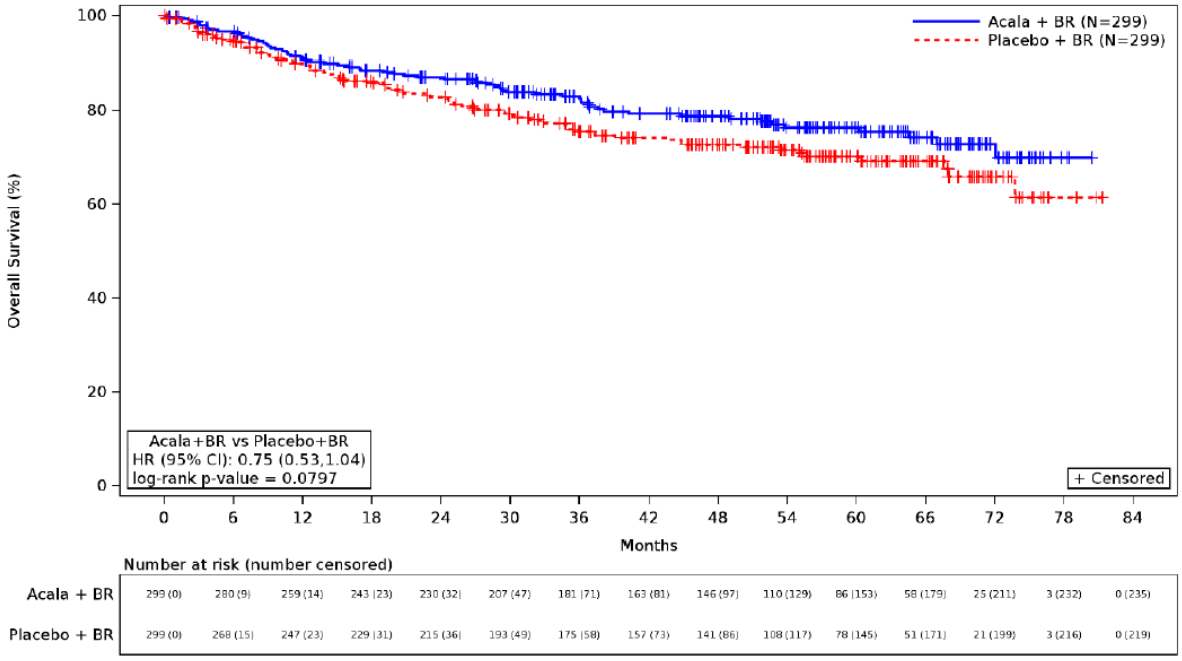
Figure 5 KM plot for PFS by IRC assessment (FAS: censoring confirmed /suspected COVID-19 death) [Reproduced from Figure 5, Section B.2.1.1.1, Document B of the CS]

Secondary endpoints: OS

With an OS maturity rate of 34% (203/598 target events), OS was numerically greater among patients receiving ABR compared with PBR (HR 0.86, 95% CI: 0.65, 1.13; p=0.2743), this difference not reaching statistical significance. The PBR arm included 51/299 (17%) of participants who crossed over to acalabrutinib monotherapy. Death events occurred in 97 cases (32.4%) in patients receiving ABR compared with 106 (35.5%) cases in patients receiving PBR. Median OS was not reached in either group.

[redacted]. In the ABR arm, [redacted], while the corresponding numbers in the PBR arm were [redacted] When patients known to have died of

COVID-19 were censored at their COVID19 death date, a treatment effect in favour of the ABR group became numerically greater with the HR of 0.75 (95% CI: 0.53, 1.04; p=0.0797) (Figure 6) relative to the HR of 0.86 in the FAS population.



Abbreviations: acala, acalabrutinib; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IXRS, interactive voice/web response system; KM, Kaplan–Meier. HR (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors as recorded in IXRS. P-value is based on stratified log-rank test, stratified by randomisation stratification factors as recorded in IXRS.

Figure 6 KM plot for (FAS: censoring confirmed/suspected COVID-19 death) [Reproduced from Figure 7, Section B.2.6.2.1.1, Document B of the CS]

Secondary endpoints: Response rate

- Overall response rate (ORR): The proportion of patients with an overall response (complete response [CR] and partial response [PR]) by IRC assessment was similar in the ABR and PBR groups (91.0% [95% CI: 87.3, 93.8] versus 88.0% [95% CI; 83.9, 91.3]).
- Duration of response (DOR): The median DOR by IRC assessment showed more durable remissions among patients in the ABR group compared with the PBR group (63.5 months [95% CI: 52.5, NE] versus 53.8 months [95% CI: 37.6, 66.1]).

- Time to response (TTR): Median time to CR and PR by IRC assessment was [redacted]).

A summary of ECHO primary and secondary outcomes is presented in Table 8 below.

HRQoL

The company reported that the patient-reported outcome (PRO) data demonstrated [redacted] No numerical data for QoL were reported in the CS.

- Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym), EQ-5D-5L and EORTC QLQ-C30 were [redacted]
- EQ-5D-5L VAS scores: There was [redacted]
- [redacted]
- [redacted]

Table 8 Summary of the outcomes assessed in the ECHO trial [Adapted from Tables 15-20, Document B of the CS]

Outcome	ABR (n = 299)	PBR (n = 299)
Primary outcome: PFS by IRC assessment		
Events, n (%)	110 (36.8)	137 (45.8)
Censored, n (%)	[redacted]	[redacted]
Median PFS (95% CI), months	66.4 (55.1, NE)	49.6 (36.0, 64.1)
HR (95% CI), stratified analysis	0.73 (0.57, 0.94), p = 0.0160	
Primary outcome: PFS by IRC assessment censoring COVID-19 deaths		
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Median PFS (95% CI), months	NE (66.4, NE)	61.6 (49.6, 68.9)
HR (95% CI), stratified analysis	0.64 (0.48, 0.84), p = 0.0017	
Secondary outcome: OS		
Total deaths, n (%)	97 (32.4)	106 (35.5)
Censored, n (%)	202 (67.6)	193 (64.5)
Median OS (95% CI), months	NE (72.1, NE)	NE (73.8, NE)
HR (95% CI), stratified analysis	0.86 (0.65, 1.13), p = 0.2743	
Secondary outcome: OS censoring COVID-19 deaths		
HR (95% CI), stratified analysis	0.75 (95% CI: 0.53, 1.04; p=0.0797	
Other secondary outcomes		
ORR, % (95% CI)	91.0 (87.3, 93.8)	88.0 (83.9, 91.3)
DOR, median (95% CI), months	63.5 (52.5, NE)	53.8 (37.6, 66.1)
TTR of CR + PR, median, months	[redacted]	[redacted]

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; CR, complete response; DOR, duration of response; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; PR, partial response; TTR, time to response;

3.2.3 Subgroup analyses

The company reports results of the subgroup analyses in Section B.2.7, Document B of the CS. Pre-planned subgroup analyses were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between the ABR and PBR arms. These included:

- Sex
- Age category
- Race
- Geographic region
- Baseline ECOG PS
- Tumour bulk
- Ann Arbor staging for lymphoma
- Histologically documented MCL
- MCL type (classic type versus blastoid variant and pleomorphic variant versus other)
- Ki-67
- Bone marrow involvement
- Extranodal disease
- Gastrointestinal disease
- Simplified MIPI score
- Lactate dehydrogenase (LDH) > upper limit of normal (ULN)
- COVID-19 vaccine status

The results of the subgroup analyses of PFS by IRC assessment [redacted]. [redacted]. The HR of IRC-assessed PFS across subgroups ranged from [redacted] due to small number of participants in each subgroup (Figure 8, Section B.2.7.1.1 of the CS).

For OS, subgroup analyses demonstrated [redacted] (Figure 9, Section B.2.7.1.2 of the CS).

3.2.4 Adverse events

The company reports adverse event (AE) data for ABR from ECHO in Section B.2.10, Document B of the CS. The safety analysis set (SAS) consisted of all randomised patients who received at least one dose of the study drug (297 patients in each group). Median follow-up was 46.1 months in the ABR group and 44.4 months in the PBR group and median duration of exposure of acalabrutinib was [redacted] months and [redacted] months, respectively. The company presents an overall summary of treatment-emergent adverse events (TEAEs; defined as any event with an onset date on or after the first dose date of study drug or any ongoing event that worsened in severity after the first dose date of study drug and prior to 30 days after the date of the last dose of study drug or the first date starting new anti-MCL therapy) in Table 26 of the CS, reproduced as Table 9 below.

Most participants experienced at least one TEAE (99.7% in the ABR group, 99.0% in the PBR group). Grade ≥3 TEAEs were reported in 88.9% and 88.2% of patients in the ABR and PBR arms, respectively, and Grade 5 TEAEs occurred in 12.1% and 10.1% of patients. Treatment-emergent serious adverse events (SAE) were experienced by 69.0% of the ABR group and 62.0% of the PBR group. Exposure-adjusted TEAEs are reported in Table 27, Document B of the CS. Exposure-adjusted event rates of any grade TEAE were 753.80 vs 719.61 per 100 patient-years of exposure, respectively.

Treatment-related TEAEs of any grade were experienced in 94.6% of the ABR group and 92.3% of the PBR group. Those of Grade ≥3 were experienced by 75.1% and 74.1%, respectively. Treatment-related TEAEs experienced in at least 10% of participants in either group are reported in Table 29, Document B of the CS. The majority of treatment-related TEAEs were experienced by a greater proportion of the ABR group as compared to the PBR group, the most notable differences being headache (22.6% of ABR vs 6.7% of PBR group), vomiting (19.5% vs 8.4%) and rash maculo-papular (11.1% vs 3.0%). In contrast, infusion-related reaction was experienced by 13.8% of the ABR group and 21.9% of the PBR group and neutropenia was experienced by a slightly larger proportion of the PBR group (40.1%) than the ABR group (38.7%).

Table 9 Overall summary of TEAEs (SAS) [reproduced from Table 26, Section B.2.10.1.1, Document B of the CS]

	ABR (N=297)	**PBR (N=297)**
TEAE, n (%)		
Any grade	296 (99.7)	294 (99.0)
Grade ≥3	264 (88.9)	262 (88.2)
Grade 5 (fatal)	36 (12.1)	30 (10.1)
Treatment-emergent SAE, n (%)		
Any grade	205 (69.0)	184 (62.0)
Grade ≥3	191 (64.3)	166 (55.9)
Grade 5 (fatal)	36 (12.1)	30 (10.1)
Treatment-related TEAE, n (%)		
Any study drug	281 (94.6)	274 (92.3)
Acalabrutinib/placebo only	202 (68.0)	165 (55.6)
Bendamustine only	139 (46.8)	111 (37.4)
Rituximab only	106 (35.7)	118 (39.7)
TEAE leading to dose reduction, n (%)		
Any study drug	94 (31.6)	77 (25.9)
Acalabrutinib/placebo only	30 (10.1)	25 (8.4)
Bendamustine only	77 (25.9)	60 (20.2)
TEAE leading to study drug discontinuation, n (%)		
Any study drug	150 (50.5)	105 (35.4)
Acalabrutinib/placebo only	127 (42.8)	92 (31.0)
Bendamustine only	46 (15.5)	35 (11.8)
Rituximab only	60 (20.2)	60 (20.2)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; MedDRA, Medical Dictionary for Regulatory Activities; PBR, placebo, bendamustine, rituximab; SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event.
MedDRA version 26.1.
A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity.

Table 59, Appendix M of the CS reports treatment-emergent SAEs, which were experienced by 69.0% of participants in the ABR group and 62.0% of the PBR group. Grade ≥3 treatment-emergent SAEs occurred in 64.3% and 55.9%, respectively, and grade≥5 in 12.1% and 10.1%, respectively. The most reported treatment-emergent

SAEs of any grade in the ABR and PBR groups were COVID-19 pneumonia (13.8% and 11.4%), pneumonia (9.4% and 7.1%), COVID-19 (8.8% and 6.4%) and pyrexia (5.7% and 5.1%). The most frequently reported SAEs of Grade 3-4 were COVID-19 pneumonia (8.1% and 6.7%), pneumonia (7.1% and 6.1%) and COVID-19 (5.1% and 4.0%). Grade 5 SAEs with an outcome of death in at least one patient included COVID-19 pneumonia (5.1% and 3.4%), pneumonia (1.0% and 0), COVID-19 (2.7% and 2.0%), sepsis (0.3% and 0.7%) and pulmonary embolism (0 and 0.7%).

Treatment-related treatment-emergent SAEs are reported in Table 60, Appendix M of the CS and were experienced by 38.4% and 33.3% of the ABR and PBR groups, respectively. Grade 3-4 events were reported in 31.6% and 26.3%, respectively, and Grade 5 events by 3.4% and 2.0%, respectively.

TEAEs leading to discontinuation are reported in Table 61, Appendix M of the CS. The proportion of patients with at least one TEAE leading to discontinuation of acalabrutinib or placebo was 42.8% in the ABR group and 31.0% in the PBR group. COVID-19 (4.7% vs 3.0%), COVID-19 pneumonia (4.4% vs 2.7%) and neutropenia (4.0% vs 3.4%) were the most frequently reported. TEAEs of Grade 3-4 leading to discontinuation of study drug were experienced by 24.6% and 16.5%, respectively, and those of Grade 5 by 6.1% and 5.7%, respectively.

The EAG's clinical advisor considered major bleeding and atrial fibrillation to be further important safety endpoints in this population. Relevant treatment-emergent adverse event (TEAE) data are provided in Table 62 of Appendix M.3.3.2 in the CS. Cardiac events of any grade occurred in 23.9% of participants in the ABR arm and 18.5% in the PBR arm, including atrial fibrillation in 6.7% and 4.4% of participants, respectively. Among these, 4.0% in the ABR arm and 1.7% in the PBR arm experienced Grade ≥3 atrial fibrillation. Haemorrhage was reported in 28.3% of participants in the ABR arm and 17.2% in the PBR arm. Major haemorrhage occurred in 2.4% and 5.4% of participants, respectively, with 2.0% and 3.4% being Grade ≥3. Additional TEAEs of clinical interest are detailed in Table 62 of Appendix M.3.3.2.

Overall, the EAG clinical expert is of the opinion that the safety profile is consistent with that expected from the use of ABR in this population and has no concerns.

3.2.5 Meta-analyses

As ECHO is the only study identified by the company as relevant to address the decision problem of this appraisal, no meta-analyses were performed.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company employed indirect treatment comparison (ITC) methods to estimate the relative efficacy of ABR, BR and R-CHOP for the treatment of people with previously untreated MCL who are unsuitable for ASCT, given that no head-to-head RCTs between ABR and R-CHOP were identified. The outcomes of interest for the ITC were PFS and OS. The company identified three studies, ECHO, BRIGHT (Flinn et al. 2019)[16] and StiLNHL1 (Rummel et al. 2013),[17] as eligible for the ITC.

An overview of the study design and conduct for the three studies included in the ITC is reproduced in Table 10 below. Appendix D of the CS highlighted notable heterogeneity across these studies in study design, population inclusion criteria, and the treatments administered across studies. These include:

- Study design: ECHO was a double-blind RCT, while BRIGHT and Stil NHL1 were open-label RCTs. ECHO was the only study which was conducted during the COVID-19 pandemic.
- Population inclusion criteria
    - Age: ECHO participants are limited to patients who were aged ≥65 years or older, while BRIGHT and Stil NHL1 included younger patients aged 18 years and above.
    - Disease status: ECHO enrolled patients with MCL (n = 598), while BRIGHT (n = 514) and Stil NHL1 (n = 447) included a mixed cohort of patients with MCL and indolent lymphoma. For BRIGHT and Stil NHL1, the ITC was based on the MCL subgroup results (n = 74 and 94, respectively).
- Treatment administration:
    - Rituximab maintenance: The use of rituximab maintenance after induction therapy varied across studies, ranging from 77.4 to 82.5% in ECHO, 13.5% in BRIGHT (MCL subgroup) and 0% in StiL NHL1.

The studies in the ITC network were not differentiated based on rituximab maintenance use.

- Choice of control arm therapy: There was difference in the control arms included in the BRIGHT and StiL NHL1 studies. BRIGHT evaluated the efficacy and safety of BR compared with treatment of physician choice of R-CHOP or R-CVP, whereas StiL NHL1 assessed BR compared with R-CHOP. For the BRIGHT study, the treatment effect for BR versus R-CHOP in the ITC was based on the MCL subgroup results for BR versus R-CHOP/R-CVP.

Baseline participant and disease characteristics of ECHO, BRIGHT and StiL NHL1 are presented in Table 11 below. Only a limited description of the characteristics of the MCL subgroups in BRIGHT and StiL NHL1 was available. The median baseline age of patients with MCL was similar across all three studies (67, 70, and 71 years for BRIGHT, StiL NHL1 and ECHO, respectively), although age ranges, and particularly the lower bound of age, in the MCL subgroups of BRIGHT and StiL NHL1, were not available. There was a lower proportion of patients with stage IV disease in BRIGHT compared with ECHO (76% versus 86%). The majority of participants were in either intermediate (42%) or high (24%) MIPI risk groups in ECHO, and low-intermediate (26%) and high-intermediate (42%) IPI risk groups in BRIGHT, although it is unclear if this denotes a difference in baseline risk between the studies. In the StiL NHL1 study, there is no additional baseline characteristic for the MCL subgroup beyond age.

Table 10 Study design and methods for studies included in the ITC [Adapted from Table 14, Appendix D of the CS]

Study ID		ECHO[18]		BRIGHT (Flinn 2019)[16]		StiL NHL1 (Rummel 2013)[17]	
Study design		Double-blind Phase 3 RCT		Open-label Phase 3 RCT		Open-label Phase 3 RCT	
Country		North America & Western Europe		North America & Western Europe		Germany	
Years of conduct	Start	2017		2009		2003	
	Finish	Ongoing		2012		2008	
DCO		15th February 2024		15th December 2016		31st October 2011	
Treatment arm		ABR (+ R)	PBR (+ R)	BR (+ R)	R-CHOP/ R-CVP (+ R)	BR	R-CHOP
Sample size		299	299	261	253	224	223
MCL sample size		299	299	37	37	46	48
R maintenance use (MCL group)		82.50%	77.40%	13.50%	13.50%	0%	0%
Median (range) follow up, months		46.1 (0.03–80)	44.4 (0.03–81)	65 (1.9–70.9		45 (IQR: 25–57	
Eligibility criteria		• Age ≥65 • ECOG ≤2		• Age ≥18 • ECOG ≤2 • Stage II–IV		• Age ≥18 • WHO ≤2 • Stage III–IV	
PFS		✓		✓		✓	
OS		✓		✓		✗	

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ITC, indirect treatment comparison; MIPI, Mantle Cell Lymphoma International Prognostic Index; PBR, placebo, bendamustine, rituximab; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RCT, randomised controlled trial; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; WHO, World Health Organization.

Table 11 Baseline characteristics from studies included in the ITC
[Reproduced from Table 15, Appendix D of the CS]

	ECHO[18]	BRIGHT (Flinn 2019)[16]	StiL NHL1 (Rummel 2013)[17]
Sample size (arms combined)	598	74†	94†
Median age (years)	71 (range: 65–86)	67	70 (IQR: 64.5, 74)
Male sex (%)	71	83.8	NR
Ann Arbor disease stage (%)			
I	1	0	NR
II	4	5	NR
III	9	19	NR
IV	86	76	NR
ECOG PS ≥2 (%)	6	NR	NR
MIPI (%)			
Low-risk	33	NR	NR
Intermediate-risk	42	NR	NR
High-risk	24	NR	NR
IPI (%)			
Low-risk	NR	19	NR
Low-intermediate risk	NR	26	NR
High-intermediate risk	NR	42	NR
High risk	NR	13	NR

†Subgroup of study population.
Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine, rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; IQR, interquartile range; ITC, indirect treatment comparison; MIPI; Mantle Cell Lymphoma International Prognostic Index; NR, not reported; R, rituximab; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, Rituximab, cyclophosphamide, vincristine, prednisolone

The treatment effect estimates for PFS and OS from the three Phase 3 RCTs included in the ITC are reproduced in Table 12 and Table 13, respectively (Table 16 and Table 17, Appendix D of the CS).

Table 12 Summary of data used in the ITC for PFS [Reproduced from Table 16, Appendix D of the CS]

Study	Treatment	n	PFS	
			Number of events	HR (95% CI)
ECHO FAS[18]	ABR	299	110	0.73 (0.57, 0.94)
	BR	299	137	-
ECHO COVID-censored analysis[18]	ABR	299	83	0.64 (0.48, 0.84)
	BR	299	117	-
BRIGHT (Flinn 2019)[16]	BR	37	NR	0.40 (0.21, 0.75)
	R-CHOP/ R-CVP	37	NR	-
StiL NHL (Rummel 2013)[17]	BR	46	NR	0.49 (0.28, 0.79)
	R-CHOP	48	NR	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; ITC, indirect treatment comparison; NR, not reported; OS, overall survival; PFS, progression free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone.

Table 13 Summary of data used in the ITC for OS [Reproduced from Table 17, Appendix D of the CS]

Study	Treatment	n	OS	
			Number of events	HR (95% CI)
ECHO FAS[18]	ABR	297	97	0.86 (0.65, 1.13)
	BR	297	106	-
ECHO COVID-censored analysis[18]	ABR	297	64	0.75 (0.53, 1.04)
	BR	297	80	-
BRIGHT (Flinn 2019)[16]	BR	37	-	0.86 (0.40, 1.83)
	R-CHOP/R-CVP	37	-	-

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; ITC, indirect treatment comparison; NE, not estimable; OS, overall survival; PFS, progression free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The EAG is happy with the methods used in the indirect comparison. The company's submission provides a thorough description of how the data used was obtained in terms of selecting subgroups and acknowledges the limitations due to study heterogeneity and small sample sizes. While it reduces the sample size, the EAG agrees with the company's decision to select the MCL subgroup of the BRIGHT and StiL NHL1 studies.

The EAG's clinical expert is of the view that COVID-19 deaths should not be censored for either PFS or OS and would therefore favour the results in Tables 22 and 24 of Section B.2.9.2.1 and B.2.9.2.2, respectively. The EAG agrees that a fixed effects analysis is the only appropriate method for overall survival and is happy that the random effects sensitivity analysis is consistent with the fixed effects estimates used in the economic modelling. The ITC of BR and R-CHOP for PFS are [redacted] and [redacted] for fixed and random effects respectively showing consistent results. The EAG performed a series of simple ITC using the Bucher method and is happy that these results are consistent with the results of the NMA used by the company.

3.5 Additional work on clinical effectiveness undertaken by the EAG

At clarification, the EAG requested a post-hoc analysis of the effect of treatment crossover from PBR to ABR on OS in the ECHO study. The EAG has reviewed the RPSFT analysis conducted by the company and is happy with both the methodology used and the level of detail provided. The EAG has also examined the analysis of the PH assumption presented in the company's submission and clarification response. They believe a consistent approach should have been applied in the economic modelling - either using NMA-derived hazard ratios for both R-CHOP and ABR or employing parametric curves for all treatments. Instead, a mixed approach was used, applying a parametric curve for ABR and the NMA hazard ratio for R-CHOP.

While the EAG acknowledges that the Schoenfeld residual test may be underpowered to reject the null hypothesis of PH, it considers the test results reliable given the ECHO trial's sample size of 299 participants per group.

3.6 Conclusions of the clinical effectiveness section

The EAG agrees that the analysis presented by the company indicates ABR is more effective than both BR alone and R-CHOP, subject to the assumptions made regarding data selection. The EAG is satisfied with the level of detail provided in this section.

The review of subgroup analyses from the ECHO study does not suggest that any subgroups significantly modify the treatment effect, with differences observed only in small subgroups. The EAG also agrees with the company's conclusion that the BRIGHT study's subgroup analysis suggests that there is no modification of the treatment effect from rituximab maintenance therapy. Moreover, the EAG is satisfied with the safety data presented and in agreement with the company's recognition of the higher rates of SAEs and TEAEs in the ABR group of the ECHO study.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

The company outlined the methods and results of their systematic literature review of cost-effectiveness studies in section B.3.2, page 80 of the CS Document B (more detail is provided in appendix G of the CS). Their review aimed to identify economic evaluations of interventions for patients with previously untreated MCL, who are ineligible for stem cell transplant, health state utility values of patients with previously untreated MCL ineligible for stem cell transplant, and evidence of the cost and HCRU associated with MCL (including caregivers and indirect costs). The inclusion and exclusion criteria are presented within table 34, page 62 of appendix G. Only English language reports were included, and those published within the last 10 years (i.e., include those published from 2014).

The search strategies appear comprehensive, and an appropriate range of databases were included (Embase, MEDLINE and Cochrane Library). Efforts were also made to search relevant conference proceedings (EMBASE, including those indexed from 2021) and grey literature using the keywords 'mantle cell lymphoma'.

The literature searches identified 4 publications and 1 conference abstract for inclusion, of which only 1 publication (Van Keep et al. 2016) included an economic evaluation.[19] Grey literature searches identified 2 reports by NICE (TA370)[20] and the SMC (No. 1075/15)[21] which include an economic evaluation. Due to the paucity published economic evaluations, the company expanded the search to include all prior NICE submissions in MCL, and previously untreated chronic lymphocytic leukaemia (CLL) indexed between 2015 and January 2024. The additional search identified 10 NICE appraisals: 3 in Mantle Cell Lymphoma (TA502, TA370 (already identified in grey literature search) & TA677)[20, 22, 23] and 7 in CLL (TA891, TA663, TA119, TA931, TA796, TA689 & TA429).[24-30] The included studies are summarised in Table 30 (page 82) of the CS Document B. Table 30 comprises of the 5 identified economic evaluations for Mantle Cell Lymphoma. A summary of the 7 NICE appraisals identified for CLL is provided in table 39, page 75 Appendix G of the CS.

None of the identified studies compared ABR with BR and R-CHOP in this indication. Furthermore, when considering all the identified studies (including those in CLL) the company noted a lack of consensus in modelling approach (Partitioned survival versus Markov). Therefore, the company chose to develop a de novo Partitioned survival model based on the literature searches.

The EAG are satisfied that the company's systematic literature review methodology is appropriate. The EAG notes that five of the six studies identified in MCL used a Markov state transition modelling approach. The company's argument that there is a lack of consensus in modelling approach (i.e. whether to use partitioned survival or markov state transition models) relates to the fact that most CLL NICE STAs utilise a partitioned survival approach. The inclusion of CLL NICE STAs in the literature search is based upon the assertion that CLL and MCL have similar disease characteristics. The EAG is not confident that CLL can be considered a proxy to MCL. Clinical advice to the EAG suggests that CLL is a less aggressive disease and patients typically present asymptomatically. Finally, only one study in MCL did not use a Markov modelling approach (TA677), and this was for an appraisal of MCL treatment at third line.[23] The EAG are of the view that partitioned survival models are more appropriate towards the end of treatment pathways where it is not necessary to model multiple subsequent treatment lines, as was the case in TA677. The EAG are of the view that the company's systematic literature review supports the use of a Markov state transition model, rather than a partitioned survival model for this appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 14 summarises the EAG's assessment of the company submission against key components of the NICE reference case.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on the company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Company submission aligns with the NICE reference case.
Perspective on costs	NHS and PSS	Company submission aligns with the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Company submission mostly aligns with the reference case. Base case deterministic and probabilistic analyses are reported as both pairwise comparisons and fully incremental analyses. For scenario analyses results are reported for ABR vs. BR and ABR vs. R-CHOP. However, in most cases R-CHOP is dominated by BR, therefore the EAG are satisfied that the results presented are sufficient to inform decision making.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Company submission aligns with the NICE reference case. A lifetime horizon is used.
Synthesis of evidence on health effects	Based on systematic review	Company submission aligns with the NICE reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Company submission is consistent with the NICE reference case. The progression free HSUV is equivalent to general population utility throughout the model time horizon. The post-progression HSUV is calculated by applying a multiplier to the progression free HSUV (general population utility) using EQ-5D utility data from the ECHO trial and HSUVs from TA502 (R/R MCL).[22] The EQ-5D utilities from TA502 align with the reference case. Adverse event disutilities and durations are sourced from TA370[20] and TA931.[27] These sources align with the reference case.
Source of data for measurement of	Reported directly by patients and/or carers	Company submission aligns with the NICE reference case. All HSUVs are patient reported.

Element of health technology assessment	Reference case	EAG comment on the company's submission
health-related quality of life		
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Company submission aligns with the NICE reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Company submission aligns with the 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	Company submission aligns with the NICE reference case. Confidential prices for comparators and subsequent treatments are provided in a confidential appendix to this report.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Company submission aligns with the NICE reference case.

Key: ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; EQ-5D, standardised instrument for use as a measure of health outcome; HSUV, health state utility values; PSS, personal social services; QALYs, quality-adjusted life years; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone.

4.2.2 Model structure

Section 3.3.2, Figure 12 of the company submission describes the company preferred partitioned survival model structure. The model has three mutually exclusive health states (progression-free, progressed disease and death). The cohort enter the progression free state, where they receive 1L MCL treatment. The proportion of the cohort in the progression free and death states in each model cycle was derived from parametric survival curves fitted independently to each arm of the ECHO study for ABR and BR. Progression free and death health state occupancy for R-CHOP was obtained by applying HRs from the ITC vs. BR. As per standard practice for PartSA

models, occupancy in the progressed disease health state was calculated as the difference between OS and PFS for each model cycle. Within the progressed disease state, the company have included costs of subsequent 2nd and 3rd treatment lines, with proportions requiring treatment post progression derived from the ECHO study and the distribution of treatments obtained from clinical expert opinion. A key driver of the company's value case is the reduction in subsequent treatment need post progression in the ABR arm compared to BR and R-CHOP arms of the model.

The EAG's clinical expert is concerned that data from the ECHO study showing differences in the proportion of patients requiring post-progression treatment may not be reflective of clinical practice in the UK, but rather that ABR might be expected to delay rather than remove the need for subsequent treatments. These specific concerns are discussed further in Section 4.2.8. Assuming however that there could, in theory, be a potential reduction in the need for subsequent treatment in the ABR arm, the EAG are concerned that the partitioned survival model structure creates a bias in favour of ABR. That is because the model implicitly includes all subsequent treatment costs but ignores PFS benefits and underestimates OS benefits of those treatments. The EAG's specific concerns are:

<u>There are assumed to be no PFS benefits of subsequent, post-progression treatments</u>
The model generates a bias in favour of ABR by predicting reductions in subsequent treatment costs without modelling any subsequent treatment PFS benefit. Given that the model predicts greater need for these treatments in the BR arm, ignoring the related incremental PFS benefit at 2nd or 3rd line creates a bias in favour of ABR as incremental QALY gains from greater use of successful subsequent treatments are ignored. For example, ibrutinib is only included as a 2nd line treatment in the BR arm of the model. The EAG's clinical expert considers this assumption plausible given that patients would be unlikely to receive ibrutinib following progression on ABR given that both acalabrutinib and ibrutinib are BTK inhibitors and the marginal benefit of one over the other would be minimal. A second treatment with BTK inhibitors would only be considered if one had previously been stopped for intolerability. NICE (TA502) recommended ibrutinib for R/R MCL following at least one line of treatment noting that despite some uncertainty, ibrutinib significantly improves progression free survival.[22] Given that ibrutinib is only included as 2nd line treatment in the BR arm of

the model, and is considered to improve PFS, exclusion of those PFS benefits from the model significantly biases the ICER for ABR vs. BR downwards. Similarly, NICE (TA677) has recommended CAR-T treatment, brexucabtagene autoleucel for R/R MCL on the CDF.[23] Despite immature data leading to uncertainty surrounding the magnitude of PFS benefit, the company pointed towards a potential plateauing of PFS curves, and the committee concluded that CAR-T was likely to be clinically effective, pending further data collection on the CDF. None of these PFS benefits at 2nd or 3rd line of treatment are captured in the partSA model structure.

<u>OS benefits of subsequent treatment lines are under-estimated</u>
The model generates a bias in favour of ABR by under-estimating the OS benefits of subsequent treatment lines. The partSA model relies on OS curves extrapolated from the ECHO study data. However, these OS curves are not sufficiently mature to adequately capture the OS benefits of subsequent treatment lines included within the ECHO study. It is therefore likely that any OS benefits of ibrutinib (2nd line) or CAR-T (3rd line) are underestimated. Because the use of these treatments is assumed to be greater in the BR arm of the model, any under-estimation of OS benefits would create a bias of uncertain magnitude in favour of ABR.

In response to clarification queries, the company provided several points of justification for their decision to use a partSA model instead of a Markov STM:

- *The company suggested that there was insufficient evidence to estimate second progression events (e.g. from the ECHO or R-CHOP studies) and that the introduction of external data adds uncertainty. However, the EAG note that there are independent studies of ibrutinib and CAR-T therapy, evaluated in NICE appraisals for R/R MCL that could have been used to estimate the PFS and OS benefits of these treatments in a STM model that incorporates 2nd and 3rd line treatments. Whilst these data are external in so far as they are not directly linked to the index treatment, it is standard modelling practice to model the treatment benefits of subsequent treatment lines. The EAG are of the view that the magnitude of bias generated by assuming subsequent treatment lines have no PFS and under-estimating their OS benefit far outweighs any uncertainty from using available data from exiting trials to attempt to estimate and model these benefits.*

- *The company contend that there is precedent for using partSA modelling for MCL, drawing specifically on the example of the NICE TA502 appraisal of ibrutinib for R/R MCL[22]. The company raised EAG concerns in TA502 that a partSA model would have been preferred to a Markov STM. However, it should also be noted that the committee for TA502 considered the Markov STM model outputs to be more clinically plausible and noted the EAG's acknowledged limitations and uncertainty underpinning the exploratory partSA results. Furthermore, the appraisal for ibrutinib was further down the treatment pathway, for relapsed / refractory disease. Any bias in a partSA model in this setting would only apply to one future line of treatment, whereas it applies to two future lines of treatment in the current appraisal. The EAG therefore considers the TA502 appraisal to support the use of a Markov STM. Indeed, the only economic model in the company's literature review (Table 30 of the company submission) to use a partitioned survival model was the NICE CAR-T appraisal (TA677) for 3L MCL.[23] However, the modelling requirements in the 3L setting are not transferrable to earlier in the treatment pathway where the limitations of partSA modelling are more of a concern.*

In summary, the EAG are not satisfied that the company have sufficiently justified the decision to use partSA modelling for 1L treatment of MCL. The EAG are concerned that the model substantially under-estimates the QALY benefits of subsequent treatment lines by ignoring PFS benefits and under-estimating OS benefits of subsequent treatment lines. If the company assumes that patients treated with BR at first line have higher requirements for subsequent treatment than ABR, under-estimation of treatment benefits generates a potentially large bias in favour of ABR. The EAG would have preferred the use of a Markov model structure that explicitly captures the PFS benefits of those subsequent treatment lines, for example, using data from TA502[22] and TA677[23] and the wider literature to estimate transition probabilities and more completely model the QALY benefits across multiple treatment lines. Given that the EAG has not had sufficient time within the STA process to rebuild a Markov model, alternative approaches to reducing bias within the partSA model structure would be to reduce the time horizon or to equalise all subsequent treatment acquisition costs in the model.

4.2.3 Population

The ECHO trial and modelled population (adults with previously untreated MCL, who are unsuitable for ASCT) is [redacted]

The EAG is satisfied that modelled population characteristics align closely with the ECHO trial. The EAG's clinical expert is satisfied that ABR would most likely be used in UK clinical practice for patients who are unsuitable for ASCT. However, the EAG raise some concerns about the treatment distributions at 2nd and subsequent treatment lines in a cohort of patients who are unsuitable for ASCT. These points are discussed further in Section 4.2.8.

4.2.4 Interventions and comparators

The intervention consists of three treatments, and a maintenance dosage of rituximab as summarised in Table 15. Comparator treatments are summarised in Table 16.

The EAG are satisfied that the dosing schedule and treatment doses are aligned with the ECHO trial. The EAG's clinical expert confirms that the dosing schedule, including maintenance rituximab treatment are as would be expected in UK clinical practice. The EAG are satisfied that the comparator BR treatment is closely aligned with the treatment schedule from the ECHO clinical trial and is as would be expected in UK clinical practice. Similarly, the R-CHOP treatment combination and dosing schedule is closely aligned with the clinical study providing R-CHOP evidence and is also aligned with the expected dosing regimen in UK clinical practice. The EAG's clinical expert agrees with the company's decision not to include VR-CAP or R-BAC as comparators for this assessment due to toxicity concerns. Despite Bortezomib being recommended as a first line treatment by NICE (TA370),[20] the EAG's clinical expert agrees with the company's view that it is rarely used in clinical practice. The EAG would welcome further confirmation from routine real-world evidence that this is the case across the whole of the UK and that it is appropriate to therefore exclude bortezomib as a treatment comparator.

Table 15 ABR intervention details

Treatment name	Strength	Admin.	Dosing schedule
Acalabrutinib	100mg	Oral	Twice daily until progression
Bendamustine	90mg/m^2	IV	Twice per 28-day cycle (days 1 and 2), up to a maximum of 6 cycles.
Rituximab	375mg/m^2	IV	Once per 28-day cycle (day 1) up to a maximum of 6 cycles.
Rituximab maintenance	375mg/m^2	IV	Once every 2 months up to a maximum of 12 additional doses up to cycle 30.

Key: IV, intravenous

Table 16 Comparator treatment details

Treatment name	Strength	Admin.	Dosing schedule
BR			
Bendamustine	90mg/m^2	IV	Twice per 28-day cycle (days 1 and 2), up to a maximum of 6 treatment cycles.
Rituximab	375mg/m^2	IV	Once per 28-day cycle (day 1) up to a maximum of 6 treatment cycles.
Rituximab maintenance	375mg/m^2	IV	Once every 2 months up to a maximum of 12 additional doses up to cycle 30.
R-CHOP			
Rituximab	375mg/m^2	IV	Once per 21-day cycle (Day 1) up to a maximum of 8 treatment cycles
Cyclophosphamide	750mg/m^2	IV	Once per 21-day cycle (Day 1) up to a maximum of 8 treatment cycles
Doxorubicin	50mg/m^2	IV	Once per 21-day cycle (Day 1) up to a maximum of 8 treatment cycles
Vincristine	1.4mg/m^2	IV	Once per 21-day cycle (Day 1) up to a maximum of 8 treatment cycles
Prednisolone	100mg	Oral	Five per 21-day cycle (Days 1-5) up to a maximum of 8 treatment cycles
Rituximab maintenance	375mg/m^2	IV	Once every 2 months up to a maximum of 12 additional doses up to cycle 30.

Key: IV, intravenous

4.2.5 Perspective, time horizon and discounting

The company adopt a UK NHS and PSS perspective for costs. The model is run for a lifetime horizon, with costs and utilities discounted at 3.5% per annum.

The EAG is satisfied that the perspective, time horizon and discounting are all aligned with the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

Progression free survival (PFS) and overall survival (OS) for ABR and BR are based on parametric survival curves fitted independently to KM curves for each arm of the ECHO trial. The company base case analysis applies censoring of covid-19 deaths for both PFS and OS as opposed to the ITT analysis set. The company have chosen to fit independent curves, as opposed to applying a HR from the trial data on the grounds that the proportional hazards assumption has not been met. The relative effectiveness (PFS and OS) of the R-CHOP comparator is based on HRs derived from a Bayesian indirect treatment comparison as described in Section 3.4. The EAG's critique of the company's modelling of treatment effectiveness and clinical assumptions is summarised in the following sections.

Covid-19 censored vs. ITT analysis sets

The company have censored Covid-19 deaths for their base case analysis, with exploration of analyses fitted to the ITT dataset as a scenario analysis.

The EAG acknowledges that the pandemic would have had an impact on overall survival and notes that this was an exceptional and unusual scenario. However, the EAG's clinical expert is of the view that BTK inhibitors could have an impact on other respiratory infections such as flu or other seasonal respiratory infections. Despite no longer being under pandemic status, Covid-19 and other respiratory illnesses remain in widespread circulation and remain relevant considerations for treatment selection as they continue to cause significant morbidity and mortality for patients with Haematological malignancies. The EAG therefore does not consider it appropriate to censor covid-19 related deaths for population of the economic model parameters. Furthermore, the EAG notes that the ITT analysis set is advantageous because it maintains the benefits of randomisation from the ECHO trial and is

therefore less biased. The EAG therefore prefers the ITT analysis set for informing the economic model.

Assessment of the proportional hazard's assumption for ABR and BR PFS and OS.

To decide whether to use independently fitted survival curves or to apply HRs for ABR vs. PBR from a joint model, the company conducted various diagnostic tests to assess the appropriateness of the PH assumption for both the covid-19 censored and ITT analyses. The PH assumption for OS and PFS was assessed using:

- visual inspection of the Schoenfeld residual plots.
- Assessment of the Schoenfeld residual test,
- Visual inspection of the log cumulative hazards plots

For the company preferred base case, using the covid-19 censored data, these diagnostics can be found in Section B.3.4.2.1 and B.3.4.3.1 of the company submission for PFS and OS respectively. Corresponding diagnostics can be found in Appendix O of the company submission for the ITT dataset. The EAG have summarised the diagnostic tests in Table 17. The company concluded that there is potential violation of the PH assumption in both analysis sets and therefore use independently fitted survival curves to model ABR and BR OS and PFS benefits.

The EAG notes that application of independently fitted curves in the economic model is inconsistent with the decision to use Cox proportional hazards modelling for the clinical effectiveness analyses. Whilst the EAG acknowledge it is plausible that PH may hold in the short, but not the longer term, the risk of that based on over 5 years of data appears low. In all cases the PH assumption test is non-significant, and log-cumulative hazard functions are mostly parallel, but there is some slight suggestion of non-linearity in Schoenfeld residual plots. The EAG accept that there is some uncertainty and that arguments could be made for both approaches. However, on the balance of evidence presented, the EAG prefers to assume that the PH assumption holds and that a HR from joint models should be applied to a PH compliant parametric survival curve for BR.

Table 17 Summary of PH diagnostic tests conducted by the company for PFS and OS using the ECHO trial data

Parameter	Schoenfeld residual test	Log cumulative hazards plots (visual)	Schoenfeld residuals plot (visual)	Company summary	EAG interpretation
Covid-19 censored					
PFS	p>0.05	Generally parallel over time	Unclear	Company suggests non-linear, non-zero	Low risk of violation of PH assumption, further scenario analyses assuming a joint model would be helpful.
OS	p>0.05	Generally parallel over time	Mostly linear	Non-linear and non-zero at the tail of the curve	Very low risk of violation of PH assumption, further scenario analyses assuming a joint model would be helpful.
ITT analysis					
PFS	p>0.05	Generally parallel over time	Unclear	Unclear	Low risk of violation of PH assumption, further scenario analyses assuming a joint model would be helpful.
OS	p>0.05	Generally parallel over time, slight convergence of curves at end.	Mostly linear and crosses zero.	Unclear	Low risk of violation of PH assumption, further scenario analyses assuming a joint model would be helpful.

Key: OS, overall survival; PFS, progression free survival; PH, proportional hazards assumption

Selection of parametric survival curves for ABR and BR PFS and OS

The company has explored a range of parametric survival models (exponential, Gompertz, gamma, log normal, log logistic, generalised gamma and Weibull) fitted to the OS and PFS arms of the ECHO study. A similar exercise was undertaken for the assessment of joint models in scenario analysis. The suitability of extrapolation curves was assessed by visual inspection of each curve's fit to the KM data, assessment of AIC and BIC statistics and external validation of long-term endpoints against data available from the SHINE and ECHO trials up to 6 years, and the opinion of n=4 UK clinical experts with experience treating MCL. Despite some uncertainty around the most appropriate curves to select, the company applied the same curves to both treatment arms.

Overall, the EAG considered the methods used to select parametric curves to be aligned with NICE TSD recommendations and is satisfied that the process is robust. Depending on assumptions about whether to apply the Covid-19 censored or ITT dataset, and the decision to use independently fitted or joint models, there are potentially 8 different OS datasets and 8 different PFS datasets to assess. The EAG has summarised AIC, BIC and key landmarks against the ECHO study for OS (Appendix 9.1) and PFS (Appendix 9.2). In general, regardless of the chosen dataset (covid-19 censored or ITT), there is little difference between the goodness of fit statistics across any of the parametric curves. Similarly, there is little difference in the visual fits of the curves to the KM data.

The most appropriate curve therefore depends on the plausibility of long-term extrapolations. The company's clinical expert opinion was generally of the view that Gompertz, Generalised Gamma, Weibull, Log-Norma and Log-Logistic curves all overestimated PFS (>30% alive and progression free beyond 10 years) and OS (>50% alive at 10 years). The EAG's clinical expert agreed with the company's clinical experts regarding long-term extrapolations. The company's clinical experts considered both exponential and Gamma curves to be plausible for both OS and PFS using the Covid-19 dataset but had a preference for the exponential curve for PFS. The EAG notes that similar conclusions result from an assessment of the ITT dataset and that the decision regarding curve selection remains consistent whether

independently fitted or joint parametric curves are applied. For all analyses, the company have chosen the gamma curve because they prefer to assume that there is a possibility that the PH assumption does not hold. Whilst the EAG agrees with the logic of applying an AFT curve when PH does not hold, we prefer to assume that the PH assumption does hold and therefore the EAG prefer to use the exponential curve in the base case with a gamma curve as a sensitivity analysis.

Impact of crossovers from ABR to BR on OS estimates

N=51/299 (17%) of participants in the PBR arm of the ECHO study crossed over to acalabrutinib monotherapy. The EAG queried whether this may have underestimated the OS benefit of ABR that might be observed relative to BR alone in UK clinical practice. In response to clarification queries, the company provided a *post-hoc* rank preserving structural failure time (RPSFT) analysis, the results of which are provided in Table 18 below. The company explained that the cross-over analysis would reflect a world where a BTK inhibitor is not available in UK clinical practice. However, ibrutinib is available at second line treatment in the control group, therefore the results of a cross-over model would be less relevant to UK clinical practice.

The EAG considers the company's justification to be appropriate. The EAG's clinical expert confirms that treatment with a BTKi would only be offered once in the treatment pathway in UK clinical practice. The EAG are satisfied that the company's base-case analysis is appropriate for decision making and note that the impact on cross-over models on the estimated HR is small and would not change overall conclusions.

Table 18 Results of updated RPSFTm analysis, alongside ITT and RPSFT for crossover and subsequent anti-MCL therapies [re-produced from Table 1 of the company response to clarification queries].

Approach to treatment effect	Re-censoring	Hazard ratio estimate	Lower 95% CI	Upper 95% CI	Exponential of Psi (95% CI)
Intention to treat results		[redacted]	[redacted]	[redacted]	[redacted]
'as treated' (on treatment)	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]
'ever treated' (treatment group)	No	[redacted]	[redacted]	[redacted]	[redacted]
	Yes	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval.

Relative PFS and OS treatment effectiveness vs. R-CHOP

The company prefers independently fitted curves to PBR and ABR arms of the ECHO trial data, with HRs from the NMA for R-CHOP vs. BR.

The EAG critique of the company's NMA methods has been discussed in Section 3.4. The EAG agrees in principle that the most appropriate comparator to apply HRs to is BR, and this is aligned with the EAG's clinical expert opinion that BR is the most widely used treatment for 1L MCL in UK clinical practice. There are, however, some uncertainties associated with the company's approach. Applying HRs to the BR curve makes the implicit assumption that the PH assumption holds between BR and R-CHOP. The company did not provide any clear evidence to support this assumption in their original submission but did in response to clarification queries (See clarification query response B4). Upon assessment of diagnostic plots from Rummel, 2013 and Flinn 2019, the EAG is satisfied the PH assumption also holds for the comparison of R-CHOP vs. BR. The EAG agrees with the company that the PH assumption is likely to hold and that the use of HRs is appropriate for modelling R-CHOP PFS and OS.

However, applying HRs to independently fitted curves, especially if non-PH, AFT curves are used may lead to uncertainty. At clarification queries, the EAG requested

an analysis from the company that assumed that the PH assumption holds for all treatment comparisons between ABR, PBR and R-CHOP, and that all OS and PFS HRs were sourced from the NMA. However, this information was not available at the point of writing the EAG report. The EAG would appreciate sight of an analysis that estimates HRs of OS and PFS, obtained from the NMA for 1) ABR vs. BR; 2) R-CHOP vs. BR. This analysis would ensure that the benefits of randomisation are maintained across all studies. Whilst useful for scenario analysis, the EAG does not consider this issue to be a major driver of cost-effectiveness conclusions, especially if committee accept the EAG's preference to use dependent models for ABR vs. PBR.

One alternative approach to modelling OS and PFS would be to consider the use of real-world OS data, for example from SACT dataset for BR. HRs for all treatment options under consideration (ABR and R-CHOP) could then be applied to the baseline BR OS and PFS curves. This would of course require access to SACT data. Whilst unlikely to have a major impact on cost-effectiveness results in this case, committee may wish to have information on the potential incremental benefits of each treatment in real-world clinical practice. It would also reassure committee that the trial is representative of UK clinical practice in terms of the outcomes that could be achieved with BR treatment in a real-world setting.

Time to treatment discontinuation

For Acalabrutinib, treatment can be given continuously until progression or unacceptable toxicity. Parametric TTD curves were therefore fitted to ECHO trial data (covid-19 censored dataset) to calculate acalabrutinib treatment acquisition costs. Acalabrutinib TTD curve selection criteria using the covid-19 censored and ITT datasets are summarised in Table 19. The company has selected the Weibull curve because it is a reasonable fit to the KM data and provides long term extrapolations beyond 10 years that remain below the company and EAG preferred PFS curves.

The EAG agree that the company's use of the Weibull extrapolation is appropriate for modelling acalabrutinib TTD. The Weibull appears appropriate for both the covid-19 censored and ITT datasets. The EAG also note that TTD curves are capped at PFS in the model, which is appropriate, and aligned with the EAG's clinical expert opinion that treatment beyond progression would be unlikely in UK clinical practice.

Table 19 Comparison of Acalabrutinib TTD curve selection using covid-19 and ITT analysis set

	Covid-19 censored dataset						ITT dataset					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
Company preferred ABR PFS	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred ABR PFS	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
KM	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	1723.3	1727.0	[redacted]	[redacted]	[redacted]	[redacted]	1968.0	1971.7	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	1707.3	1714.7	[redacted]	[redacted]	[redacted]	[redacted]	1959.4	1966.8	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	1705.2	1712.7	[redacted]	[redacted]	[redacted]	[redacted]	1962.0	1969.4	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	1706.3	1713.7	[redacted]	[redacted]	[redacted]	[redacted]	1959.1	1966.5	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	1710.7	1718.1	[redacted]	[redacted]	[redacted]	[redacted]	1959.3	1966.7	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	1706.0	1717.1	[redacted]	[redacted]	[redacted]	[redacted]	1959.2	1970.3	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	1709.0	1716.4	[redacted]	[redacted]	[redacted]	[redacted]	1960.8	1968.2	[redacted]	[redacted]	[redacted]	[redacted]
Generalised F	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	1961.2	1976.0	[redacted]	[redacted]	[redacted]	[redacted]

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

For the initial phase of treatment with bendamustine and rituximab (BR) components of both the ABR and PBR arms of the model, treatment duration was for a fixed duration up to a maximum of 6 cycles. This was followed by maintenance treatment with rituximab for ABR or BR patients who achieved a complete or partial response after 6 cycles. KM data from the ECHO trial showed that almost all patients were off treatment by the end of trial follow up. TTD was therefore sourced from KM curves directly for rituximab (initial + maintenance phase) and no further extrapolation was required.

Given the maturity of the TTD curves for rituximab, the EAG considers the company's approach to modelling TTD for rituximab to be appropriate.

Adverse event rates included in the economic model

The company's base case economic model includes treatment emergent adverse events (TEAEs) with a severity of Grade ≥3 that occurred in >5% of patients in either arm of the ECHO trial. AEs for R-CHOP were sourced from the LYM3002 study.[31] A summary of AE incidence rates included in the model were originally summarised in Table 45 of the company submission. At clarification queries, the EAG noticed a minor discrepancy in the rates report, and these were subsequently corrected by the company (See Table 11 of the company response to clarification queries). The impact on the ICER was minimal. Whilst the approach taken by the company is commonly used in technology appraisals, the EAG note that there are some uncertainties with the approach taken:

- *The economic model underestimates the total impact of adverse events on costs and QALYs by excluding rare, but severe and costly adverse events such as major haemorrhage and atrial fibrillation. As some events occurred in both arms of the study it is unlikely that inclusion of all adverse events would have had a material impact on the ICER.*
- *Adverse events were applied as a one-off cost and disutility adjustment in the economic model, which does not completely capture the total impact of adverse events over time. However, the EAG accept that this is also unlikely to be a major driver of cost-effectiveness conclusions.*

Summary of EAG and company preferred clinical parameters in the economic model

Table 20 provides a summary of the company and EAG preferred clinical parameters and assumptions for the economic model. Company and EAG preferred OS, PFS and TTD curves are presented in Figures 7, and 8 respectively.

Table 20 Comparison of company and EAG preferred clinical assumptions and parameters.

Clinical assumption / parameter	Company preferred base case	EAG preferred base case	EAG comments
Analysis set for PFS and OS parameters.	Covid-19 mortality censored dataset	ITT dataset	ITT dataset is less biased, covid-19 is still a consideration as are other respiratory infections. ITT aligns with EAG clinical expert opinion and is more methodologically robust for parameter estimation.
ABR and BR OS and PFS extrapolation approach	Independently fitted curves to ECHO trial data.	Extrapolations from joint (dependent) models.	The EAG considers the risk of violation of the PH to be low over the trial follow-up. Jointly fitted models are aligned with EAG's view that, on balance, PH assumption is reasonable and allows for consistency of approach when modelling R-CHOP effectiveness.
OS and PFS parametric curve selection	Gamma for OS and PFS, applied independently to ABR and BR	Exponential for OS and PFS, applied in a dependent model.	Most curves provide acceptable fit to the KM data. Longer term projections from both the Gamma and Exponential curves were deemed reasonable by clinical experts, with a slight preference for exponential. The EAG also prefer exponential, and the selection is

Clinical assumption / parameter	Company preferred base case	EAG preferred base case	EAG comments
			aligned with the EAG's preference to assume that PHs hold.
Approach to handling crossovers on OS estimates for ABR	Crossover modelling not required.	Crossover modelling not required.	Despite some uncertainty, the EAG are satisfied that proportion crossing over is reasonably small. In UK clinical practice, ibrutinib would be offered at 2L to patients receiving BR at 1L, thereby reducing the bias of any over-estimation of OS in the BR arm of the model. Scenario analyses provided by the company exploring a cross-over model have only a small impact on the ICER.
Approach to modelling R-CHOP treatment effects	HR from NMA applied for R-CHOP vs. BR	As per company base case, but some uncertainty.	Agree with company base case analysis, but an analysis providing HRs for all treatment comparators from the NMA would have been helpful, particularly given the EAG's preference that the PH assumption holds.
Time to treatment discontinuation assumptions for acalabrutinib	Weibull fitted to ECHO trial data	Weibull fitted to ECHO trial data	Company and EAG preferred approaches are aligned.
Adverse event rates	TEAE of grade 3 or above,	As per company base case, but	Company approach excludes rare but potentially costly, and high quality of life impact AEs such as

Clinical assumption / parameter	Company preferred base case	EAG preferred base case	EAG comments
	occurring in at least 5% of either trial arm.	some uncertainties exist	major haemorrhage and atrial fibrillation. However, the impact on the ICER of changing the AE modelling approach would be minimal.
Adverse event rates	One-off AEs	One-off AEs are reasonable, but some uncertainty.	A per cycle AE probability, applied for the duration of time on treatment, would more fully capture the impact of adverse events on costs and QoL. However, the magnitude of bias is likely to be small.

Key ABR, acalabrutinib + bendamustine + rituximab; AE, adverse events; BR, bendamustine + rituximab; ITT, intention to treat; PFS, progression free survival; OS, overall survival.

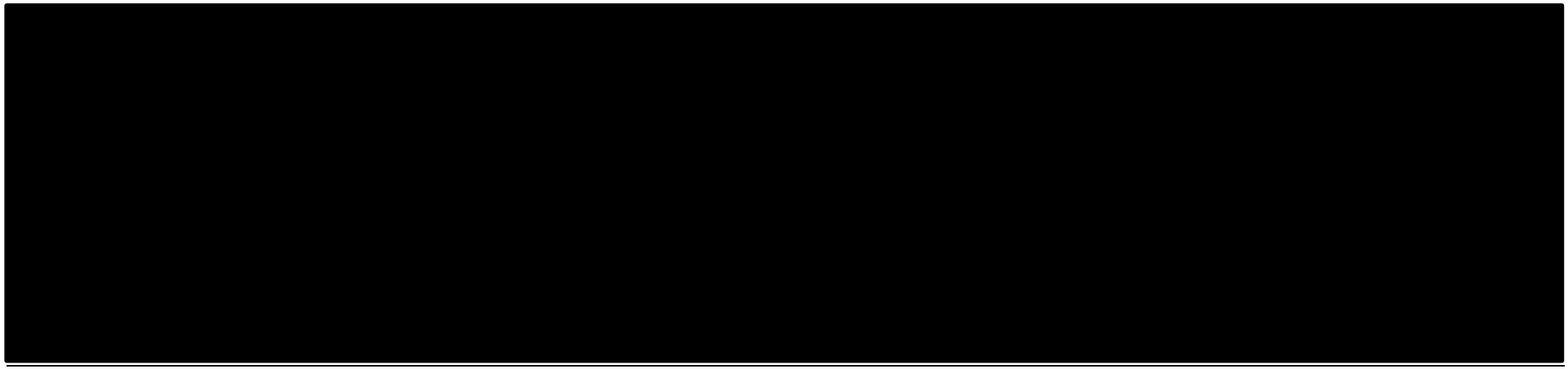


Figure 7 Company preferred OS, PFS and TTD curves, by treatment arm [adapted from company economic model]

Figure 8 EAG preferred OS, PFS and TTD curves, by treatment arm [adapted from company economic model]

4.2.7 Health related quality of life

HSUVs derived from ECHO trial data

Quality of life was captured in the model by applying utility weights to progression free and post progression health states with disutilities applied to adverse events. Quality of life data were based on EQ-5D-5L data of the FAS, collected during the interim analysis (15th February 2024 datacut) of the ongoing ECHO trial. Utility weights were derived using the NICE DSU TSD 22[32] recommendations – Health state utility values were cross-walked to the EQ-5D-3L using methods described in Hernandez-Alava et al (2023).[33] Multivariate repeated measures mixed effect regressions were conducted to estimate the utility values for the progression-free and progressed disease health states. Several covariates (E.g., health state, treatment arm and an interaction term) were explored, the model with the lowest AIC statistics was selected. This model contained only a covariate for progression status and no statistically significant difference in utility between treatment arms was identified. Adjustments were not made for baseline disease characteristics and EQ-5D in the chosen model. In response to clarification queries, the company conducted an additional analysis which included EQ-5D-5L utility score, age and gender as model covariates. The additional analysis had a minimal impact on the results and did not alter the interpretation. The MMRM analysis excluded observations recorded after participants were censored for progression. This is due to the EQ-5D-5L no longer being routinely collected once progression is observed (page 119 Document B details EQ-5D-5L collection timepoints), therefore these observations carried an unknown health status. The company presents marginal (least squares) means and 95% CIS for progression free and progressed disease in table 43, page 120 Document B of the CS. The results indicated a negligible difference between progression free and progressed disease estimates ([redacted] (95% CI: [redacted]) vs. [redacted] (95% CI: [redacted])).

The EAG are satisfied that the company submission has used appropriate methodology to estimate utilities from the ECHO trial.

Progression free HSUV

The company base case uses the progression-free HSUV estimated from the MMRM analysis, capped by general population utilities for the entire model time horizon due to estimated PFS utilities being higher than general population.

The EAG agrees that PFS HSUVs have been appropriately estimated and is satisfied that applying a general population utility cap in the model is appropriate. However, it has not been established within the company submission whether it is reasonable for newly diagnosed patients to realise HRQoL benefits equal to, or above, that of the general population in the long term. Within table 16, page 31 of the company response to CQs, the company compares the progression free HSUV from ECHO with that from previous TAs in MCL and CLL. All presented HSUVs exhibited a lower HSUV than that observed in the ECHO trial. It should also be noted that those in MCL (TA370 and TA502),[20, 22] which were also informed by clinical trials in MCL (LYM-3002, RAY and SPARK) had a comparatively younger population. All patients within the ECHO trial were older than 65 years, whereas between 53.6% and 37.8% were younger than 65 years in the LYM-3002(TA370), RAY(MCL3001) (TA502) and SPARK(MCL2001) (TA502) studies respectively. The EAG therefore accepts the use of ECHO trial progression-free utilities, capped at general population, based on the available data. However, it may also be helpful for committee to consider alternative PFS HSUVs from previous appraisals through scenario analysis.

Progressed disease HSUV

The ECHO trial derived estimate for progressed disease is not used in the company's base analysis for the following reasons:

- the estimate is [redacted]
- the estimate is [redacted] than age-gender matched general population utility (0.787),
- findings from interviews with three UK clinicians stated that the "*...quality of life for progressed patients would be considerably worse than progression free patients."* (B8A, page 30 of Company CQ response),
- the ratio of HSUVs from previous NICE STAs in MCL were lower than that observed within ECHO (see table 16, page 31 of Company CQ response).

Consequently, the company concludes that the ECHO trial derived estimate of [redacted] for progressed disease lacks face validity and precedent, rendering it unsuitable to use within the model to inform the progressed disease state.

A systematic literature search was conducted to inform the HSUV of the progressed disease state. Details of the search strategy and methodology of the review are provided in page 56, appendix G of the CS. The search identified five publications, where one reported HSUVs.[19]

The publication sourced the HSUVs from the LYM-3002 trial – VR-CAP and R-CHOP in transplant eligible patients with untreated, newly diagnosed MCL.[31] An additional search of previous NICE appraisals identified two appraisals reporting utilities from a UK perspective – TA370 and TA502.[20, 22] TA370 HSUVs were sourced from the LYM-3002 trial and TA502 HSUVs were sourced from the RAY(MCL3001) and SPARK(MCL2001) trials. The company selected the progressed disease estimate from TA502 to inform the progressed disease utility value in their base case.[22] This is based upon the following: TA502 is the most recent appraisal in MCL, anecdotal reports from clinicians that clinical outcomes have improved since the publication of TA370 in 2015 and comments from the EAG in TA370 that utility impact due to progression is underestimated as LYM-3002 participants were still receiving treatment at the time of progression.

The progression free HSUV is the age-sex matched general population utility throughout the model time horizon as the ECHO derived progression free estimate is [redacted] than age sex matched general population utility ([redacted]0.787). Therefore, the calculation of Progressed disease HSUV is based upon the general population utility value multiplied by a progressed disease HSUV multiplier ([redacted]). The progressed disease HSUV multiplier is calculated by removing the absolute decrement of HSUVs in TA502 from the ECHO trial derived estimate for the progression free state ([redacted]). This is then divided by the ECHO trial derived estimate ([redacted]). Therefore, the HSUV for the progressed disease state in the first model cycle is as follows:

$$\text{Cycle 1 Progressed disease HSUV} = \frac{\left([\text{redacted}] - (0.780 - 0.680)\right)}{[\text{redacted}]} \times 0.787$$

$$= [\text{redacted}] \times 0.787 = [\text{redacted}]$$

The EAG agrees with the company that the ECHO trial-derived utility score for progressed disease lacks face validity. This is likely a result of small patient numbers and the timepoint in which the EQ-5D instrument was collected. The lack of EQ-5D-5L data beyond progression in the ECHO trial is likely to be an area of uncertainty in the long-term extrapolation.

The EAG disagrees with the company's arguments for TA502 being the most appropriate source of progressed disease utility values for use in this indication for the following reasons:

1. *TA502 considers a comparatively more severe patient population. The indication for TA502, and the trials which inform it, is patients with relapsed or refractory MCL.[22] The indication for TA370 aligns with this appraisal, previously untreated MCL.[20]*
2. *The EAG accepts that it is probable that clinical outcomes have improved since the publication of TA370. However, as the EQ-5D was not found to be statistically significantly different between treatment arms in the company's MMRM analysis, the EAG does not find there is sufficient evidence to support a difference in HSUV between ECHO (which includes bendamustine) and TA370.*
3. *The economic model within TA370 was a Markov model consisting of several health states which capture patients who progress whilst not being on treatment prior to receiving a subsequent line of treatment.[20] Patients HSUVs were modelled in the following manner through the health states: Progression-free 1L (0.764) to Progressed from 1L (0.693) to Progression-free 2L (0.764) to Progressed from 2L (0.45). The EAG comments that the 0.693 is underestimated is based on the fact that the patients within the Progressed from 1L health state were modelled to receive no treatment yet the majority of the patient population which informed the 0.693 estimate were receiving treatment at the point of completion of the EQ-5D instrument. This is not the case in the model for this appraisal – where patients are assumed to receive a basket of subsequent treatments upon progression. Therefore, it could be argued that this estimate is more appropriate for this appraisal than that used within TA502.*

Therefore, in absence of an appropriate estimate of progressed disease utility from the ECHO trial, the EAG finds that the HSUVs utilised within TA370 are more appropriate than that within TA502. In particular, that the utility value of progressed disease declines over time with subsequent treatment lines. The company presents scenario analysis of alternative HSUVs from different TAs in their base case in table 17, page 32 of the company response to CQs. When HSUVs from TA370 and TA502 are used it leads to a minor impact of the ICER and does not alter cost-effectiveness conclusions. The EAG explores the use of declining the PD HSUV over time to the progressed from 2L preferred in TA370 (0.45). This is discussed in more detail on the next page.

<u>Progressed disease HSUV over time, across multiple lines of treatment</u>

The company submission applies a single PD multiplier, regardless of subsequent stage of disease.

The EAG is concerned that the use of the progressed disease multiplier may lead to an overestimation of progressed disease utility in the long term. Particularly when we consider that the progressed disease health state captures all future treatment lines in a largely incurable disease. Throughout the model time horizon, the progression-free HSUV is equal to general population utility thus it reduces with age. Therefore, the difference in magnitude of the HSUV between the progression free and progressed disease health states decreases over time. For example, at the beginning of the model, the difference between progression free and progressed disease HSUVs is [redacted] *whereas by age 100 the difference becomes* [redacted]*. Whilst the use of a multiplier and the general population utility cap aligns with the preferred NICE approach(4.3.7).*[34] *The EAG's concern around the validity of longer-term progressed disease utilities relates to the economic model structure concerns described in Section 4.2.2.*

The EAG attempts to explore alternative methods of calculating the progressed disease HSUV within the partitioned survival model structure that would reduce the magnitude of bias related to not explicitly modelling longer term utility decrements for subsequent lines of progression in the model. Therefore, the EAG will explore scenarios which decrease the progressed disease HSUV over time in relation to the progression free HSUV. This attempts to capture the progressive nature of MCL and subsequent decline in HRQoL in relation to the general population. In the absence of HRQoL data for later treatment lines of MCL, we explore scenarios which reduce the PD utility to the committee preferred utility of the progressed from 2L treatment state of TA370 (0.45) at differing timepoints. After these timepoints the utility value will remain at 0.45. The duration to reach 0.45 will be informed by an estimate of progression from BTK inhibitors for relapsed and refractory disease from external literature, alongside 5-years and 10-years to explore the uncertainty. This will likely bias in favour of acalabrutinib. This is due to patients in the acalabrutinib arm spending comparatively more time in the progression-free state overall. HSUVs for the company and EAG preferred base case analyses as well as alternative scenario analyses are summarised in Table 21 below.

Table 21 Summary of company base case, EAG base case and alternative HSUVs for scenario analyses

Health state	Company base case	EAG base case	Committee accepted TA502	Committee accepted TA370	EAG scenario
PFS	ECHO PFS utility capped at general population utility. Therefore, equivalent to general population utility throughout the model.	Equivalent to company	0.78	0.764	None, the EAG agrees with the company that ECHO is the most appropriate data to inform HSUV of the PFS state.
PD	Progressed disease HSUV multiplier ([redacted]) based on ECHO PFS value and the absolute difference between PFS and PD utility in TA502.	Equivalent to PFS HSUV in cycle 0 then reduces to 0.45 at 2.06 years using an exponential function. PD HSUV equal to 0.45 after 2.06 years.	0.68	Progressed from 1L treatment: 0.693 Progression-free from 2L treatment: 0.764 Progressed from 2L treatment: 0.45	Alternate durations (5-years, 10-years) in which PD HSUV reduces to 0.45.

Key: HSUV, health state utility value; PD, progressed disease; PFS, progression free survival.

Disutilities of adverse events

Adverse event disutilities were applied as a one-off disutility within the first model cycle. The company included the disutilities of all grade 3+ treatment emergent adverse events (TEAE) that occurred in at least 5% of patients for all 1L treatments within the model. TEAE rates were informed by the ECHO trial for the ABR and PBR arms, whereas the R-CHOP arm was informed by LYM-3002. Disutilities for most events were informed by those used within TA370 aside from hypertension which was informed by TA931. In the absence of utility data for COVID-19 events (COVID-19 pneumonia and COVID-19) and rash maculo-papular – the company assumed the disutility and duration to be equal to average of other grade 3+ disutility values. Lab based adverse events (neutrophil count decrease, white blood cell counts decreased and lymphocyte count decreased) were assumed equal to their associated condition (Neutropenia, leukopenia and lymphopenia respectively).

The EAG is agreeable to the sources of the disutilities. Aside from the discussion in the preceding section regarding how AEs events are applied in the model (See section 4.2.6), the EAG has not been able to recreate the disutility and duration assumed for COVID-19 pneumonia, COVID-19 and rash maculo-papular. The EAG notes that the resultant duration (23.78 days) is longer than all other included adverse events. In terms of face validity, the EAG is uncertain why pneumonia would have a higher disutility yet a lower duration than COVID-19 pneumonia. Therefore, the EAG prefers to assume equal disutility and duration of pneumonia and COVID-19 pneumonia.

4.2.8 Resources and costs

Treatment acquisition costs for intervention and comparator treatments

The treatment acquisition cost per cycle for each component of the intervention and comparator treatment regimens is determined by the dosage, treatment cycle duration, number of administrations / doses per cycle according to the dosing schedule described in Section 4.2.4. Treatment acquisition cost for acalabrutinib is [redacted] per pack, reflecting a patient access scheme discount of [redacted]% on the list price. All treatment acquisition costs used in the economic model are provided in Table 53 of the CS. Treatment exposure to bendamustine was [redacted]. For treatments where dosing is dependent upon body surface area (all IV administered treatments), a BSA from the ECHO trial of 1.9m^2 is assumed for all cost calculations. Total required mg of each treatment per

cycle is then multiplied by a relative dose intensity obtained from the ECHO trial (ABR and BR)[18] and the BRIGHT trial (R-CHOP).[16] The company's economic model assumes that vial sharing is allowed for all IV administered treatments, thereby assuming no treatment wastage.

The EAG consider the dosing regimens to be appropriate, aligned with the dosing in the respective clinical trials and a reasonable reflection of treatment delivery in UK clinical practice. The EAG also consider it reasonable to apply RDIs based on the observed clinical trial data for ABR and BR and consider the unit costs of treatment acquisition to be appropriate. The RDI for rituximab maintenance therapy is calculated as the pooled average of rituximab RDIs across the ABR and BR arms of the ECHO trial and the EAG consider this assumption to be reasonable. With regards to the company's assumption of vial sharing, the EAG's clinical expert does not consider this appropriate, and that in UK clinical practice vials would not be shared across patients. Even within patients receiving IV treatment on consecutive days, given that there are different BSAs for every patient, the EAG are therefore not convinced that a dosage based on BSA could be administered without any wastage. The EAG preferred base case therefore assumes vial sharing is not possible.

Treatment administration costs for intervention and comparator treatments

Table 56 of the company submission summarises treatment administration costs applied in the model.

The EAG considers the company's approach to estimating treatment administration costs to be appropriate and justified. The EAG agree with the company that there is some uncertainty regarding the administration costs of CAR-T therapy but accept that the estimate of £41,101 is aligned with previous TAs. The EAG note however that the administration costs for CAR-T may be an underestimate of total CAR-T health service costs over the longer term, for example excluding costs for bridging therapy, consolidation SCT, and hypogammaglobulinemia management. Whilst CAR-T administration costs are an important consideration in the company's base case model, these are less important in the EAG's preferred base case given that the EAG prefers to assume equal proportions of patients receiving 3rd line treatment and equal use of CAR-T across model arms.

Subsequent treatment costs – proportion requiring 2L and 3L treatment

The company base case analysis uses data from the ECHO study which shows that ABR leads to a reduction in the proportion of patients with non-fatal progression events that are eligible for further lines of treatment compared to PBR. It is assumed that proportions requiring subsequent treatment for R-CHOP are equal to PBR. The proportion of progressed patients receiving 2L and 3L treatments from the ECHO trial are summarised in Table 22 below.

Table 22 Proportion of patients with progressed disease requiring subsequent treatment

Model parameter	ABR	PBR	R-CHOP
Proportion of PD patients receiving 2L treatment	[redacted]	[redacted]	Assume equal to PBR
Proportion of PD patients receiving 3L treatment	[redacted]	[redacted]	Assume equal to PBR

At clarification queries, the EAG queried why a large proportion of patients with progressed disease, particularly in the ABR arm were not deemed suitable for further lines of treatment after progression. The company noted that there was no further information from the trial data to help understand the reasons for treatment ineligibility, or why differences might be expected across arms. Clinical expert opinion sought by the company during clarification suggested that some patients may not be suitable for further treatment lines due to accumulation of co-morbidities or due to age. The EAG accepts that this may be the case, but it does not necessarily explain why differences between arms would be observed. The EAG further queried, at clarification stage, whether differences between arms might be due to longer time between progression and initiation of next treatment line for ABR compared to PBR. The company provided these data in response to clarification queries (see Table 21). Whilst a [redacted] *between progression and initiation of the next treatment line is observed, the EAG does not consider this to sufficiently explain observed differences in observed subsequent treatment proportions. Therefore, on the balance of evidence available to the EAG, both in the company submission, expert opinion, and*

clarification responses, it remains unclear whether differences between treatment arms observed in the ECHO trial would translate to UK clinical practice. Longer term follow-up of the ECHO trial data may help to reduce the uncertainty and better understand whether differences in subsequent treatment lines across groups are due to extended PFS in the ABR arm of the study. Further evidence from routine clinical practice, for example using the SACT data would be helpful to better understand the baseline proportion of patients requiring subsequent lines of treatment for previously untreated MCL, who are unsuitable for ASCT, in UK clinical practice. Whilst these data might not resolve issues of incremental differences between ABR and PBR, they would help better understand the treatment pathway in UK practice. Despite the uncertainty in proportions requiring 2nd line treatment, the EAG retains this in the base case analysis, but notes that the substantial residual uncertainty. Given the time taken to reach 3rd line treatment and small numbers progressing twice in the ECHO trial, the EAG considers differences in 3rd line treatment proportions to be highly uncertain, and not sufficiently robust for decision making. The EAG therefore removes 3rd line treatment costs from the model in our preferred base case set of assumptions pending further evidence, longer-term follow-up or a restructured Markov state transition model being presented.

Distribution of 2nd and 3rd line subsequent treatments

The company base case analysis assumes a distribution of subsequent treatments informed by UK clinical expert opinion. The company considered the ECHO trial data to not fully represent treatment distributions in UK clinical practice. At clarification stage, the EAG requested a comparison of subsequent treatment distributions obtained from the company sought clinical expert opinion against the observed distributions from the ECHO trial. These alternative model inputs are summarised in Table 23.

Table 23 2nd and 3rd line treatment distributions obtained from ECHO trial compared to company sought clinical expert opinion [Re-produced from Tables 18 and 19 of the company response to clarification queries]

Treatment	ECHO trial distribution		Company sought clinical expert distribution	
	ABR	BR	ABR	BR
2nd line treatment distribution				
Ibrutinib	[redacted]	[redacted]	0.00%	100.00%
R-CHOP	[redacted]	[redacted]	74.44%	0.00%
Lenalidomide + rituximab	[redacted]	[redacted]	0.00%	0.00%
Rituximab	[redacted]	[redacted]	0.00%	0.00%
RBAC	[redacted]	[redacted]	11.11%	0.00%
VR-CAP	[redacted]	[redacted]	14.44%	0.00%
3rd line treatment distribution				
R-CHOP	[redacted]	[redacted]	16.67%	15.63%
Ibrutinib	[redacted]	[redacted]	0.00%	15.63%
Lenalidomide + Rituximab	[redacted]	[redacted]	0.00%	0.00%
Lenalidomide	[redacted]	[redacted]	0.00%	0.00%
Venetoclax	[redacted]	[redacted]	0.00%	0.00%
CAR-T	[redacted]	[redacted]	50.00%	37.50%
R-BAC	[redacted]	[redacted]	16.67%	15.63%
VR-CAP	[redacted]	[redacted]	16.67%	15.63%

Key: ABR, acalabrutinib, bendamustine + rituximab; BR, bendamustine + rituximab; CSR, clinical study report; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

The EAG note that the distribution of subsequent treatment is an important driver of cost-effectiveness in the economic model, particularly due to expensive treatments such as CAR-T. The EAG considers there to be advantages and disadvantages of using either the ECHO trial distribution or UK clinical expert opinion. The EAGs clinical expert partly agrees with the opinion sought from the company (for example relating to the proportion receiving ibrutinib as second line treatment). However, the EAG's expert also noted that the use of CAR-T treatments seemed high for a population already ineligible for SCT and that it is difficult to

justify a difference in the proportion of patients requiring CAR-T at 3rd line based on different treatments administer at 1L. The EAG note that whilst clinical expert opinion may be a closer reflection of treatment practices in the UK NHS, they are more biased than relying on ECHO trial data. OS benefits modelled using the trial OS curves are derived from the treatment distribution, including subsequent treatments included in the ECHO study. Applying a treatment distribution based on UK clinical expert opinion leads to uncertainty because the modelled OS benefits might not be realised with the clinical practice treatment distribution. Whilst the EAG accepts that the company's use of expert opinion is likely to more accurately predict treatment pathway costs in general, it may lead to more biased estimates of the ICER. The EAG are of the view that both should be considered for decision making. The EAG's base case retains the company's approach, but noting substantial uncertainty and the risk for bias, note that subsequent treatment distributions from the trial should also be considered. The EAG apply a scenario analysis using these data to the EAG preferred base case.

The EAG sought to better understand variability in clinical expert opinion and asked for specific responses from clinical experts who provided advice to the company. These were helpfully provided in response to clarification queries and are summarised in Table 24 below. The EAG considers the distributions from clinical expert opinion to be reasonable for 2nd line treatment, but notes that for 3rd line treatments, only one expert provided a response for both ABR and BR (expert number 1). The EAG therefore considers expert number one to be more appropriate and aligned with the EAG's sought clinical expert opinion.

Table 24 Summary of company sought clinical expert opinion regarding 2nd and 3rd line subsequent treatment distributions [re-produced from Tables 5 and 6 of the company clarification response]

	ABR					BR					R-CHOP				
Clinician	**1**	**2**	**3**	**4**	**Average**	**1**	**2**	**3**	**4**	**Average**	**1**	**2**	**3**	**4**	**Average**
2nd line treatment distribution															
Ibrutinib	0%	NR	0%	0%	0%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
R-CHOP	90%	NR	33.33%	100%	74%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
VR-CAP	10%	NR	33.33%	0%	14%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
R-BAC	0%	NR	33.33%	0%	11%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line treatment distribution															
Ibrutinib or chemotherapies	50%	NR	NR	NR	50%†	50%	25%	NR	NR	62.50%†	50%	10%	20%	60%	65.00%†
CAR-T	50%	NR	NR	NR	50%	50%	75%	NR	NR	37.50%	50%	90%	80%	40%	35.00%

Key: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; R-BAC, rituximab, bendamustine, cytarabine; NR, not reported; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone.

†ABR patients receiving chemotherapies are equally split across R-CHOP, R-BAC and VR-CAP in the economic model. BR and R-CHOP patients receiving chemotherapies are equally split across R-CHOP, R-BAC, VR-CAP and ibrutinib in the company's economic model

Subsequent treatment costs – Relative dose intensities

The company's base case approach assumes that RDIs for several subsequent, post progression, treatments (R-CHOP, R-BAC, VR-CAP, lenalidomide, and venetoclax) are equal to 100%.

The EAG considers the assumption of an RDI=100% to substantially overestimate the treatment acquisition costs of subsequent treatment lines in the company's economic model. It is unlikely that there would be no dose adjustments or interruptions for these treatments, for example, due to adverse events. The EAG therefore prefers to use existing data for RDIs for the respective treatments in the economic model. Company and EAG preferred RDIs are summarised in Table 25.

Table 25 Company and EAG preferred RDIs for subsequent treatments

Model parameter	Company preferred RDI	EAG preferred RDI	EAG notes
Ibrutinib	94%	94%	Consistent with company
R-CHOP	100%	Rituximab: 96% Doxorubicin: 96% Vincristine: 72% Cyclophosphamide: 96% Prednisolone: 94%	Equivalent to 1L RDI
CAR-T	Brex autoleucel: 100% Rituximab: 37% Bendamustine: 37% Cytarabine: 37%	Brex autoleucel: 100% Rituximab: 37% Bendamustine: 37% Cytarabine: 37%	Consistent with company
R-BAC	100%	Rituximab: 91% Bendamustine: 87% Cytarabine: 93%	Rituxumab & Bendamustine equivalent to 1L; Cytarabine equivalent to R-Chemo in TA370
VR-CAP	100%	Bortezomib: 82% Rituximab: 93% Cyclophosphamide: 93% Doxorubicin: 93% Prednisolone: 93%	TA370

Key: CAR-T, Chimeric antigen receptor T-cell; R-BAC; Rituximab, bendamustine, cytarabine; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; VR-CAP, Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

Subsequent treatment costs – Treatment durations

A one-off cost for subsequent treatment was applied in the economic model accounting for the assumed duration of each subsequent treatment at 2nd and 3rd line. These are reported in Table 68 of the company submission.

The EAG note that the company has assumed a variety of approaches for calculating subsequent treatment durations, using mean treatment duration (ibrutinib), median PFS (R-BAC and VR-CAP) and maximum treatment duration (R-CHOP). The EAG are concerned that using PFS data may over-estimate subsequent treatment duration as a proportion of progression free patients will discontinue treatment prior to progression for a variety of reasons, including adverse events and patient preference. It should also be acknowledged that most R-Chemo regimens are given for a maximum of 6 treatment cycles. Conversely, median time on treatment might under-estimate treatment duration. The net impact of these uncertainties is unclear but could potentially have an important impact on the ICER, particularly in the company's base case model where both 2nd and 3rd line treatments are modelled. The EAG prefers to adopt an alternative, more consistent approach to subsequent treatment durations in the model that rely, where possible on mean estimates of treatment duration. In the case of chemotherapy treatments, the EAG prefers to assume that these would be given for a maximum of 6 treatment cycles which is consistent with R-CHOP in the first-line. Company and EAG preferred subsequent treatment durations are compared in Table 26 below. Finally, within the model, acquisition and administration costs are calculated based on a cycle length of 28 days (4 weeks). The company base case multiplies these by the monthly treatment duration (4.35 weeks). For consistency, the EAG prefers to convert the treatment durations into number of 4 week periods prior to multiplying them by the 4 weekly drug acquisition and administration cost.

Table 26 Company and EAG preferred subsequent treatment durations

Subsequent treatment	Company preferred		EAG preferred	
	Time on treatment (months)	Source	Time on treatment (months)	Source
Ibrutinib	22.00	RMST cross over (Acalabrutinib), ECHO	12.72*	Based on median duration of treatment (11.70 months) of MCL presented in the SmPC for Ibrutinib
R-CHOP	5.52	Maximum treatment duration, LYM3002	4.14	Consistent with 1L R-CHOP. 6 21-day treatment cycles
CAR-T	One-off	Assumption	One-off	Assumption
R-BAC	10.10	Median PFS, R-BAC in R/R MCL	5.52	Assumption. 6 28-day treatment cycles
VR-CAP	30.50	Median PFS, VR-CAP in 1L MCL	5.52	Assumption. 6 x 28-day treatment cycles

*Estimation of the mean assuming an exponential distribution based on median duration of 11.70 months and dividing by ln(2).
Key: CAR-T, Chimeric antigen receptor T-cell; MCL, mantle cell lymphoma; R-BAC; Rituximab, bendamustine, cytarabine; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RMST, restricted mean survival time; R/R, relapsed or refractory; VR-CAP, Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone.

Coding error in subsequent treatment cost calculations

During the EAG validation checks, the EAG noted an inconsistency in the calculation of third-line acquisition and administration cost of fixed regimen subsequent treatments. The duration of CAR-T therapy (one-off) was used to inform the treatment duration of both RBAC and VR-CAP in the Acalabrutinib arm, essentially applying one-month of treatment duration for these treatments. The CAR-T administration cost was used to inform the cost of RBAC, and the RBAC administration cost was used to inform the cost

of CAR-T in the BR arm. This coding error led to an underestimation of cost in the ABR arm and overestimation in the BR arm.

Two further errors were identified which relate to the calculation of drug acquisition cost. The first was a typographical error, where the incorrect strength was inputted for four medications sourced from the eMIT: cytarabine (1000mg, 2000mg and 5000mg) and bortezomib (3.5mg). For cytarabine, all strengths inputted were too low by a factor of ten. For bortezomib, the strength of 2.5mg was inputted in error. The second relates to the cost of some treatments whose dosage is based on the BSA. The assumed dosage of applicable treatments within CAR-T, R-BAC and VR-CAP regimens was not adjusted for BSA (e.g., the dose of rituximab should be 375mg multiplied by the BSA). Therefore, the dosage per treatment cycle was too low. This meant that the acquisition cost of these treatment regimens was too low. The correction of these two errors has a minor impact on the ICER. This is due to cytarabine and bortezomib carrying a low cost per mg both before and after the correction in the vial sharing scenario (company base case). The second correction increases the cost per model cycle of R-BAC and VR-CAP by approximately 80% but the impact on the ICER is small. This is because in the subsequent treatment distribution at second-line, only the ABR arm includes RBAC and VR-CAP. At third-line, the distribution of patients receiving these treatments is equal between arms but fewer patients in the ABR arm are modelled to go on to receive any third-line treatment. The implication is that the this increase in acquisition cost is balanced out across the second and third-line subsequent treatments.

Table 27 below presents the impact of correcting this error on third line subsequent treatment costs in the model. The impact of correcting this error is a substantial increase in the ICER.

Table 27 Impact of coding error in the calculation of third-line fixed regimen subsequent treatment costs

	Submitted model	After EAG correction
Drug acquisition cost errors: cost per model cycle		
CAR-T	£316,275	£316,398
R-BAC	£425	£757
VR-CAP	£450	£855
Drug acquisition cost errors plus fixed regimen cost errors		
ABR arm: Third-line fixed regimen acquisition cost	[redacted]	[redacted]
BR arm: Third-line fixed regimen administration cost	[redacted]	[redacted]

Key: CAR-T, Brexucabtagene autoleucel + rituximab + bendamustine + cytarabine, RBAC, rituximab + bendamustine + cytarabine, VR-CAP, bortezomib + rituximab + cyclophosphamide + doxorubicin + predinisolone, ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab

Adverse event costs

Adverse event costs are applied as one-off costs in the economic model. Summary costs are provided in Table 71 of the CS and unit costs for each event reported in Table 72.

The EAG are satisfied that the company's unit costs of adverse events are broadly appropriate. Despite some risk that recurrent AEs are not fully costed within the economic model, the EAG note that adverse event costs are not a major driver of cost-effectiveness estimates.

Healthcare resource use

Health state costs for progression free and progressed disease are applied per cycle in the model, summarised in Table 69 of the company submission.

The EAG are satisfied that the company's approach to calculating health state costs is appropriate and is aligned with previous NICE appraisals for MCL. The EAG's clinical expert considers the management and frequency of attendance underpinning the health state costs to be appropriate and reflective of UK clinical practice.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's submitted base case ICER, with the correction to TEAE rates applied within their response to CQs and a correction to subsequent treatment cost applied by the EAG, is presented in Table 28 below. Further detail of the EAG correction is provided within section 4.2.8. With the PAS discount ([redacted]) applied, acalabrutinib is associated with an incremental cost of [redacted] an incremental QALY gain of [redacted] and an ICER of £26,256 per QALY gained compared to BR. This ICER does not include confidential PAS discounts to the treatment acquisition cost of the comparators or subsequent treatments. A confidential appendix to the report is provided which details all ICERs with confidential prices applied. No ICER is presented for R-CHOP as it is dominated by BR in the fully incremental analysis.

The dominant driver of cost-effectiveness of acalabrutinib in the model is the lower duration that patients spend in the progressed disease state compared to the comparators. Figures 9 and 10 present the occupancy of each state over the model time horizon. The progressed disease state carries a higher cost and a lower HSUV than the progression-free state. The main cost driver in the progressed disease state is subsequent treatment cost, which accounts for ~[redacted] of the total cost for acalabrutinib, and [redacted] of the total cost for BR and R-CHOP. QALYs accrued in the progressed disease state account for [redacted] of the total QALY for acalabrutinib, [redacted] of the total QALY for BR and [redacted] of the total QALY for R-CHOP.

Table 28 Deterministic company base case with corrections applied by company post clarification and EAG correction (Corrections applied independently)

Description	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Company submitted	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£10,153
Company corrected post CQ	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£10,003
EAG corrected subsequent treatment cost calculation	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,029
EAG corrected BSA dose for CAR-T, RBAC & VR-CAP subsequent treatment regimens	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£10,212
	R-CHOP	[redacted]	[redacted]				

EAG corrected strength of cytarabine and bortezomib sourced from eMIT	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£10,155
Corrected company base case	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	**BR dominates R-CHOP**	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£26,256**

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 9 Health state occupancy of Acalabrutinib arm of company partitioned survival model (Sourced from company model)

Figure 10 Health state occupancy of BR arm of company partitioned survival model (Sourced from company model)

5.2 Company's sensitivity analyses

The EAG presents the probabilistic results of the corrected company base case ICER within table 29. The cost-effectiveness plane and cost-effectiveness acceptability curves are presented in figures 11 and 12 respectively. The probabilistic results are broadly in line with the deterministic results. Similarly, BR dominates R-CHOP in the incremental analysis. The probabilistic analyses show substantial uncertainty regarding the most cost-effective treatment option at threshold values of £20,000 to £30,000 per QALY gained in the EAG corrected version of the company base case analysis. As stated by the company within page 173 Document B of the CS, R-CHOP exhibits high variation in total QALYs. This is due to large CIs applied to the HRs applied to the efficacy estimates of R-CHOP.

Table 29 Company corrected base case probabilistic fully incremental results (corrected by company post-CQs and additional EAG correction)

Comparator	Total costs (£)	Total LYG	Total QALYs	Δ costs (£)	Δ LYG	Δ QALYs	ICER (£/QALY)
R-CHOP	[redacted]	[redacted]	[redacted]				
BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP
ABR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,668

Key: Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

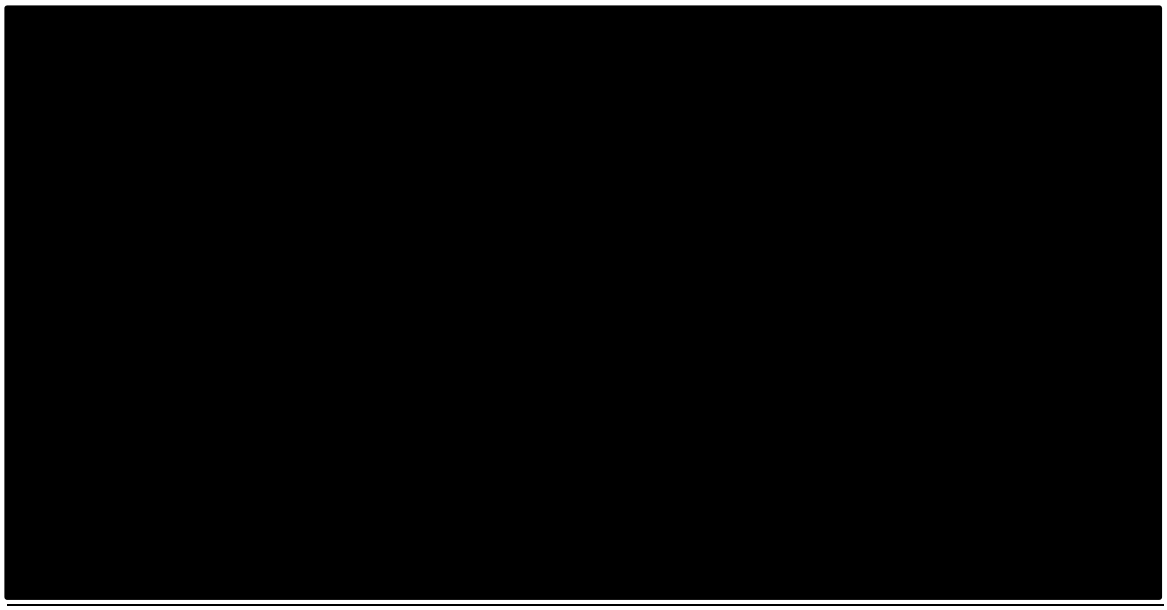


Figure 11 Cost-effectiveness plane of the corrected company base case (re-produced from the company's economic model)

Figure 12 Cost-effectiveness acceptability curve of the corrected company base case (re-produced from the company's economic model)

The company provide results of their deterministic sensitivity analysis against their submitted ICER in Table 84 and figure 33 of their submission. The EAG has run the company's analysis against the corrected company base case and the parameters that the ICER are most sensitive to remain the same. The ICER was most sensitive to variation in the duration of

subsequent ibrutinib treatment (due to its high list price), followed by the proportion of non-fatal PFS events in the BR arm and total use of 1L subsequent treatment in the BR arm.

With respect to scenario analyses conducted by the company, covering methodological, parameter and structural uncertainties and assumptions, detail of these scenarios are provided in Table 85 document B of the company submission. Within document B, the company provided limited exploration of alternative survival curve extrapolations for ABR and PBR. The company analysis focussed on altering the parametric distribution for both PFS and OS curves in both arms to exponential as a more conservative alternative. The company only explored one alternative curve for TTD, log-normal, which had the best statistical fit. In response to clarification, the company conducted additional scenario analysis which explored: utilising individual clinical estimates to inform subsequent treatment durations (table 7, page 17 of company response to CQs), using the HR for ABR versus R-CHOP rather than BR versus R-CHOP (table 10, page 19 of company response to CQs) and utilising HSUVs from other appraisals within MCL and CLL (table 17, page 32 of company response to CQs). The ICER was most sensitive to the log-normal extrapolation of the TTD curve for acalabrutinib, individual clinician estimates of subsequent treatment distribution (clinician 1 &2) and the use of the ECHO trial subsequent treatment distribution. The EAG presents the results of the company scenarios (document B and CQ response) against the corrected company base case in table 30 below.

Table 30 Deterministic scenario analysis against the corrected company base case (scenarios presented in table 85 document B of company CS response and company response to clarification questions)

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Company base case (corrected post CQ and EAG corrected)	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
Document B Table 85							
ITT population, using exponential for OS and PFS for ABR and BR, and log-logistic for TTD for ABR	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£41,011
OS and PFS for ABR and BR: exponential (most conservative long-term projection)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£22,809
TTD for acalabrutinib: log-normal (best statistical fit)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£46,035
Joint models for OS and PFS (using Gamma, per the base case curve selection)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£20,884

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Alternative HR of [redacted] to estimate R-CHOP's PFS	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
No age adjustment for utility values	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
PFS and PD health state utilities are uncapped by general population utility	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£24,905
Use TA502 utility values for PF and PD	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,245
Use ECHO utility values for PF and PD	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£30,640
No vial sharing	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£28,709
Adverse events for lab-based	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
abnormalities incur cost and disutility of 0	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£25,974
Discount rate (costs) = 1.5%	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£29,458
Discount rate (outcomes) = 1.5%	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£21,920
End of life care costs excluded	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,555
Company clarification response							
Table 7. Individual clinician estimates. Clinician 1	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£10,105
Table 7. Individual clinician estimates. Clinician 2	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-£27,332
Table 7. Individual	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
clinician estimates. Clinician 3	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£33,229
Table 7. Individual clinician estimates. Clinician 4	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£21,267
Table 9. R-CHOP HR applied to ABR arm rather than BR arm.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
Table 17. Utilities. PF:PD ratio=0.99. ECHO trial	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£30,640
Table 17. Utilities. PF:PD ratio=0.91. TA502 R/R MCL	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,245
Table 17. Utilities. PF:PD ratio=0.87. TA370 1L MCL	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£28,032
Table 17. Utilities. PF:PD ratio=0.77. TA931 CLL	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£23,095
	R-CHOP	[redacted]	[redacted]				

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Table 17. Utilities. PF:PD ratio=0.90. TA663 1L CLL	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£31,489
Table 17. Utilities. PF:PD ratio=0.75. TA119 1L CLL	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£22,563
Table 20. ECHO trial subsequent treatment distribution	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£83,239

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; MCL, mantle cell lymphoma; OS, overall survival; PD, progressed disease; PF, progression free; PFS, progression-free survival; QALY, quality adjusted life year; R/R, relapsed / refractory; TTD, time to treatment discontinuation.

5.3 Model validation and face validity check

In section B.3.15.1 of document B of the company submission, the company describe technical validation and clinical validation conducted on the model. An independent health economist to the team involved in the submission conducted validation using the TECH-VER checklist. The EAG has similarly conducted its own model validation checks, using a combination of formula checking and completing the TECH-VER checklist.[35]

These TECH-VER checklist identified two issues with the model: (1) when swapping all parameters between treatment arms it became apparent that the calculation for subsequent treatment acquisition and administration costs was not consistent between treatment arms, (2) the PSA was returning extremely low estimates of treatment acquisition cost for acalabrutinib this was due to an underestimation of the TTD curve for acalabrutinib. Detail of Issue (1) is provided in section 4.2.8, briefly, the incorrect treatment duration and administration cost were applied to some subsequent treatments of the subsequent treatment basket in the ABR and BR arms. Issue (2) was due to an error in the matrix multiplication function in the PSA of the "data_parameters" sheet of the model. The multiplication required cells to be filled, whereas the source of these cells from the "data_survival" sheet columns EA onwards was blank. This issue affected several extrapolations, however not those selected for OS and PFS in the company base case. Therefore, the EAG inputted "0" into all required areas on the "data_survival" sheet, where blank, so that alternative curve extrapolations can be explored in the PSA.

The full range of Techver checks completed by the EAG are summarised in Appendix 9.3.

6 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Chapter 4 has identified several key differences between the EAG, and company preferred assumptions. These concerns mostly relate to EAG concerns regarding the appropriateness of a partitioned survival model for this appraisal, specifically that costs of subsequent treatments are included for 2nd and 3rd line treatments, but none of the progression free survival benefit, and only some of the overall survival benefit of those treatments is modelled from the parametric OS and PFS curves fitted to the ECHO trial data. It was however not possible for the EAG to re-build a Markov state transition model in the time available for this appraisal. The EAG therefore has conducted several scenario analyses, reported in this chapter, using a partitioned survival model, but attempting to minimise the biases described in Section 4.2.2. Additional scenario analyses contributing to the EAG preferred base case are described in Table 31. All scenario analyses in Chapter 6 are applied to a company preferred base case ICER that contains company corrections during the clarification phase, and EAG corrections to treatment cost calculations in the company base case model.

Table 31 Summary description and justification for EAG preferred model base case assumptions

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
Clinical effectiveness parameters					
1.	OS and PFS analysis set	Company prefers to censor covid-19 deaths	**EAG preferred scenario:** ITT analysis set with covid-deaths included.	The EAG's clinical expert is of the opinion that COVID-19 deaths, and other respiratory infections remain a relevant consideration.	4.2.6
2.	OS and PFS extrapolation curves for ABR and BR	Based on parametric curves fitted individually to each arm of the ECHO trial data.	**EAG preferred scenario:** Joint models with a HR for ABR applied to the PBR arm of the ECHO study	The company suggest that PHs might not be appropriate. However, the EAG considers the risk of non-proportional hazards to be low, especially in the EAG preferred ITT analysis set. The EAG therefore prefers jointly fitted models.	4.2.6
3.	OS and PFS extrapolation curves for ABR and BR	Gamma curves preferred for all analysis sets and treatment arms.	**EAG preferred scenario:**	The EAG's preference aligns with 2 above where the EAG prefers to assume that the PH assumption holds. The exponential curve was also deemed to provide a more	4.2.6

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
			Exponential curves preferred for all analysis sets and treatment arms.	plausible, conservative estimate of PFS for the PBR arm of the ECHO study according to both the company and EAG clinical experts.	
4.	HSUVs	Duration and disutility of COVID-19 pneumonia based on average of other unspecified events equal to 23.78 days and -0.032	**EAG preferred scenario:** Assume cost and disutility associated with COVID-19 pneumonia is equal to pneumonia (16.03 days and -0.058)	In the absence of disutility and duration data for COVID-19 pneumonia, the EAG finds it more reasonable to assume it is equal to pneumonia rather than assume an average across other events.	4.2.7
5.	HSUVs	Duration and disutility of COVID-19 pneumonia,	**EAG preferred scenario:** Duration and disutility of COVID-19 and rash	Whilst the EAG prefers to assume the disutility and duration of COVID-19 pneumonia is equivalent to pneumonia (see 4. Above), the EAG was not able to	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
		COVID-19 and rash maculo-papular equal to 23.78 days and -0.032	maculo-papular equal to average of all other included events from TA370 (11.35 days and -0.037)	recreate the average duration and disutility calculated by the company applied to events which they could not source an applicable disutility and duration. Given the company calculation is longer than all other included events, the EAG prefers to use the average disutility and duration of events included in the model.	
6.	HSUVs	PFS: ECHO PFS utility value. PD: Multiplier applied to PFS value consisting of: ECHO PFS utility value, absolute difference between	**EAG preferred scenario:** Progressed disease health state utility value which starts at PFS utility value in cycle 0 and decreases to TA370 committee preferred utility value for	The progressed disease health state of the model attempts to capture all subsequent treatment lines and progression in a progressive disease. Therefore, the EAG finds model structure too simplified in its assumption of a constant multiplier over the entire model horizon. It was accepted in TA370 that the 2L treatment state carried	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
		PFS and PD utility values in TA502 multiplied by general population utility	progressed from 2L treatment in MCL (0.45). An exponential function is fitted so that the PD state utility reaches 0.45 at 2.06 years (based on estimated mean PFS for BTK inhibitors of 24.7 months (median PFS = 17.1 months)).	equivalent HSUV to the 1L treatment state. Therefore, the EAG has adopted a simplifying approach which commences the PD utility at the PFS utility value but decreases the utility to the utility of the progressed from 2L treatment state accepted by the committee in TA370 (0.45). The timepoint in which this occurs is based upon the weighted average PFS of BTK treatments in R/R MCL. The PD utility value is then held at 0.45 following this timepoint.	
7.	Vial sharing	Include vial sharing	**EAG preferred scenario:** Assume no vial sharing possible between patients,	The EAG's clinical expert does not agree that vials would be shared across patients, or within patients receiving IV treatment on consecutive days, in UK clinical practice.	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
			or within patients over different administrations		
8.	RDIs for subsequent treatments	Assume RDIs for R-Chemo regimens (R-CHOP, R-BAC & VR-CAP) are = 100%	**EAG preferred scenario:** Assume that RDIs for subsequent treatments are equal to those assumed in 1L (R-CHOP and Rituximab & Bendamustine in RBAC). Where data are not available, assume RDI equal to TA370 (VR-CAP & Cytarabine in RBAC).	The EAG's clinical expert does not consider it reasonable to assume that RDI for subsequent treatment lines is equal to 100%. Such an assumption would not be aligned with previous NICE guidance for MCL.[20, 22, 23]	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
9.	Duration of subsequent treatments	Variety of approaches as per Table 68 of the company submission.	**EAG preferred scenario:** Maximum 6 Tx cycles for R-Chemo regimens (R-CHOP, RBAC & VR-CAP). Ibrutinib MCL treatment duration of 11.70 months sourced from the SmPC for Ibrutinib.	R-chemo regimens are typically given for 6 treatment cycles whilst the assumed durations within the company base case are greater than this. In particular, VR-CAP is assumed to be given for 30.5 months. The EAG does not find the durations used by the company to be plausible. The EAG also prefers to use the treatment duration specific to Ibrutinib sourced from the SmPC. It is not clear from the company submission whether the estimate of 22 months is based upon TTD data.	4.2.8
10.	Inclusion of third-line subsequent treatment costs	Company includes costs of both second- and third-line treatments.	**EAG preferred scenario:** Remove 3rd line treatments from the	There is no evidence from the ECHO trial that treatment with ABR at first line would impact on the proportion of patients receiving 3rd line treatments, including	4.2.8

Analysis number	Parameter/ Analysis	Company base case assumptions	EAG preferred / exploratory analysis	Justification for EAG's assumption	EAG report section
			partitioned survival model.	expensive CAR-Ts. The EAG's clinical expert is of the view that whilst some subsequent treatment lines might be delayed due to improved ABR PFS, they would not be displaced from the average patient's clinical pathway. It is also unlikely that expensive CAR-Ts would be used in clinical practice in a group of patients who are already unsuitable for ASCT at 1st line treatment.	
11.	EAG preferred base case analysis: Scenarios 1-10 combined.				

Key: ASCT, autologous stem cell transplant; CAR-T, chimeric antigen receptor T cell therapy; EAG: external assessment group, HSUV: health state utility values; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression free survival; QALY: quality adjusted life years.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

Table 32 reports the independent impact of each of the EAG's preferred scenario analyses on the ICER. These analyses are all applied to the EAG corrected base case analysis. The key differences in assumptions between the EAG and company preferred base case analyses, with the greatest impact on the ICER are:
The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The company prefers to use a partitioned survival analysis model to estimate cost-effectiveness, but the EAG would have preferred the company to use a Markov state transition model that more accurately captures the benefits of subsequent lines of treatment. The EAG consider the partitioned survival modelling approach to under-estimate OS benefits of subsequent treatments and does not model any of their PFS benefit.

- The company prefers to estimate ABR and BR OS and PFS using independently fitted parametric survival curves to the respective arms of the ECHO trial, based on an analysis set where covid-19 deaths are censored. The EAG prefers to use dependent survival extrapolations and to assume that the proportional hazards assumption holds. The EAG also prefers to base extrapolations on the intention to treat analysis set.

- The company prefers gamma parametric extrapolations for OS and PFS in both the ABR and PBR arms of the model. The EAG prefers the exponential extrapolations because they more closely align with expert opinion and are aligned with the EAG's view that the PH assumption is likely to hold.

- The company prefers progressed disease utilities that are fixed over time, whereas the EAG prefers PD utilities that reduce over time, given that the modelled cohort progress through several lines of treatment with an expectation that each progression event would reduce quality of life. The EAG consider a reducing utility to reduce the magnitude of bias associated

with not fully modelling the treatment benefits of subsequent treatment lines in the partitioned survival model.

- The company prefers to include 3rd line progression subsequent treatment costs, but the EAG prefers not to include these costs given that there is limited evidence to support the impact of acalabrutinib on subsequent need for 3rd line treatment. The EAG also prefers to use different assumptions to the company about relative dose intensities, treatment distributions and vial sharing.

It should be noted that the EAG preferred base case analysis refers to analyses which the EAG were able to implement within the company's current partitioned survival economic model structure. Where possible, the EAG has attempted to adapt the partitioned survival model assumptions, particularly around subsequent treatment costs to minimize the magnitude of bias associated with the model's limited capture of subsequent treatment benefit. However, the EAG re-iterate that their preferred model structure would be a Markov state transition model that models these subsequent lines of treatment explicitly.

Table 32 also presents the EAG preferred probabilistic ICER. Figures 13 and 14 illustrate the uncertainty surrounding the EAG's preferred base case scenario analysis showing a very low probability of cost-effectiveness at a willingness to pay threshold of £20,000 to £30,000 per QALY gained. Additional scenario analyses applied to the EAG preferred base case are provided in Table 33.

Table 32 EAG's preferred model assumptions (applied independently to the corrected company base case (Company post CQ and EAG corrected)

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Company base case (corrected post CQ and EAG corrected)	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
Scenarios applied to corrected Company base case independently							
1. OS & PFS analysis set. ITT analysis set with covid-deaths included.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£23,335
2. OS & PFS extrapolation curves for ABR & BR. Joint models with a HR for ABR applied to the PBR arm of the ECHO study	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£20,884
3. OS & PFS extrapolation curves for ABR & BR.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Exponential curves preferred for all analysis sets and treatment arms.	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£22,809
4. HSUVs Assume disutility and duration associated with COVID-19 pneumonia is equal to pneumonia (16.03 days and -0.058)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,256
5. HSUVs Duration and disutility of COVID-19, COVID-19 pneumonia and rash maculo-papular equal to average of all other included events (11.80 days and -0.051)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,254
6. HSUVs Decreasing utility value of progressed disease based upon	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
exponential function where utility equals 0.45 at 2.06 years	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£19,714
7. Vial sharing Remove vial sharing assumption	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£28,741
8. RDIs for subsequent treatments Assume that RDIs for subsequent treatments are equal to those assumed in 1L (R-CHOP and Rituximab & Bendamustine in RBAC). Where data are not available, assume RDI equal to TA370 (VR-CAP & Cytarabine in RBAC).	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£26,129
9. Duration of subsequent treatments	R-CHOP	[redacted]	[redacted]				

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Maximum 6 Tx cycles for R-Chemo regimens (R-CHOP, RBAC & VR-CAP). Ibrutinib MCL treatment duration of 11.70 months sourced from the SmPC for Ibrutinib.	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£69,512
10. Inclusion of third-line subsequent treatment costs Remove 3rd line treatments from the partitioned survival model.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£54,794
[redacted]							
Deterministic base case: Scenarios 1-10 combined	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£79,837
Probabilistic base case: Scenarios 1-10 combined	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£78,174

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Figure 13 Scatter plot of the cost-effectiveness plane for the EAG preferred base case analysis

Figure 14 Cost-effectiveness acceptability curves for the EAG preferred base case analysis

Table 33 Additional scenario analyses conducted by the EAG, applied independently to the EAG preferred base case analysis

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
EAG preferred base case	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£79,837
Scenarios applied independently unless described otherwise							
1. OS & PFS curve extrapolation Gamma curves from dependent models using the ITT analysis set.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£79,505
2. OS & PFS curve extrapolation Weibull curves from dependent models using the ITT analysis set.	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£79,502
3. HSUVs ECHO utility values for PF & PD health states (removes	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
exponential decrease of PD utility)	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£119,309
4. HSUVs Decrease PD health state utility to reach 0.45 at 5-years (exponential assumed)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£82,664
5. HSUVs Decrease PD health state utility to reach 0.45 at 10-years (exponential assumed)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£88,952
6. Proportion receiving subsequent treatment Equalise proportion receiving 2L treatments (ACA = PBR arm of ECHO)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£82,627

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
7. Proportion receiving subsequent treatment Equalise proportion receiving 3L treatments (ACA = PBR arm of ECHO) & include subsequent treatment at 3L	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£72,256
6 + 7	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£75,046
8. Subsequent treatment distribution at 3L Use clinician 1's estimates but assume 50% is applicable to R-Chemo regimens	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
in equal proportions (exclude ibrutinib from 50% share) and include subsequent treatments at 3L	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£44,051
6 + 7 + 8	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£63,848
9. Subsequent treatment distributions at 2L and 3L Use ECHO trial subsequent treatment distributions and include subsequent treatments at 3L	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£93,019
6+7+9	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		£102,713

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

6.3 Conclusions of the cost effectiveness section

The main issues of residual uncertainty for decision making are as follows:

The OS and PFS benefits of either adopting ABR or BR as first line treatment for untreated MCL in patients unsuitable for ASCT are likely to be under-estimated by the company's partitioned survival economic model structure. The EAG would have preferred a Markov state transition model, that more explicitly models the costs and effectiveness (OS and PFS) of subsequent treatment lines in the pathway. This approach would be more closely aligned with other NICE appraisals of MCL, especially at earlier stages of disease. The EAG attempt to conduct scenario analyses within the partitioned survival model structure to minimise bias, but these should be interpreted cautiously.

The company prefers to estimate ABR and BR OS and PFS using independently fitted parametric survival curves to the respective arms of the ECHO trial, based on an analysis set where covid-19 deaths are censored. The EAG prefers to use dependent survival extrapolations and to assume that the proportional hazards assumption holds. The EAG also prefers to base extrapolations on the intention to treat analysis set.

The company prefers progressed disease utilities that are fixed over time, whereas the EAG prefers PD utilities that reduce over time, given that the modelled cohort progress through several lines of treatment with an expectation that each progression event would reduce quality of life. The EAG consider a reducing utility to reduce the magnitude of bias associated with not fully modelling the treatment benefits of subsequent treatment lines in the partitioned survival model.

The company prefers to include 3rd line progression subsequent treatment costs, but the EAG prefers not to include these costs given that there is limited evidence to support the impact of acalabrutinib on subsequent need for 3rd line treatment. The EAG also prefers to use different assumptions to the company about relative dose intensities, treatment distributions and vial sharing.

7 SEVERITY WEIGHTING

The company and EAG agree that this appraisal does not qualify for the application of a severity weighting.

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9 APPENDICES

9.1 OS and PFS parametric curve selection using the covid-19 censored dataset

Table 34 Overall survival, independently fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	89.9%	82.8%	65.9%	--	--	--	91.0%	87.0%	72.8%	--
SHINE	--	--	87.5%	83.0%	63.1%	--	--	--	--	--	--	--
Exponential	966.3	970.0	92.5%	85.5%	62.5%	45.6%	808.4	812.1	94.2%	88.7%	69.9%	55.1%
Weibull	962.7	970.1	90.1%	83.4%	64.8%	52.1%	808.1	815.5	92.8%	87.5%	71.3%	59.5%
Lognormal	962.6	970.0	89.0%	82.0%	66.5%	57.8%	805.1	812.5	92.3%	86.5%	72.3%	63.8%
Loglogistic	961.7	969.1	89.9%	82.9%	65.1%	54.5%	807.2	814.6	92.7%	87.1%	71.5%	61.3%
Gompertz	961.4	968.8	89.9%	82.3%	66.2%	60.1%	806.4	813.8	92.5%	86.6%	72.6%	66.3%
Generalised Gamma	963.6	974.7	89.6%	82.7%	65.5%	55.2%	806.9	818.0	92.1%	86.3%	72.6%	64.8%
Gamma	963.2	970.6	90.2%	83.6%	64.6%	51.2%	808.4	815.8	92.9%	87.6%	71.2%	58.2%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

Table 35 Overall survival, jointly fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	89.9%	82.8%	65.9%	--	--	--	91.0%	87.0%	72.8%	--
SHINE	--	--	87.5%	83.0%	63.1%	--	--	--	--	--	--	--
Exponential	1774.7	1783.5	92.5%	85.5%	62.5%	45.6%	NA	NA	94.2%	88.7%	69.9%	55.1%
Weibull	1768.9	1782.1	90.3%	83.6%	64.5%	51.5%	NA	NA	92.5%	87.2%	71.6%	60.2%
Lognormal	1765.8	1778.9	89.1%	82.1%	66.2%	57.3%	NA	NA	92.2%	86.5%	72.6%	64.3%
Loglogistic	1767.0	1780.2	90.0%	83.0%	64.9%	54.1%	NA	NA	92.5%	87.0%	71.7%	61.8%
Gompertz	1765.9	1779.1	90.0%	82.5%	66.0%	59.3%	NA	NA	92.3%	86.4%	72.8%	67.1%
Generalised Gamma	1767.3	1784.9	89.5%	82.4%	65.7%	56.0%	NA	NA	92.3%	86.7%	72.3%	63.4%
Gamma	1769.7	1782.9	90.5%	83.9%	64.3%	50.5%	NA	NA	92.6%	87.4%	71.4%	59.6%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

Table 36 Progression free survival, independently fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	78.6%	69.2%	37.0%	--	--	--	86.7%	80.3%	53.4%	--
SHINE	--	--	80.0%	68.2%	43.5%	--	--	--	--	--	--	--
Exponential	1251.9	1255.6	85.6%	73.2%	39.3%	21.1%	964.4	968.1	90.6%	82.1%	55.3%	37.3%
Weibull	1250.5	1257.9	83.2%	71.6%	42.1%	26.1%	964.0	971.4	88.9%	80.8%	57.6%	42.5%
Lognormal	1249.1	1256.5	81.3%	69.4%	46.0%	35.1%	961.1	968.5	87.9%	79.3%	60.1%	49.7%
Loglogistic	1248.7	1256.1	82.5%	70.3%	44.0%	32.0%	963.2	970.6	88.6%	80.1%	58.7%	46.6%
Gompertz	1249.7	1257.1	83.0%	70.5%	44.2%	33.7%	963.5	970.9	88.8%	80.0%	59.3%	49.9%
Generalised Gamma	1249.7	1260.8	82.2%	70.2%	44.3%	31.7%	963.1	974.2	87.9%	79.3%	60.2%	50.0%
Gamma	1251.1	1258.5	83.6%	72.0%	41.6%	24.8%	964.4	971.8	89.1%	81.0%	57.3%	41.4%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

Table 37 Progression free survival, jointly fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	78.6%	69.2%	37.0%	--	--	--	86.7%	80.3%	53.4%	--
SHINE	--	--	80.0%	68.2%	43.5%	--	--	--	--	--	--	--
Exponential	2216.3	2225.1	85.6%	73.2%	39.3%	21.1%	NA	NA	90.6%	82.1%	55.3%	37.3%
Weibull	2212.5	2225.7	83.2%	71.6%	42.2%	26.1%	NA	NA	88.9%	80.8%	57.6%	42.4%
Lognormal	2208.6	2221.8	81.1%	69.5%	46.9%	36.3%	NA	NA	88.3%	79.3%	59.1%	48.2%
Loglogistic	2210.1	2223.2	82.3%	70.2%	44.5%	32.7%	NA	NA	88.9%	80.3%	58.1%	45.7%
Gompertz	2211.2	2224.4	83.0%	70.5%	44.2%	33.7%	NA	NA	88.8%	80.0%	59.3%	49.9%
Generalised Gamma	2209.5	2227.1	81.8%	69.9%	45.3%	33.3%	NA	NA	88.6%	79.8%	58.5%	46.6%
Gamma	2213.4	2226.6	83.6%	72.0%	41.6%	24.8%	NA	NA	89.1%	81.0%	57.3%	41.5%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

9.2 Appendix 2 OS and PFS parametric curve selection using the ITT dataset

Table 38 Overall survival, independently fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	88.5%	79.1%	57.7%	--	--	--	91.0%	83.8%	59.8%	--
SHINE	--	--	87.5%	83.0%	63.1%	--	--	--	--	--	--	--
Exponential	1220.0	1223.7	90.1%	81.2%	53.6%	35.4%	1143.6	1147.3	91.4%	83.5%	58.1%	40.5%
Weibull	1219.0	1226.4	88.1%	79.5%	55.3%	39.9%	1145.6	1153.0	91.5%	83.6%	58.0%	40.1%
Lognormal	1219.6	1227.0	86.8%	77.6%	57.6%	47.1%	1143.9	1151.3	90.9%	82.0%	59.9%	47.7%
Loglogistic	1217.0	1224.4	87.9%	78.7%	55.9%	43.5%	1143.7	1151.1	91.5%	83.0%	58.5%	44.1%
Gompertz	1216.1	1223.5	87.5%	78.0%	57.1%	48.4%	1145.0	1152.4	90.6%	82.5%	59.2%	45.1%
Generalised Gamma	1219.4	1230.5	87.7%	78.6%	56.2%	43.4%	1145.3	1156.4	91.2%	82.6%	59.2%	45.4%
Gamma	1219.5	1226.9	88.4%	79.8%	55.1%	38.9%	1145.5	1152.9	91.7%	83.7%	57.9%	39.8%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; PBR, placebo + bendamustine + rituximab.

Table 39 Overall survival, jointly fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	88.5%	79.1%	57.7%	--	--	--	91.0%	83.8%	59.8%	--
SHINE	--	--	87.5%	83.0%	63.1%	--	--	--	--	--	--	--
Exponential	NR	NR	90.1%	81.2%	53.6%	35.4%	NR	NR	91.4%	83.5%	58.1%	40.5%
Weibull	NR	NR	89.1%	80.3%	54.5%	37.7%	NR	NR	90.4%	82.6%	58.9%	42.8%
Lognormal	NR	NR	87.5%	77.8%	56.2%	45.0%	NR	NR	90.1%	81.6%	61.5%	50.4%
Loglogistic	NR	NR	88.8%	79.3%	54.9%	41.6%	NR	NR	90.6%	82.3%	59.6%	46.4%
Gompertz	NR	NR	88.4%	79.1%	56.0%	44.7%	NR	NR	89.8%	81.5%	60.3%	49.5%
Generalised Gamma	NR	NR	88.4%	79.0%	55.2%	41.8%	NR	NR	90.4%	82.1%	60.2%	47.0%
Gamma	NR	NR	89.3%	80.6%	54.3%	37.0%	NR	NR	90.6%	82.8%	58.7%	42.1%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reported in the company submission; PBR, placebo + bendamustine + rituximab.

Table 40 Progression free survival, independently fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	77.3%	66.2%	32.6%	--	--	--	86.7%	76.7%	40.4%	--
SHINE	--	--	80.0%	68.2%	43.5%	--	--	--	--	--	--	--
Exponential	NR	NR	83.3%	69.4%	33.5%	16.2%	NR	NR	87.7%	77.0%	45.6%	27.1%
Weibull	NR	NR	81.5%	68.2%	35.5%	19.3%	NR	NR	87.6%	76.9%	45.8%	27.4%
Lognormal	NR	NR	79.3%	65.5%	39.8%	28.5%	NR	NR	86.3%	74.7%	49.5%	37.2%
Loglogistic	NR	NR	80.7%	66.4%	37.7%	25.9%	NR	NR	87.4%	75.9%	47.6%	33.7%
Gompertz	NR	NR	80.8%	66.9%	37.7%	26.2%	NR	NR	87.0%	76.2%	47.0%	31.2%
Generalised Gamma	NR	NR	80.5%	66.6%	37.6%	24.5%	NR	NR	87.1%	75.7%	47.7%	32.9%
Gamma	NR	NR	81.9%	68.5%	35.0%	18.3%	NR	NR	87.8%	77.0%	45.6%	27.0%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reported in the company submission; PBR, placebo + bendamustine + rituximab.

Table 41 Progression free survival, jointly fitted curves

	PBR						ABR					
	AIC	**BIC**	**1**	**2**	**6**	**10**	**AIC**	**BIC**	**1**	**2**	**6**	**10**
ECHO	--	--	77.3%	66.2%	32.6%	--	--	--	86.7%	76.7%	40.4%	--
SHINE	--	--	80.0%	68.2%	43.5%	--	--	--	--	--	--	--
Exponential	NR	NR	83.3%	69.4%	33.5%	16.2%	NR	NR	87.7%	77.0%	45.6%	27.1%
Weibull	NR	NR	82.2%	68.6%	34.7%	18.1%	NR	NR	86.8%	76.3%	46.7%	29.2%
Lognormal	NR	NR	79.4%	65.5%	39.4%	28.2%	NR	NR	86.1%	74.7%	49.9%	37.7%
Loglogistic	NR	NR	81.0%	66.5%	37.2%	25.2%	NR	NR	87.0%	75.7%	48.2%	34.6%
Gompertz	NR	NR	81.6%	67.6%	36.5%	23.4%	NR	NR	86.3%	75.4%	48.4%	35.1%
Generalised Gamma	NR	NR	80.8%	66.6%	37.1%	23.8%	NR	NR	86.7%	75.5%	48.4%	34.2%
Gamma	NR	NR	82.5%	68.9%	34.3%	17.3%	NR	NR	87.1%	76.5%	46.4%	28.4%

Key: ABR, acalabrutinib + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; NR, not reported in the company submission; PBR, placebo + bendamustine + rituximab.

9.3 Detailed Techver validation checks

Table 42 Technical validation checks conducted by the EAG (TECH-VER checklist)

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Pre-analysis calculations		
Does the technology (drug/device, etc.) acquisition costs increase with higher prices?	Yes	Yes Increased cell L13 of "Unit Costs" sheet
Does the drug acquisition cost increase for higher weight or body surface area?	Yes	Yes Body surface area(N17) is used which is based upon Height(N15) and Weight(N16) of the "Dashboard" sheet. Increasing height or weight increases the acquisition costs of Acalabrutinib +BR, BR and R-CHOP in rows 48:50 of the "Results" sheet.
Does the probability of an event, derived from an odds ratio (OR)/ relative risk (RR) / hazard ratio (HR) and baseline probability, increases with higher OR/RR/HR?	Yes	Yes Explored HRs applied to the OS, PFS and TTD curves for PBR to generate curves for R-CHOP. The TTD curve is the KM ECHO data for PBR and HR of 2.21(Same as the HR for PFS vs OS) to generate TTD for R-CHOP.
If survival parametric distributions are used in the extrapolations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) under some parameter transformations?	Yes	Yes See rows 330 onwards in "data_parameters" sheet to alter parameters.

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
In a partitioned survival model, does the progression free survival curve or the time on treatment curve crosses the overall survival curve?	No	No ABR: None of the curves cross. However, they all meet general population mortality at the following timepoints: 16 years (OS), 23 years (PFS) and 28 years (TTD). PBR: None of the curves cross. OS and PFS meet general population mortality at 19 years (OS) and 28 years (PFS).
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (the Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes	Yes
Is hazard ratio calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No, it is better if the treatment effect that is applied to the extrapolation comes from the same survival regression in which the extrapolation parameters are estimated.	Derived from results of ITC of ECHO, BRIGHT and SriL NHL1 trials.
For the treatment effect inputs, if the model uses outputs from WINBUGs, are the OR, HR and RR values all within plausible ranges? (should be all non-negative and the average of these WINBUGs outputs should give the mean treatment effect)	Yes	N/A

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Event-state calculations		
Calculate the sum of the number of patients at each health state	Should add up to the cohort size	Yes Summed columns S,T & V of "Intervention", "Comp_1" and "Comp_2" sheets. All rows summed to 100%.
Check if all probabilities and number of patients in a state are greater than or equal to zero	Yes	Yes
Check if all probabilities are smaller than or equal to one	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Should be larger	Yes Occupancy of the death state is higher in each subsequent cycle for all comparators.
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes	No. However, approximately an equal percentage of patients remain alive at age 100 across comparators (Between 1.2%-1.5%).
Discrete event simulation specific: sample one of the "time to event" types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Sample mean and variance & the simulation outputs should reflect the distribution it is sampled from.	N/A
Set all utilities to one Set all utilities to zero	The QALYs accumulated at a given time would be the same as	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
	the life years accumulated at that time No utilities will be accumulated in the model	Not possible to set to 0 as utilities within the trace are based upon multipliers returning a "#DIV/0!" error. However, The model behaves as expected.
Decrease all state utilities simultaneously (but keep event based utility decrements constant)	Lower utilities will be accumulated each time	Yes Altered utilities on "data_utility" sheet cells C14 and C24.
Set all costs to zero	No costs will be accumulated in the model at any time	Yes Changed all costs within the "Unit Costs" sheet leads to total cost of £0 for all cost categories within the model trace: "Intervention", "Comp_1" & "Comp_2".
Put mortality rates to 0	Patients never die	Yes All parametric OS extrapolations changed to 100% throughout time horizon on "data_survival" sheet. Background mortality changed to 100% throughout on "Background mortality" sheet. As R-CHOP is calculated based on HR on "data_traces" sheet no changes had to be made to OS R-CHOP curve.
Put mortality rate extremely high	Patients die in the first few cycles	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Set the effectiveness, utility and safety related model inputs for all treatment options equal	Same life years and QALYs should be accumulated for all treatment at any time	Yes Equalised all survival curve parameters to COVID-19 ABR for BR and set HR of R-CHOP vs BR to 1.
In addition to the inputs above, set cost related model inputs for all treatment options equal	Same costs, life years and QALYs should be accumulated for all treatment at any time	No Coding error in "Subsequent Treatments" sheet cells D48 and E49. Car-T treatment duration (1 month) used for RBAC and VRCAP for Acalabrutinib arm. CAR-T administration cost used for RBAC and RBAC administration cost used for CAR-T in the PBR arm. This leads to an underestimation in the Acalabrutinib arm and overestimation in the PBR arm.
Change around the effectiveness, utility and safety related model inputs between two treatment options	Accumulated life years and QALYs in the model at any time should be also reversed	Yes
Check if the number of alive patients estimate at any cycle is in line with general population life table statistics	At any given age, the % alive should be lower or equal in comparison to the general population estimate	Yes
Check if the QALY estimate at any cycle is in line with general population utility estimates	At any given age, the utility assigned in the model should be lower or equal in comparison to the general population estimate	Yes

Test description (Please document how the test is conducted, as well)	**Expected result of the test**	**Results**
Set the inflation rate of the previous year higher	The costs (which are based on a reference from previous years) assigned at each time will be higher	N//A
Calculate the sum of all ingoing and outgoing transition probabilities	Both should be one	Yes
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Numbers entering = Numbers leaving	N/A
Check if the time conversions for probabilities were conducted correctly.	Yes	Yes
Decision tree specific: calculate the sum of the expected probabilities of the terminal nodes	Should sum up to one	N/A
Patient-level model specific: check if common random numbers are maintained for sampling for the treatment arms?	Yes	N/A
Patient-level model specific: check if correlation in patient characteristics is taken into account when determining starting population?	Yes	N/A
Increase the treatment acquisition cost	Costs accumulated at a given time will increase during the period when the treatment is administered	Yes
Population model specific: set the mortality and incidence rates to zero	Prevalence should be constant in time	N/A

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Result calculations		
Check the incremental life years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less effective treatments	Yes
Check the incremental cost results. Are they in line with the treatment costs?	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs.	Yes
Total life years > total quality adjusted life years	Yes	Yes
Undiscounted results > discounted results	Yes	Yes
Divide undiscounted total QALYs by undiscounted life years.	This value should be within the outer ranges (maximum and minimum) of the all utility value inputs.	Yes
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Better outcomes for better baseline health conditions and worse outcomes for worse health conditions are expected.	N/A
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes	Yes
Does the total life years, QALYs and costs decrease if a shorter time horizon is selected?	Yes	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Is the reporting and contextualization of the incremental results correct?	The use of the terms such as: "dominant"/ "dominated"/ "extendedly dominated"/ "cost-effective" etc. should be in line with the results. In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment.	Yes, however the model does not have the functionality to run a fully incremental analysis in each scenario. I.e., ordering the comparators by efficacy, finding the dominated strategies and presenting the ICER against the next best alternative. Model presents pairwise comparison of the comparators versus acalabrutinib. Appropriate results are provided to conduct a fully incremental analysis.
Are the reported ICERs in the fully incremental analysis non-decreasing?	Yes	See comment above.
If disentangled results are presented, do they sum up to the total results? (e.g. different cost types sum up to the total costs estimate)	Yes	Yes
Check if half cycle correction is implemented correctly (total life years with half cycle correction should be lower than without)	The half cycle correction implementation should be error free. Also check if it should be applied for all costs, for instance if a treatment is administered at the start of a cycle, half cycle correction might be unnecessary.	Yes No switch exists in the model to remove the correction. However, it is implemented correctly. QALYs are corrected, costs are not to account for all patients receiving treatment at the start of a cycle and accounts for potential wastage.
Check the discounted value of costs/QALYs after 2 years	Discounted value=undiscounted/$(1+r)^2$	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Set discount rates to zero	The discounted and undiscounted results should be the same	Yes
Set mortality rate to zero	The undiscounted total life years per patient should be equal to the length of the time horizon	Yes
Put the consequence of adverse event/discontinuation to zero. (zero costs and zero mortality/utility decrements)	The results would be the same as the results when AE rate is set to zero.	Yes
Divide total undiscounted treatment acquisition costs by the average duration on treatment.	This should be similar to treatment related unit acquisition costs	Yes
Set discount rates to a higher value	Total discounted results should decrease	Yes
Set discount rates of costs/effects to an extremely high value	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Yes
Put adverse event/discontinuation rates to zero and then to extremely high level.	Less costs higher QALYS/LYs when adverse event rates are 0, higher costs and lower QALYS/LYs when AE rates are extreme	Yes
Double the difference in efficacy and safety between new intervention and comparator and report the incremental results.	Approximately twice of the incremental effect results of the base case. If this is not the case :	No issues envisaged. Not possible given the partSA structure. However, all other tests regarding the HR

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
	report and explain the underlying reason/ mechanism	and parametric curves reveal they behave as expected.
Do the same for a scenario in which the difference in efficacy and safety is halved.	Approximately halve of the incremental effect results of the base case. If this is not the case : report and explain the underlying reason/ mechanism	See above.
Uncertainty analysis calculations		
Are all parameters subject to uncertainty included in the one-way sensitivity analysis (OWSA)? Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters).	Yes No	Yes
Are the upper and lower bounds used in the one-way sensitivity analysis used confidence intervals based on the statistical distribution assumed for that parameter? Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes Yes	Yes Yes
Check that all parameters used in the sensitivity analysis have an appropriate associated distributions - upper and lower bounds should surround the deterministic value (i.e. Upper bound ≥ mean ≥ Lower bound) - standard error and not standard deviation used in sampling - Lognormal / gamma distribution for hazard ratios and costs/ resource use	Yes	Yes Checked a sample and all behaved as expected.

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
- Beta for utilities and proportions/probabilities - Dirichlet for multinomial - Multivariate normal for correlated inputs (e.g. survival curve or regression parameters) - Normal for other variables as long as samples don't violate requirement to remain positive when appropriate		
Check PSA output mean costs, QALYs and ICER compared to the deterministic results. Is there a large discrepancy?	No (in general)	No Moderate increase/decrease in R-CHOP total cost and QALY. Does not impact CE conclusions.
If you take new PSA runs from the excel model do you get similar results?	Yes	No Error in matrix multiplication of blank cells within the "data_parametrs" sheet. This resulted in a large underestimation of the ACA TTD Weibull curve and other curves not used in the company base case. The EAG altered affected cells to return "0.00" which corrected the issue.
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or has an unusual shape?	No	Yes However, the was corrected when fixed the issue described above.
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes	Yes

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
Do the explored scenario analyses provide a balanced view on the structural uncertainty? (i.e. not always looking at more optimistic scenarios)	Yes	Yes (In general) The company explored pessimistic extrapolations of PFS/OS and TTD. However, the company did not explore independently changing the extrapolations for each arm (i.e., both were changed to exponential). It should also be noted that the model is highly simplified, in the context of early-stage disease, this limits the models ability to explore alternative assumptions regarding long term modelling assumptions.
Are the scenario analysis results plausible and in line with a priori expectations?	Yes	Yes
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random streams are used for different arms	Very low correlation.
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are they scattered evenly between 0-1 when they are plotted?	Yes	Yes
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter, use graphical methods to examine distributions, functions	The sample means and the point estimates will overlap, the graphs will be similar to the corresponding distribution	Yes Tested a sample which behaved as expected.

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
	functions (e.g. Normal, Gamma, etc.)	
Check if sensitivity analyses include any parameters associated with methodological/ structural uncertainty (e.g. annual discount rates, time horizon).	No	Yes Company tested lowering the discount rates. However, alternate time horizons were not explored. The time horizon aligns with the references case, reducing the time horizon behaves as expected.
Value of information analysis if applicable: Was this implemented correctly? Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions? Is EVPI larger than all individual EVPPI? Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)? Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	Yes	N/A
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (additional macro can be embedded to PSA code, which stops the PSA when an error such as negative transition probability, is detected)	Yes	Not tested.
Check the correlation between 2 PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Should be very low (very high) if different (same) random	Very low

Test description (Please document how the test is conducted, as well)	Expected result of the test	Results
	streams are used for different arms	
OWSA=one-way sensitivity analysis; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; WTP = willingness to pay; CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; LY = life years; QALYs = Quality adjusted life years; OR = odds ratio; RR= relative risk; HR = hazard ratio		

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Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

EAG critique of company submission addendum

Produced by Aberdeen HTA group

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Version: **1.0**

Strictly confidential: Contains [redacted] information

Overview & Timeline

The original company submission for this topic was received in November 2024, and the EAG report completed in February 2025. The appraisal was subsequently paused (June 2025) and re-started in December 2025, at which point the company were provided with an opportunity to submit an addendum to the original company submission. The following key information were provided to the EAG:

- A company submission addendum consisting of additional analyses using a new, updated data cut was provided. For consistency with the company submitted addendum, the EAG documentation refers to the interim data cut used for the original company submission (15/02/2024) as DCO1, with the most recent data cut (15/02/2025) referred to as DCO2, provided to the EAG on Jan 6th, 2026.
- In response to concerns raised in the EAG report, and given that the company were unable to source SACT data, patient characteristics (age, gender) and OS outcomes were sourced by NICE and provided to the EAG and company for critique.

The following sections provide the EAG's critique of the company submitted addendum ahead of the first committee meeting for this appraisal. The EAG critique of the company's updated clinical effectiveness analysis using DCO2 is reported first, followed by a critique of the impact of using DCO2 results on the assumptions originally preferred in the EAG report. ICERs corresponding to company and EAG preferred scenarios, described in Chapters 5 and 6 of the EAG report are replicated using the most recent DCO2 data cut. Comparator and subsequent treatments for this appraisal are subject to confidential pricing arrangements. A confidential appendix to this critique reproduces all ICERs from this critique document, with confidential prices applied.

EAG commentary and critique of the company updated clinical effectiveness evidence from DCO2.

The EAG reviewed the addendum produced by the Company. The EAG conclusion is the same as for the main submission. The EAG agree that the analysis presented by the Company shows that there is a benefit from Acalabrutinib in combination with

Bendamustine and Rituximab in comparison to PBR for progression-free survival and time to next treatment. The EAG is also happy with the analysis which produces a hazard ratio favouring ABR for overall survival. As the median OS is not observable in either the ABR or PBR group, this suggests that the data is not yet mature enough to observe an OS benefit.

The EAG is still in favour of using the full analysis set without censoring the data for COVID-19 deaths. This was the recommendation of the EAG's clinical expert. As indicated in the first EAG report, BTK inhibitors could have an impact on other respiratory infections such as flu or other seasonal respiratory infections and with Covid-19 continuing to circulate it is not appropriate to ignore this as a source of mortality. Censoring the analyses for Covid-19 deaths might over-estimate the treatment benefit of ABR. The complete ITT analysis set also maintains the benefits of randomisation from the ECHO trial and is therefore less biased.

The EAG notes the Schoenfeld residuals plots in figures 18 and 22 of the company addendum document respectively. These correspond to the analyses of PFS and OS shown in figures and tables 1 and 3 of the company addendum document respectively. These are the EAG's favoured analyses. In neither instance is the test on the residuals rejected and the solid line on the plots is not suggesting major fluctuation in the hazard ratio across time. In both figures 1 and 3 respectively, the difference between the curves is small and there is also little divergence in the curves. The EAG's conclusion based on the hazard curves, Schoenfeld residual plots, and test on the residuals is that the proportional hazard assumption holds. The EAG opinion is that a suitable analysis would apply a hazard ratio to an appropriate parametric distribution of both the PFS and OS, or use joint dependent models as applied in company scenario analyses in the original company submission, but which have not been replicated in the company addendum document.

SACT data

The EAG report raised some concerns that might helpfully be addressed by access to SACT data for this appraisal. Specifically, key issue 4 in the EAG report raised concerns that the duration and distribution of subsequent treatments at both second and third line are uncertain and that SACT data might be able to help resolve uncertainty around the proportion and type of 2nd and 3rd line treatments most likely to be used in routine UK clinical practice for the BR and RCHOP arms of the model. Specifically, the company were asked to investigate real-world, including SACT data where possible, evidence to inform:

- The Kaplan-Meier (KM) curve(s) for overall survival (OS) (including age and gender breakdown, if possible)
- Where possible, the KM curve(s) for OS for people whose condition is not suitable for autologous stem cell transplant (ASCT)
- The proportion of people that have any 2nd line treatment; the distribution of 2nd line treatments; and the duration of 2nd line treatments
- Where possible, for people whose condition is not suitable for ASCT: the proportion of people that have any 2nd line treatment, the distribution of 2nd line treatments; and the duration of 2nd line treatment.
- The proportion of people that have any 3rd line treatment; the distribution of 3rd line treatments; and the duration of 3rd line treatments.
- Where possible, for people whose condition is not suitable for ASCT: the proportion of people that have any 3rd line treatment, the distribution of 3rd line treatments; and the duration of 3rd line treatments

The company were unable to provide the requested information using SACT data, and subsequently NICE sought access directly to the SACT data. The cohort of patients included in the SACT analysis were aged 18 or over, with a known gender, ICD-O-3 code 9673, diagnosed between 2017 and 222, whose first systemic treatment was BR or R-CHOP. Patients with a known previous ASCT were excluded to more closely match the scope of the appraisal. The following parameters were provided to the EAG separately for BR and R-CHOP:

- Age and gender distribution

- Overall survival KM curves
- A range of parametric survival curves fitted to the KM data.

Subsequent treatment proportions and distribution of treatment types were not provided to the EAG for analysis.

The EAG has included functionality within the company's economic model to integrate the SACT OS data for both BR and R-CHOP. As can be seen from the comparison of ECHO trial data and SACT data provided by NICE, there are substantial differences in OS extrapolations for the BR arm. This raises some uncertainty about the generalisability of OS outcomes from the ECHO trial (BR arm) to the cohort of patients receiving BR in UK clinical practice. On average, the SACT population are slightly older (BR only) than the corresponding BR arm of the ECHO trial. However, as can be seen in Table 1 below, OS outcomes are significantly worse in the SACT dataset compared to the BR arm of the ECHO trial (ITT analysis), with SACT LYGs = [redacted] of those modelled based on the BR arm of ECHO (all analyses using Gamma OS curves). Whilst the EAG initially envisaged utilizing the SACT dataset and applying HRs from the ECHO trial to the underlying OS curves to estimate the impact on cost-effectiveness, this would not necessarily be helpful for decision making in the current context because corresponding PFS data are not available from SACT.

The data are, however, useful for contextualizing the outcomes that might be feasible in a UK clinical setting. If one was to assume that real-world PFS for BR was also lower in UK clinical practice than in the ECHO trial, then applying both OS and PFS HRs from the trial to the UK population most likely to receive ABR and BR treatment might be expected to result in lower incremental LY and QALY gains that a similar approach using higher baseline PFS and OS proportions as observed in the ECHO trial. Whilst the scenario described would plausibly lead to higher ICERs using real-world data than observed using the trial data, the magnitude of any impact on the ICER remains unclear.

Table 1 compares the available patient characteristics and key overall survival outcomes from the ECHO trial and available SACT data.

Table 1 Comparison of summary data from ECHO trial data and SACT data

	ECHO ABR DCO 1	ECHO ABR DCO 2	ECHO BR DCO 1	ECHO BR DCO 2	SACT BR	SACT R-CHOP
Mean age	71.6	71.6	71.6	71.6	74.7	69.5
% Male	71.6%	71.6%	69.9%	69.9%	72.8%	74.6%
PFS (mths), IRC, ITT, Median (95% CI)	66.4 (55.1, NE)	72.5 (60.7, NE)	49.6 (36.0, 64.1)	47.8 (36.1, 60.8)	Not Available	Not Available
PFS by IRC assessment, covid-19 censored, Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	Not Available	Not Available
OS, ITT, Median (95% CI)	NE (72.1, NE)	NE (73.3, NE)	NE (73.8, NE)	NE (73.8, NE)	40.51 (NR, NR)	38.80 (NR, NR)
Modelled LYGs, (ITT, independent, gamma OS curve)	[redacted]	[redacted]	[redacted]	[redacted]	4.21	--

N/A = Not applicable; NE = Not estimable (median timepoint not reached); NR = Not Reported.

EAG commentary and critique of company updated cost-effectiveness analyses

OS and PFS curves:

The EAG refers to the critique of cost-effectiveness evidence provided in Chapter 4 of the EAG report and note that those critique points remain unchanged unless specified otherwise in this document.

As noted in the critique of clinical effectiveness evidence, the EAG prefers to use the ITT analysis set, with joint (dependent models) to extrapolate OS and PFS data from the trial

over the model time horizon. Within the company preferred parametric curve selection for this specific analysis, the company's economic model specifies the use of Gamma curves. However, the company has not provided a justification for the selection of the gamma curve for the EAG preferred joint models using the ITT analysis set. The EAG note that, for DCO1 exponential curves had the best fit to the KM data and lowest combined AIC / BIC scores amongst the set of PH compliant parametric survival curves. Whilst not reported within the company addendum submission, AIC and BIC scores were available from within the company's economic model for joint models, applied to the ITT analysis set, using DCO2 and are summarised for OS and PFS in Table 2 below. The EAG note that the Gompertz model is the best statistical fit to the data amongst the set of PH compliant curves from DCO2 and is preferred by the EAG for both OS and PFS.

Table 2 Comparison of AIC and BIC fit for alternative parametric survival curves for joint models using the ITT analysis, DCO2.

	ITT Dependent (joint) survival models, DCO2, OS				ITT Dependent (joint) survival models, DCO2, PFS			
Distribution	**AIC**	**Rank**	**BIC**	**Rank**	**AIC**	**Rank**	**BIC**	**Rank**
Exponential	2622.5	7	2631.3	3	2831	7	2839.8	5
Weibull	2621.5	5	2634.7	5	2828.6	5	2841.8	6
Lognormal	2618.7	4	2631.9	4	2822.3	3	2835.5	2
Generalized Gamma	2618.2	3	2635.7	7	2822.2	2	2839.7	4
Loglogistic	2616	2	2629.2	2	2821.4	1	2834.6	1
Gompertz	2615.9	1	2629.1	1	2822.6	4	2835.7	3
Gamma	2622.4	6	2635.5	6	2830	6	2843.2	7

Subsequent treatment proportions and distribution of subsequent treatments at 2nd and 3rd line

The proportion of patients receiving subsequent 2nd line treatment was updated using the DCO2 data-cut and included in the economic model. The EAG considers it appropriate to include the updated proportions receiving 2L subsequent treatment. The EAG note that no further information was available on the proportion or distribution of 3rd line treatments and the proportions remain unchanged from the original company submission. The EAG agree with the company's assumption about the proportion of patients receiving 2nd line treatments.

The EAG note the company's additional analysis of time to next treatment and appreciate the observed reduction in the proportion of patients requiring a 3rd line of treatment over the observed time period. However, it remains unclear whether this represents a delay in treatment need driven by longer PFS, or an absolute effect that would be continued indefinitely over the modelled time horizon. Due to this uncertainty, the EAG retains our original preference to remove 3rd line treatment costs from the economic model. The EAG approach helps to reduce the risk of bias in the estimates of the ICER associated with capturing 3rd line treatment costs, but not capturing the added OS benefits of those 3rd line treatments. Indeed, the same logic applies, albeit to a lesser extent for 2nd line treatment costs. The EAG are concerned that the company preferred approach is likely to bias the ICER in favour of ABR and the magnitude of that bias could be substantial. The EAG re-iterates the link between this point around subsequent treatments and the EAG's critique of the appropriateness of using a partitioned survival model at this early point in the treatment pathway as opposed to a Markov model that more explicitly captures the respective impacts of different lines of treatments (See Section 4.2 of the EAG report).

Whilst the EAG agrees with the updated subsequent treatment proportions from DCO2, no further changes are made to the EAG's preferred subsequent treatment assumptions about duration of subsequent treatments or removal of 3rd line treatment costs from the partitioned survival model.

Summary of company and EAG preferred assumptions following DCO1 and DCO2 and impact of updated DCO2 on ICERs

Table 3 summarises the company and EAG preferred base case assumptions following the additional DCO2 data-cut from the ECHO trial. Full details of the justification for EAG preferred assumptions are detailed in Chapter 6 of the EAG report. The impact of the new DCO2 data-cut on company and EAG preferred ICERs are provided in Tables 4-6 below.

Table 3 Company and EAG original (DCO1) and updated (DCO2) base case preferences

Key parameter / assumption	Company original preference, DCO1	EAG report preference, DCO1	Company preference with DCO2	EAG preference with DCO2
Analysis set	Covid-19 censored	ITT	Covid-19 censored	ITT
Independent vs. joint models of OS and PFS	Independent	Joint	Independent	Joint
OS and PFS extrapolation curves, ITT analysis set, joint models	Gamma	Exponential	NR [A]	Gompertz
ABR TTD curve	Weibull	Weibull	Weibull	Weibull
HSUV assumptions	As per EAG report, Table 31			
Vial sharing	Yes	No vial sharing **across or between** patients	No vial sharing **across** patients	No vial sharing **across or between** patients
RDI	As per EAG report, Table 31			
Subsequent treatment costs and durations	As per EAG report, Table 31			

[A] Assume company preference for Gamma curve as per DCO1 but requires company confirmation. Note that choice of curve has not yet been validated with clinical expert opinion.

Table 4 Deterministic company base case with corrections applied by company post clarification and EAG correction, Corrections applied independently (Update of EAG report, Table 28 using DCO2)

Description	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
(1) Company submitted	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£2,049**
(2) Company corrected post CQ (corrected TEAE incidence rates)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£1,885**
(3) EAG corrected subsequent treatment cost calculation	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£19,323**
(4) EAG corrected BSA dose for CAR-T, RBAC & VR-CAP subsequent treatment regimens	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£2,154**
(5) EAG corrected strength of cytarabine and bortezomib sourced from eMIT	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£2,051**

(6) Remove vial sharing [A]	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£4,132**
Corrected company base case, scenarios 1-5 combined	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£19,603**
Company preferred base case, addendum submission, scenarios 1+2+3+6	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£21,849**
Company preferred base case (addendum), with all EAG corrections applied, scenarios 1-6 combined.	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,404**

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[A] Vial sharing removed by the company in updated company submission addendum.

Table 5 Company corrected base case probabilistic results, company preferred addendum + all EAG corrections applied (Update of EAG report, Table 29 using DCO2)

Comparator	Total costs (£)	Total QALYs	Δ costs (£)	Δ QALYs	ICER (£/QALY)
R-CHOP	[redacted]	[redacted]			
BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP
ABR	[redacted]	[redacted]	[redacted]	[redacted]	£21,389

Key: Δ, incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.

Table 6 EAG's preferred model assumptions (applied independently to the EAG corrected, company preferred addendum base case; (Update of EAG report Table 32 using DCO2)

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
Company base case (corrected post CQ and EAG corrected)	R-CHOP	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,404**
Scenarios applied to corrected Company base case independently							
1. OS & PFS analysis set. ITT analysis set with covid-deaths included.	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,790**

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
2. OS & PFS extrapolation curves for ABR & BR. Joint models with a HR for ABR applied to the PBR arm of the ECHO study (company preferred gamma curves) [A]	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£21,335**
3. OS & PFS extrapolation curves for ABR & BR. Gompertz curves preferred for all analysis sets and treatment arms (EAG curve preference based on ITT, joint models)	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£30,821**
4. EAG preferred OS and PFS curves and datasets Scenarios 1-3 combined.	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£15,518**
5. HSUVs Assume disutility and duration associated with COVID-19 pneumonia is equal to pneumonia (16.03 days and -0.058)	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,404**

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
6. HSUVs Duration and disutility of COVID-19, COVID-19 pneumonia and rash maculo-papular equal to average of all other included events (11.80 days and -0.051)	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,402**
7. HSUVs Decreasing utility value of progressed disease based upon exponential function where utility equals 0.45 at 2.06 years	R-CHOP	[redacted]	[redacted]	-	-		
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£14,925**
8. Vial sharing EAG prefer to assume not vial sharing within or between patients [B]	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£22,424**
9. RDIs for subsequent treatments Assume that RDIs for subsequent treatments are equal to those assumed in 1L	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
(R-CHOP and Rituximab & Bendamustine in RBAC). Where data are not available, assume RDI equal to TA370 (VR-CAP & Cytarabine in RBAC).	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£21,881**
10. Duration of subsequent treatments Maximum 6 Tx cycles for R-Chemo regimens (R-CHOP, RBAC & VR-CAP). Ibrutinib MCL treatment duration of 11.70 months sourced from the SmPC for Ibrutinib.	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£70,762**
11. Inclusion of third-line subsequent treatment costs Remove 3rd line treatments from the partitioned survival model.	R-CHOP	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£55,087**

Scenario detail	Comparator	Total cost	Total QALY	Incr. cost	Incr. QALY	Dominants	ICER
EAG preferred base case							
Deterministic base case: Scenarios 4-11 combined	**R-CHOP**	[redacted]	[redacted]	-	-	-	-
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£75,589**
Probabilistic base case: Scenarios 1-10 combined	**R-CHOP**	[redacted]	[redacted]				
	BR	[redacted]	[redacted]	[redacted]	[redacted]	BR dominates R-CHOP	
	Acalabrutinib + BR	[redacted]	[redacted]	[redacted]	[redacted]		**£74,221**

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

[A] The company's economic model does not automatically select the company preferred Weibull TTD curve when switching to joint models of OS and PFS – applied manually here by the EAG.

[B] Company removal of vial sharing assumptions applied only to between patients. EAG also prefers to remove vial sharing within patients across appointments.

Single Technology Appraisal

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma [ID6155]

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 Monday 24 February 2025** 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 [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Economic model structure., p. xix: The description of the issue notes that the partitioned survival model structure "does not incorporate PFS benefits and likely underestimates the OS benefits of subsequent treatment lines following progression after treatment with ABR and BR". This statement could be considered misleading and is repeated several times throughout the report. The company provided model does capture some benefits in 2nd line PFS as the curves presented capture crossover from BR to ABR.	The text should be updated to: "The company preferred partitioned survival model structure may not fully capture PFS benefits of subsequent treatment lines following progression after treatment with ABR and BR, and likely underestimates the OS benefits of subsequent treatment lines following progression after treatment with ABR and BR"	The original text could be interpreted as implying that the chosen model structure does not account for PFS benefits at all, therefore should be updated to clarify that this issue only partially applies to subsequent treatments.	The EAG does not consider this to be a factual inaccuracy. As cross-over to acalabrutinib from the PBR arm of the ECHO trial only occurred after progression, the presented PFS curves only capture the PFS benefit of the initial decision to treat with ABR versus BR. No amendment to the EAG report is required.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Economic model structure., p. xix: “The magnitude of bias could be substantial. All else held equal, the direction of bias would be expected to favour the initial line of treatment with a longer time to progression (ABR). This could mean that the ICER for ABR vs. BR is substantially underestimated”	The text should be updated to remove quantification and direction of bias from the chosen model structure and instead reference the uncertainty of using a partitioned survival model structure. For example, the text could state: “There is a potential for bias, introducing uncertainty around the ICER for ABR vs. BR”.	The size and direction of bias from an alternative model structure (proposed Markov model) is unknown as there is no alternative structure available to compare the company submitted model to. Therefore, it is speculative to state that the magnitude of bias could be substantial and that the ICER may be underestimated.	Not a factual inaccuracy. The partitioned survival model under-estimates benefit (i.e. QALYs gained) from subsequent treatment lines. Given that ABR has improved PFS compared to BR, the QALY under-estimation at 2nd and 3rd lines is greater in the BR. This biases in favour of ABR. However, the EAG report is updated to reflect uncertainty around the magnitude of this bias.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Extrapolation of OS and PFS data., p. xx: “The EAG would appreciate full details of parametric curve selection for the ITT analysis set, for joint models, including AIC and BIC criterion, which were not available to the EAG.”	This text requires removing.	Full details of parametric curve selections for the ITT population for the joint models were presented in Appendix P to Document B, for OS and PFS.	Not a factual inaccuracy. Appendix P of the company submission provides parametric curve selections for joint models, applied to the Covid-19 censored analysis set. Corresponding curve selection information for the ITT analysis set (joint models) is not available in the company submission appendices. No amendment to the EAG report is required.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6, Covid-19 censored vs. ITT analysis, p. 45: "*Covid-19 continues to circulate widely within communities and in hospitals, suggesting it is not appropriate to ignore Covid-19 mortality when future planning."* This statement is potentially misleading as it suggests the impact of COVID-19 at the height of the pandemic reflects the current health climate.	The company would suggest the EAG contextualises that the health landscape has shifted since the pandemic and whilst COVID-19 continues to have an impact, it is not to the same extent as when the trial was conducted.	Update for clarity.	The EAG has reworded the sentence to provide a more balanced assessment of clinical decision-making in NHS practice. For clarity, we have updated the quoted text in the EAG report as follows: *"Despite no longer being under pandemic status, Covid-19 and other respiratory illnesses remain in widespread circulation and remain relevant considerations for treatment selection as they continue to cause significant morbidity and mortality for patients with*

			Haematological malignancies. The EAG therefore does not consider it appropriate to censor covid-19 related deaths for population of the economic model parameters."

Issue 5

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 4.2.8, Subsequent treatment costs – proportions requiring 2L and 3L treatment, p. 68: "Given the time taken to reach 3rd line treatment and small numbers progressing twice in the ECHO trial, the EAG does not consider differences in 3rd line treatment proportions to be evidence based"	This text should be updated to "Given the time taken to reach 3rd line treatment and small numbers progressing twice in the ECHO trial, the EAG does not consider differences in 3rd line treatment proportions to be certain".	Update for clarity as the proportions requiring 3rd line treatment is derived from ECHO trial data.	For clarity, we have updated the quoted text in the EAG report as follows: *Given the time taken to reach 3rd line treatment and small numbers progressing twice in the ECHO trial, the EAG considers differences in 3rd line treatment proportions to be highly uncertain, and not*

			sufficiently robust for decision making"

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Health State Utility Value for progressed disease., p. xxi The description of issue 3 says: *"The company has applied a fixed PD utility across all subsequent lines of treatment. This is important because it likely over-estimates PD utilities early in the model trace, but over-estimates them later."* We believe this should say *"The company has applied a fixed PD utility across all subsequent lines of treatment. This is important because it likely under*estimates PD utilities early in the model trace, but over-estimates them later."	The text should be updated to "The company has applied a fixed PD utility across all subsequent lines of treatment. This is important because it likely underestimates PD utilities early in the model trace, but over-estimates them later."	Update for clarity/to avoid confusion.	The EAG report has been updated as requested.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 8, p.24	“Secondary outcome: OS” the title “Median PFS” is used instead of “Median OS”. Please relabel to correct title.	Update to ensure accuracy in data presented.	The EAG report has been updated as requested.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Subsequent treatment durations and distributions for 2nd and 3rd line treatment, p. xxii, Description of issue - there is a typo where ‘ABR’ is incorrectly reported as ‘ARB’.	‘ARB’ should be changed to ‘ABR’	Minor typo; update for readability.	The EAG report has been updated as requested.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.3., p25 There is a typo where 'ABR' is incorrectly reported as 'ARB'.	'ARB' should be changed to 'ABR'	Minor typo; update for readability.	The EAG report has been updated as requested.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4., p26 There is a minor error in the language reporting adverse events. The text currently reads: *"Most participants experienced at least one TEAE (99.7% in the ABR group, 99.0% in the PBR group). Of these, 88.9% and 88.2%, respectively, were Grade ≥3 and 12.2% and 10.1%, respectively, were Grade 5 with a fatal outcome."* However, the	The text should instead read: *"Most participants experienced at least one TEAE (99.7% in the ABR group, 99.0% in the PBR group). Grade ≥3 TEAEs were reported in 88.9 and 88.2% of patients in the ABR and PBR arms, respectively, and Grade 5 TEAEs occurred in 12.1% and 10.1% of patients."*	Update to ensure accuracy in data presented.	The EAG report has been updated as requested.

percentages for Grade ≥3 TEAEs are as a proportion of the overall SAS population, not a proportion of patients who experienced at least one TEAE. The percentage of Grade 5 TEAEs in the ABR arm is also incorrectly stated as 1.2% instead of 12.1%.			

Issue 11

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Section 3.2.4., p28 The percentage of Grade 3-4 COVID-19 SAEs in the PBR arm is reported as 4.1%, however the correct value is 4.0%.	The sentence should be corrected to: The most frequently reported SAEs of Grade 3-4 were COVID-19 pneumonia (8.1% and 6.7%), pneumonia (7.1% and 6.1%) and COVID-19 (5.1% and 4.0%).	Typo; update to ensure accuracy in data presented.	The EAG report has been updated as requested.

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3., p29 There is a repeated typo of 'Stil HHL', when referring to one of the trials in the ITC. This should be 'StiL NHL'.	'Stil HHL' should be corrected to 'Stil NHL' throughout.	Minor typo; correct name for any trials is necessary to avoid any confusion and allow cross reference.	The EAG report has been updated as requested.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3., p30 The ECHO trial is incorrectly referred to as 'ECO'.	'ECO' should be updated to 'ECHO'.	Minor typo; update for readability.	The EAG report has been updated as requested.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1., p36 The NICE TA identified from the grey literature search was TA370, but the EAG report incorrectly notes TA570. The reference (#20) is also incorrect.	TA570 (and the associated reference #20) should be replaced with TA370.	Update to ensure accuracy in reporting of grey literature findings.	The EAG report and reference list have been updated as requested.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.1., p36 The text reads “The additional search identified 7 NICE appraisals: 3 in Mantle Cell Lymphoma (TA502, TA370 (already identified in grey literature search) & TA677) and 7 in CLL (TA891, TA663, TA119, TA931, TA796,	The text should be updated to say that 10 NICE appraisals were identified.	Update to ensure accuracy in reporting of grey literature findings.	The EAG report has been updated as requested.

TA689 & TA429).” However the total number of TAs listed is 10, not 7.			

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 16, p. 44 All treatments within the R-CHOP regimen should be administered for a maximum of 6 cycles, not 8 cycles.	Update rows for R-CHOP treatments i.e. rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, to ‘up to a maximum of 6 cycles’.	Update to ensure accuracy in dosing schedule for the comparator.	Not a factual inaccuracy. Data in the EAG report reflect those reported on page 92 of the company submission. However, for clarity, the table has been updated to reflect that the cycles refer to “treatment” rather than “model” cycles.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.6., p. 50 'Flinn 2019' is incorrectly referred to as 'Finn 2019'	'Finn 2019' should be updated to 'Flinn 2019'	Minor typo; update for readability.	The EAG report has been updated as requested.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 19, p. 52 The value for year 10, ITT dataset, generalised gamma, is incorrectly stated as [redacted] instead of [redacted]	The value for year 10, ITT dataset, generalised gamma, should be updated to [redacted]	Update to ensure accuracy in data presented.	The EAG report has been updated as requested.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7., p. 62 The text "For example, at the beginning of the model, the difference between	Sentence should be updated to "For example, at the beginning of the model, the difference between progression free and progressed	Update to ensure accuracy in data presented.	The EAG report has been updated as requested.

progression free and progressed disease HSUVs is [redacted] whereas by age 100 the difference becomes [redacted] " is incorrect. By age 100, the difference is [redacted].	disease HSUVs is [redacted] whereas by age 100 the difference becomes [redacted] "		

Issue 20

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Table 23, p. 68 Table caption is incorrect. Table is reproduced from Table 18 and 19 of the company response to clarification queries, not Tables 19 and 20.	Change 'Tables 19 and 20' to 'Tables 18 and 19'.	Update to allow cross reference between documents	The EAG report has been updated as requested.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 5.3, p. 86 There is a typo where 'ABR' is incorrectly reported as 'ACA'.	Update 'ACA' to 'ABR'	Typo; update for readability/to avoid confusion.	The EAG report has been updated as requested.

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 31, p. 91 Table suggests that EAG preferred scenario is to include vial sharing, however Section 4.2.8 (p. 65) suggests 'The EAG preferred base case therefore assumes vial sharing is not possible.'	Update the table to note that the EAG preferred base case assumes no vial sharing (assuming the wording in Section 4.2.8 is correct)	Update to ensure consistency/avoid confusion.	The EAG report has been updated to clarify that the preferred EAG base case assumption is to assume no vial sharing across patients, or within patients across administrations. Upon further review of the vial-sharing assumptions in the economic model, the EAG have noticed that there are two typographical errors in the calculation of drug acquisition cost in the company submitted economic model. The first relates to the strength of cytarabine and bortezomib within the "Unit Costs" sheet. Where the strength was inputted

			as 100mg, 200mg & 500mg whereas it should be 1000mg, 2000mg & 5000mg for cytarabine. The strength of 2.5mg was used for 3.5mg for bortezomib. The second relates to the formulae used to calculate the dosage requirements for medications which are based on BSA (See Sheet “Dosing & Admin”, Cell References K31:K42). The formula in these cells references column E rather than column F. This meant that the dosage was not multiplied by the BSA. The implication is an under-estimate of treatment acquisition costs, especially for rituximab. The EAG have also noted that turning off vial sharing in the model assumes “no vial sharing across patients” but continues to assume vial sharing “within patients across administrations”. The EAG has also updated this analysis so that it correctly reflects the EAG’s preferred modelling assumptions. The EAG has also corrected the described errors in the company’s economic model and updated the vial sharing scenario as described above. The applied corrections are described in Section 4.2.8, and the impact of model

			corrections on the ICER has been updated in Section 5.1, Table 28. All relevant results tables in Chapters 5, 6 and the executive summary have been updated accordingly.

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3. 2. 2., p. 23 There is a typo where 'PBR' is incorrectly reported as 'PRB'.	Update 'PRB' to 'PBR'	Typo; update for readability/to avoid confusion.	The EAG report has been updated as requested.

Issue 24

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3. 2. 1, p. 15 There is a typo where 'PBR' is incorrectly reported as 'PBM'.	Update 'PBM' to 'PBR'	Typo; update for readability/to avoid confusion.	The EAG report has been updated as requested.

Issue 25

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3. 2. 1, p. 19 The statement in brackets "median PFS not reached [95% CI: 66.4, NE] vs. 61.6 months [49.6, 68.9];" is not factually accurate.	Update "median PFS not reached [95% CI: 66.4, NE] vs. 61.6 months [49.6, 68.9];" to "median PFS NE [95% CI: 66.4, NE] vs. 61.6 months [49.6, 68.9];	Update to ensure accuracy in data presented.	The EAG report has been updated as requested.

Issue 26

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 9, p. 27 Under "Treatment-related TEAE, n (%) the title reading "Acalabrutinib/placebo only" should read "Acalabrutinib only".	Update title reading "Acalabrutinib/placebo" only to "Acalabrutinib only"	Update to ensure accuracy in data presented.	Not a factual inaccuracy. Table 9 of the EAG report was reproduced verbatim from Table 26 of the updated Document B of the company submission.

			No amendment to the EAG report is required.

Issue 27

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7, p.58 For bullet point 2 discussing differences in HSUVs the EAG states "*the EAG does not find there is sufficient evidence to support a difference in HSUV between ECHO (which includes bortezomib) and TA370.*" The ECHO trial did not include bortezomib. The company suspects this has been confused with bendamustine.	Correct to say *"the EAG does not find there is sufficient evidence to support a difference in HSUV between ECHO (which includes bendamustine) and TA370.*	Update to ensure accuracy.	The EAG report has been updated as requested.

Issue 28

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7, p.58 The EAG states – "*At clarification queries, the EAG requested an analysis from the company that assumed that the PH assumption holds for all treatment comparisons between ABR, PBR and R-CHOP, and that all OS and PFS HRs were sourced from the NMA. However, this information was not available at the point of writing the EAG report. The EAG would appreciate sight of an analysis that estimates HRs of OS and PFS, obtained from the NMA for 1) ABR vs. BR; 2) R-CHOP vs. BR. This analysis would ensure that the benefits of randomisation are maintained across all studies. Whilst useful for*	The company has provided an analysis for ABR vs R-CHOP in the clarification questions as requested. This can be found in the clarification question responses question B4, section B. Hazard ratios are reported in Table 9 of the same document.	The company carried out the analysis requested by EAG and reported in the clarification responses.	Not a factual inaccuracy. The specific HRs reported on page 58 of the EAG report were not provided within the company clarification response. The EAG notes that this is unlikely to be a major driver of cost-effectiveness results. No amendment to the EAG report is required.

scenario analysis, the EAG does not consider this issue to be a major driver of cost-effectiveness conclusions, especially if committee accept the EAG's preference to use dependent models for ABR vs. PBR."			

Issue 29

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4, p. 28. The reported value of incidence of atrial fibrillation is 6.7% rather than 6.1%. *"Cardiac events of any grade occurred in 23.9% of participants in the ABR arm and 18.5% in the PBR arm, including atrial fibrillation in 6.7% and 4.4% of participants, respectively."*	Update statement to – "*Cardiac events of any grade occurred in 23.9% of participants in the ABR arm and 18.5% in the PBR arm, including atrial fibrillation in 6.1% and 4.4% of participants, respectively."*	Update to ensure accuracy of reported data.	The EAG note that Table 62 of Appendix M.3.3.2 in the company submission reports the incidence of atrial fibrillation as 6.7% and 4.4%. This corresponds to the value reported in the EAG report (6.7% and 4.4%). Given this and given that the company have not noted that there was a typographical error in the company submission, the text of the EAG

			report has not been revised.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
ID6155 acalabrutinib Final EAG report v1.0, Table 19, p. 52	All TTD values should be marked as CIC, as in the model.	See below	Thank you for flagging the error in CIC marking. The EAG report has now been updated as requested.

(Please add further lines to the table as necessary)

Table 19 Comparison of Acalabrutinib TTD curve selection using covid-19 and ITT analysis set

	Covid-19 censored dataset						ITT dataset					
	AIC	BIC	1	2	6	10	AIC	BIC	1	2	6	10
Company preferred ABR PFS	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred ABR PFS	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
KM	--	--	[redacted]	[redacted]	[redacted]	[redacted]	--	--	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	1723.3	1727.0	[redacted]	[redacted]	[redacted]	[redacted]	1968.0	1971.7	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	1707.3	1714.7	[redacted]	[redacted]	[redacted]	[redacted]	1959.4	1966.8	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	1705.2	1712.7	[redacted]	[redacted]	[redacted]	[redacted]	1962.0	1969.4	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	1706.3	1713.7	[redacted]	[redacted]	[redacted]	[redacted]	1959.1	1966.5	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	1710.7	1718.1	[redacted]	[redacted]	[redacted]	[redacted]	1959.3	1966.7	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	1706.0	1717.1	[redacted]	[redacted]	[redacted]	[redacted]	1959.2	1970.3	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	1709.0	1716.4	[redacted]	[redacted]	[redacted]	[redacted]	1960.8	1968.2	[redacted]	[redacted]	[redacted]	[redacted]
Generalised F	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	1961.2	1976.0	[redacted]	[redacted]	[redacted]	[redacted]