Medicinrådet

Bilag til Medicinrådets vurdering af acalabrutinib i kombination med bendamustin og rituximab til behandling af voksne patienter med ubehandlet mantle celle lymfom, som er uegnede til stamcelletransplantation

Førstelinjebehandling

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. acalabrutinib i komb. med bendamustin og rituximab
2. Amgros' forhandlingsnotat vedr. acalabrutinib i komb. med bendamustin og rituximab
3. Ansøgning vedr. acalabrutinib i komb. med bendamustin og rituximab

Medicinrådet
Dampfærgevej 21-23, 3. Sal
2100 København Ø

Notat til Medicinrådets evalueringsrapport på Calquence (Acalabrutinib) + bendamustin + rituximab til behandling af til behandling af patienter med ubehandlet mantle celle lymfom, som ikke er egnede til stamcelletransplantation (ECHO).

AstraZeneca vil gerne takke Medicinrådets for muligheden for at kommentere på evalueringsrapporten. I rapporten vurderes det samlet set at Calquence i kombination med bendamustin og rituximab giver en klinisk relevant gevinst i progressionsfri overlevelse uden væsentlig øget toksicitet.
Det noteres samtidig at sygdommens kliniske variation og sjældenhed gør nuværende behandlingsalgoritme kompleks og at patienter med højrisikosygdom har markant ringere overlevelse ved standard kemoimmunterapi.

Astrazeneca anerkender kompleksiteten, men mener ikke at den sundhedsøkonomiske analyse præsenteret i rapporten kan anvendes som beslutningstøtte til vurderingen af ECHO. Dette er beskrevet herunder.

Højrisikosygdom har markant ringere overlevelse ved standard kemoimmunterapi
Vi deler Medicinrådets vurdering af, at højrisiko patienter (pleomorf/blastoid morfologi, Ki67 over 30% og p53 overekspression) i dag har væsentligt ringere effekt af standard kemoimmunterapi. Gruppen er velkendt, klart afgrænset og identificeres rutinemæssigt i klinikken.
Vi håber, at Medicinrådet vil anerkende, at acalabrutinib i kombination med bendamustin og rituximab væsentligt kan forbedre både progressionsfri overlevelse og samlet overlevelse i denne gruppe og at Medicinrådet kan anbefale, at den afgrænsede patientgruppe tilbydes acalabrutinib i kombination med bendamustin og rituximab som 1.-linjebehandling uagtet om den bredere population anbefales.
Dette vil også harmonere med den netop udgivne kliniske retningslinje for mantlecellelymfom.(1)

Behandlingslængde i 2. linje er justeret kortere uden at antage en forskel i effekt
I base case har AstraZeneca benyttet data fra ECHO studiet i tilfælde af at patienter progrediere på 1. linje og bliver behandlet med Ibrutinib i 2. linje. Data viser en gennemsnitlig behandlingslængde på 22 måneder. I evalueringsrapporten fremgår det at dette er ændret baseret på et dansk studie (Trab et al) der viser at danske patienter historisk behandles i mediant 4.8 måneder med ibrutinib, patienterne i samme studie har en median OS på 1.9 måned efter de stopper ibrutinib.

Denne ændring i den sundhedsøkonomiske model er væsentlig, fordi omkring 90 % af patienterne i dag forventes at modtage ibrutinib i 2. linje, og behandlingslængden derfor driver en stor del af komparatorens omkostninger og effekt.
Yderligere, er behandlingslængden forkortet uden at justere overlevelsen i komparatorarmen. Det virker ikke klinisk plausibelt at patienter i komparator-armen, har en forventet overlevelse på 8,7 år (medicinrådets base case), med kun 4,8 måneders behandling i 2. linje. I ECHO (4 års opfølgning) er 64 % af patienterne i komparatorarmen i live, og tiden på behandling med BTKi i 2. linje er 22 måneder.

For at sikre konsistents bør der, ved antagelse af en kortere behandlingslængde på mediant 4,8 måneder som rapporteret i Trab et al.(2), bør der lilgeledes anvendes tilsvarende lavere effekt for den aktuelle 2. linje-behandling (dvs. effektestimater på Trab et al.-niveau, mediant 1.9 måned OS efterstop på ibrutinib). Hvor base case i evalueringsrapporten benytter data for behandlings effekten fra ECHO--niveau hvor effekten er opnået under 22 måneders BTKi-eksponering.

Denne antagelse står også i kontrast til Medicinrådets vurdering af Calquence (acalabrutinib) til behandling af voksne patienter med recidiverende eller refraktær mantle celle lymfom -vurderingen om, at Trab et al.'s lave effekt og varighed sandsynligvis afspejler inkluderingen af patienter fra 2010, og derfor anvender 12 måneders varighed for BTKi ved R/R MCL.

Skiftet fra 22 til 5 måneder ændrer ICER med over 800.000 DKK ved listepriser.

Indvirkning af COVID-19 på ECHO studiet

Medicinrådet anerkender, at en betydelig andel af COVID-19-relaterede dødsfald i ECHO-studietsandsynligvis kunne være blevet undgået i dag, men rapporten konkluderer, at FAS-populationen (full analysis set) er den mest plausible og metodisk korrekte til den sundhedsøkonomiske analyse

AstraZeneca forstår, at censurering af dødsfald og behandlingsophør tilskrevet COVID-19 kan introducere potentiel bias på grund af informativ censurering. Uden en pandemi er det imidlertid ukendt, hvor længe disse patienter (selv hvis de havde højere risiko for infektion eller død af andre årsager) ville have overlevet, fx én, tre, seks måneder eller længere, hvilket ville have påvirket ECHO's time-to-event-resultater.
Følgelig indlejrer FAS-populationen også bias i sine PFS-, TTD- og OS-resultater og kan ikke betragtes som mere plausibel end de COVID-19-censurerede resultater, da der ikke er en pandemi i dag.
Dette understøttes af den opdaterede PFS-hazard ratio præsenteret på ASH i december 2025 (3): FAS PFS HR og COVID-19-censureret PFS HR rapporteret i ansøgningen var henholdsvis 0,73 og 0,64, og den opdaterede FAS PFS HR er 0,6, hvilket bevæger sig tydeligt mod det covid-censurerede estimat. Disse data er delt med Medicinrådet under vurderingsprocessen.

Derfor finder AstraZeneca det også kritisk at denne data er brugt I den sundhedsøkonomiske analyse, da det må forventes at fremtidig behandling i dansk praksis ikke er påvirket af en pandemi.

Referencer

1. **https://www.dmcg.dk/siteassets/kliniske-retningslinjer/opdelt-paa-dmcg/lymfom/dlg_mcl_v2.0_admgodk03122025.pdf**
2. https://www.sciencedirect.com/science/article/pii/S2950328025000639?via%3Dihub
3. https://meetings-api.hematology.org/api/abstract/vmpreview/296447

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22.12.2025

MBA/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	AstraZeneca
Lægemiddel	Calquence (acalabrutinib)
Ansøgt indikation	I kombination med bendamustin og rituximab (BR) til behandling af voksne patienter med tidligere ubehandlet mantle celle lymfom (MCL), som ikke er egnede til autolog stamcelletransplantation (ASCT).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Calquence (acalabrutinib):

Tabel 1: Aftalepris.

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Calquence	100 mg /(60 stk. Tabletter)	40.994,30	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

[redacted]

Calquence anvendes i kombination med bendamustin og rituximab og da komparator er bendamustin og rituximab, angives udelukkende den årlige lægemiddeludgift for Calquence i nedenstående tabel 2.

Tabel 2: Lægemiddeludgift per patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Calquence	100 mg, (60 stk.)	200 mg daglig, oral	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
England	Under vurdering		Link til status
Sverige	Delvist anbefalet	Anbefalet til CLL samt MCL i anden linje	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Calquence in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

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Tables and Figures

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Abbreviations

[Include a list of all abbreviations used in this application.]

ABR	Acalabrutinib plus bendamustine and rituximab
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BCR	B cell antigen receptor
BID	Twice Daily
BR	Bendamustine and rituximab
BSH	British Society for Haematology
BTK	Bruton tyrosine kinase
CD	Cluster of Differentiation
CI	Confidence interval
CIT	chemoimmunotherapy
CLL	Chronic lymphocytic leukaemia
CMH	Cochran–Mantel–Haenszel test
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
DCO	Data cut-off
DHA	dexamethasone and cytarabine
DILI	Drug-induced liver injury
DOR	Duration of response
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FU	Follow-up
GRD	Global reimbursement dossier
HR	Hazard ratio
HRQoL	Health-related quality of life
ICC	Internation Consensus Classification
ICT	Immunochemotherapy
IGHV	Immunoglobulin heavy chain variable gene
IKK	Inhibitor of kappa-B kinase
INV	Investigator
IRC	Independent review committee
ITC	Indirect treatment comparison
ITK	Inducible T cell kinase
ITT	Intention-to-treat

IXRS	Interactive voice/web response system
LYN	Lck/Yes novel tyrosine kinase
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	Minimal residual disease
MRU	Medical resource use
MSSO	Maintenance and Support Services Organization
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NFAT	Nuclear factor of activated T cells
NHL	Non-Hodgkin lymphoma
NLG	Nordic Lymphoma Group
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PBR	Placebo plus bendamustine and rituximab
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PPPM	Per patient per month
PR	Partial response
PRO	Patient-reported outcome
PS	performance status
RAS	Rat sarcoma
RBC	Red blood cell
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
R-CVP	Rituximab, cyclophosphamide, vincristine and prednisolone
RCT	Randomised controlled trial
SAE	Serious adverse event
SAS	Safety analysis set
SCT	Stem cell transplantation
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results cancer registries
SLL	Small lymphocytic lymphoma
SLR	Systematic literature review
SMQ	Standardised MedDRA Query
SOC	System organ class
SYK	Spleen tyrosine kinase
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of the normal range
VR-CAP	Rituximab, cyclophosphamide, doxorubicin and prednisone
WBC	White blood cell

WHO World Health Organization

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Calquence
Generic name	Acalabrutinib
Therapeutic indication as defined by EMA	Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologus stem cell transplant (ASCT).
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01EL02
Combination therapy and/or co-medication	Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologus stem cell transplant (ASCT).
(Expected) Date of EC approval	2 June 2025
Has the medicine received a conditional marketing authorization?	AstraZeneca
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	• Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. • Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy. • Calquence as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) not previously treated with a BTK inhibitor.Calquence in combination with venetoclax with or without obinutuzumab is indicated for the treatment of adult

Overview of the medicine	
	patients with previously untreated chronic lymphocytic leukaemia (CLL).
Other indications that have been evaluated by the DMC (yes/no)	• Calquence as monotherapy or in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia. Calquence as monotherapy is indicated for the treatment of adult patients with chronic lymphocytic leukaemia who have received at least one prior therapy. https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/a/acalabrutinib-calquence-kronisk-lymfatisk-leukaemi-cll
Joint Nordic assessment (JNHB)	No.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Strength: 100 mg Package: 60 stk. tablets

2. Summary table

Summary	
Indication relevant for the assessment	Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated MCL who are not eligible for ASCT.
Dosage regiment and administration	• Acalabrutinib 100 mg, day 1-28 in a 28-day cycle, oral twice daily until progression. • Bendamustine 90 mg/m2, day 1 and 2 of each 28-day cycle, IV Administered for a max of 6 cycles. • Rituximab 375 mg/m2, day 1 of each 28-day cycle, IV Administered for a max of 6 cycles.

Summary	
	Patients completing 6 cycles of acalabrutinib or placebo + BR (PBR) who achieved a response (PR or better) received rituximab maintenance (RM) (375 mg/m2) on Day 1 of every other cycle (starting on the next even numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses through no later than Cycle 30). Thereafter, patients continued to receive acalabrutinib monotherapy or placebo (100 mg BID or last tolerated dose) until PD or unacceptable toxicity. Patients randomised to PBR who, at any time during the study, had PD assessed by the investigator and confirmed by an unblinded non-study team physician of the sponsor and were eligible to crossover, could have received treatment with acalabrutinib monotherapy at a dose of 100 mg BID until PD or unacceptable toxicity.
Choice of comparator	Bendamustine + Rituximab
Prognosis with current treatment (comparator)	MCL is characterized by an aggressive clinical course and remains generally incurable despite the availability of effective treatments (1). Its aggressive nature, coupled with the side effects of treatment regimens, significantly impacts the health-related quality of life (HRQoL) of MCL patients (2). According to findings from the retrospective Swedish MCLcomplete study, the median overall survival for patients with MCL treated with BR as a front-line therapy is 4.1 years (3). However, the phase II/III ENRICH study demonstrated that patients treated with BR in first line, followed by rituximab maintenance, had a median PFS of 50.5 months and 5-years OS probability of 58.1% (4).
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	PFS, OS, HRQoL, Safety
Most important serious adverse events for the intervention and comparator	The most frequently occurring 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%). The most frequent grade 3 to 4 SAEs reported in 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%) (5).

Summary	
Impact on health-related quality of life	Clinical documentation: The ECHO trial demonstrated superior efficacy of ABR over PBR, with similar quality of life between the two arms measured using EQ-5D-5L. In the trial there was a general trend in improved health for both treatment groups. Health economic model: The cost-effectiveness model uses treatment independent health state utility values. In terms of quality-adjusted life years, the cost-effectiveness model shows an increase for ABR versus PBR due to increased survival, lower adverse event disutility and more time spent progression-free.
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis Type of model: Partitioned survival model
Data sources used to model the clinical effects	ECHO trial (6)
Data sources used to model the health-related quality of life	ECHO trial (6) NICE TA370 (LYM-3002) (7)
Life years gained	0.79 years
QALYs gained	0.74 QALY
Incremental costs	1 268 705 DKK
ICER (DKK/QALY)	1 706 836 DKK/QALY
Uncertainty associated with the ICER estimate	The model assumptions with the highest impact on the ICER are choice of parametric functions for overall survival and time to treatment discontinuation, choice of subsequent treatments and treatment duration, health care resource utilization, discount rates, utility in the progressed state.
Number of eligible patients in Denmark	Incidence: 1.48 per 100 000 Prevalence: 4 per 100 000 (estimated by Danish clinician)
Budget impact (in year 5)	40 588 865 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL) with complex pathophysiology. In Denmark, the median age at diagnosis is 65, and MCL represents about 6–9% of NHL cases in Western Europe (1). MCL poses significant treatment challenges and is often considered incurable (1, 8). This section outlines the disease's pathophysiology, clinical presentation, prognosis, and impact on quality of life, providing context for MCL management and unmet clinical needs.

Pathophysiology

MCL features abnormal B lymphocytes in the mantle zone of lymph nodes (8). Most cases are CD5 and SOX11 positive, with the genetic abnormality involving the t(11;14)(q13;q32) translocation being the most common driver of MCL pathogenesis. This translocation is present in more than 95% of patients and leads to the overexpression of cyclin D1, promoting cell division and proliferation resulting in the accumulation of abnormal cells (1, 9, 10). Per the International Consensus Classification (ICC)/WHO 2022, MCL can be divided into nodal and non-nodal subgroups. Nodal MCL, constituting 80%-90% of cases, has a more aggressive course, characterized by unmutated IGHV and SOX11 overexpression. Non-nodal leukemic MCL, typically presents with a more indolent course and mutated IGHV and SOX11 negativity. Additionally, blastoid and pleomorphic variants are distinguishable and represent high-risk MCL subtypes (11, 12). Other predictors for unfavorable outcomes include high Ki-67 (≥30%), and high TP53 expression (13, 14).

Clinical Presentation

Many MCL patients do not experience any symptoms during early stages of the disease, however, patients may eventually seek medical help due to persistent swelling of lymph nodes. Some patients may also develop non-specific symptoms such as lack of appetite, nausea, abdominal swelling and/or pain (8). At advanced stages, when the disease has spread to extra-nodal sites, patients may present with widespread systemic symptoms, such as fever, night sweats, unexplained weight loss and fatigue (15). Due to the aggressive nature of MCL and often asymptomatic early stages, over 80% of patients present with advanced-stage disease (stage III or IV), typically characterized by lymphadenopathy and involvement of the liver, spleen, bone marrow, and gastrointestinal tract (16). Diagnosis follows WHO guidelines and involves histological examination of surgical biopsies, immunophenotyping, and genetic testing. Diagnostic

imaging assesses lymph node enlargement and potential extra-nodal involvement, along with a complete blood test (1, 17). Most patients require treatment at diagnosis, while a minority may be managed initially with a "watch and wait" (W&W) approach (3).

Staging of MCL is performed using the Lugano staging system for MCL which is based on the Ann Arbor system for NHLs (18).

Patient Prognoses

Despite available treatments, MCL is still generally considered incurable. The ABR treatment is intended for patients with previously untreated MCL who are ineligible for autologous stem cell transplant (ASCT) due to age and/or comorbidities. According to a Danish MCL expert, approximately 60% of newly diagnosed MCL patients that require systemic therapy fall into this category. In Denmark, most of these patients are treated with R-Bendamustine (BR), and in some cases R-BAC (BR plus Cyterabine). Both regimens are followed by Rituximab maintenance therapy (1).

While there is a lack of Danish studies detailing the prognosis of MCL patients, robust real-world evidence from Sweden can provide meaningful perspective. The *MCLcomplete* study, evaluating outcomes for patients diagnosed with MCL in Sweden between 2006 and 2018, reported a median overall survival of 4.1 years for those treated with BR as first-line therapy (3). However, it is important to recognize that ibrutinib was not available as a relapse therapy during the treatment period of this cohort, thereby limiting the applicability of these results to the present therapeutic landscape in Denmark. To more accurately reflect current outcomes for Danish patients treated with BR in front line, the phase II/III ENRICH study may offer more relevant insights. In this study, patients aged ≥ 60 years, from Nordic and UK sites, with previously untreated, stage II-IV MCL (randomized between 2015 and 2021) experienced a median PFS of 50.5 months and 5-years OS probability of 58.1% when treated with BR followed by rituximab maintenance (4).

In addition to treatment regimens, several clinical and biological characteristics are recognized as prognostic factors for MCL. Higher age, poorer ECOG performance status, elevated lactate dehydrogenase (LDH), and a higher white blood cell count (WBC) are independently associated with shorter overall survival among MCL patients (19).

Impact on Quality of Life

Mantle cell lymphoma significantly impacts the health-related quality of life (HRQoL) due to its aggressive nature and the side effects of treatment regimens. Patients often experience a decline in physical, cognitive, and role functioning following induction chemotherapy, with HRQoL potentially stabilizing or modestly improving after maintenance therapy (2).

3.2 Patient population

The annual incidence rate of MCL in Denmark has shown an upward trend over the years, currently estimated at approximately 1.5 per 100,000, compared to 0.9 per

100,000 reported in a Danish population-based study from 1992 to 2000 (20, 21). Table 1 describes the annual incidence of MCL in Denmark from 2020 to 2024. Data from 2020 to 2023 were obtained from the Danish Lymphoma Database (LYFO), and the incidence rates per 100,000 has been calculated using the respective annual population sizes, reported by *Danmarks Statistik* (20, 22). The incidence of MCL for 2024 has not yet been published and was, therefore, projected by calculating the average from the preceding four years. To our knowledge, the prevalence of MCL has not been documented either in Denmark or globally. However, a Danish MCL expert estimates the prevalence to be around 4 per 100,000 in Denmark. Based on this estimate, the annual population sizes were used to calculate the predicted number of patients living with MCL in Denmark between 2020 and 2024 (22). The results are described in Table 1.

Table 1 Incidence and prevalence of MCL in Denmark in the past 5 years.

Year	2020	2021	2022	2023	2024
Incidence in Denmark (per 100, 000) (20)	84 (1.44)	86 (1.47)	92 (1.57)	90 (1.52)	88 (1.48)
Prevalence in Denmark (per 100,000)	233 (4)	234 (4)	236 (4)	238 (4)	239 (4)
Global prevalence *	N/A	N/A	N/A	N/A	N/A

* For small patient groups, also describe the worldwide prevalence.

The ABR treatment is intended for patients with previously untreated MCL who are unsuitable for ASCT. In Denmark, this encompasses treatment-naïve patients who are deemed ineligible for ASCT due to age and/or comorbidities and require systemic chemotherapy treatment (1). According to a Danish MCL expert, approximately 80% of newly diagnosed patients start systemic therapy at diagnosis, with about 60% of this group comprising of those ineligible for ASCT as described above. The remaining 20% of patients who do not initiate systemic treatment upon diagnosis include those with asymptomatic indolent disease managed through a watch and wait strategy, patients in stages I-IIA who are suitable for radiation therapy, and those who are compromised and receiving palliative care (1). The estimated annual number of patients eligible for ABR treatment in Denmark are presented in Table 2.

Table 2 Estimated annual number of patients eligible for treatment with ABR in Denmark

	Proportion	Number of patients per year
Incidence of MCL in Denmark (20)	100%	88 (average from 2020-2023)
Proportion of patients starting systemic therapy each year	80%	70
Patients suited for ABR and ineligible for ASCT	60%	42

Table 3 describes the estimated number of MCL patients eligible for treatment with ABR in the coming years, assuming stable incidence (20). Population growth has not been accounted for due to the small numbers.

Table 3 Estimated number of MCL patients eligible for treatment with ABR in the coming years (18).

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	42	42	42	42	42

3.3 Current treatment options

The current Danish treatment guideline for MCL is closely aligned with the 2017 ESMO guidelines. Detailed information can be found in the Danish clinical guideline for MCL(1)

Unmet Need in current Frontline MCL Treatment

According to Danish treatment guidelines and leading MCL experts, patients newly diagnosed with MCL ineligible for autologous stem cell transplant (ASCT) due to age or comorbidities are typically treated with R-Bendamustine or, in select cases, R-BAC (BR plus cytarabine). These regimens are generally followed by rituximab maintenance therapy (1). Prognostic outcomes associated with these approaches are outlined in Section 3.1: *Patient prognosis*.

Despite this standard, clinicians point to a significant unmet need in the frontline setting, particularly for patients with high-risk disease features such as blastoid morphology, high proliferation index, and TP53 mutation. These patients often experience suboptimal outcomes with current chemoimmunotherapy regimens (13, 14).

As noted by a leading Danish MCL expert, there is a growing scientific consensus that first-line treatment needs to evolve beyond traditional chemotherapy backbones to include targeted therapies. The aim is to improve efficacy while reducing toxicity, especially for those with biologically high-risk disease. Integrating targeted agents with chemotherapy could offer a more tailored, effective approach to address these clinical challenges from the outset.

In recent years, there have been significant advancements in the treatment of newly diagnosed MCL patients. A key area of innovation has been the incorporation of BTK inhibitors into first-line combination regimens. The Phase II/III ENRICH study and the Phase II ALTAMIRA study have both investigated combining first-generation (ibrutinib) and second-generation (acalabrutinib) BTK inhibitors with rituximab, reporting favourable outcomes. However, these regimens have not been approved by EMA (4, 23).

The TRIANGLE study examined whether ibrutinib could replace or compliment a transplant-based regimen in patients eligible for ASCT. The indication has recently received approval, offering a new treatment option for these patients. In contrast, the Phase III SHINE study, which evaluated the combination of ibrutinib and BR versus BR alone was withdrawn from EMA assessment by the marketing authorization holder. When the application was withdrawn, the EMA's view was that the benefits of ibrutinib in previously untreated MCL patients did not outweigh the associated risks (24). As a result, there are currently no targeted therapies approved for use in the first-line treatment of elderly or transplant-ineligible MCL patients.

Danish Real-World Evidence from the Relapse Setting Highlights Need for More Potent Frontline Therapies

According to the Danish treatment guideline and Danish MCL experts, most patients who relapse after first-line treatment are currently managed with targeted monotherapies—most commonly ibrutinib, a BTKi. However, real-world outcomes from a population-based study of all Danish MCL patients treated with ibrutinib between 2010 and 2022 reveal lower than expected efficacy metrics (25). Among patients receiving ibrutinib as second-line or later therapy:

- Median progression-free survival was 6 months
- Median overall survival was 12 months
- Adverse events led to treatment discontinuation in 15%, dose reduction in 16%, and were directly related to death in 8% of patients (25). These real-world data underscore the potential limitations of relying on ibrutinib monotherapy in the relapsed setting. This in turn highlights a broader issue: current frontline treatments may not be adequately controlling the disease, resulting in early relapses and poor salvage outcomes.
- The limited efficacy of ibrutinib in the relapse setting shown in the Danish real-word evidence study, coupled with emerging data on frontline BTKi-based combinations, underscores a need to incorporate targeted agents earlier in the treatment course—especially for high-risk MCL patients that are ineligible for ASCT.

3.4 The intervention

Acalabrutinib is a selective small-molecule BTK inhibitor (26). An effector molecule in the B cell antigen receptor (BCR) pathway, BTK transmits and amplifies the pathway signal and is a key contributor to B cell survival and function. Over signalling of the BCR pathway independent of antigen activation may contribute to B cell malignancies such as MCL and CLL. Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue (Cys481) in the BTK active site, inhibiting activation of

downstream signalling proteins CD86 and CD69 thus inhibiting malignant B cell proliferation and tumour growth BTK selectivity (27).

Acalabrutinib was developed to minimise off-target activity. In competitive binding assays, acalabrutinib demonstrated higher selectivity for BTK than ibrutinib when profiled against a panel of 395 non-mutant kinases (28, 29), and did not have activity against similar kinases such as EGFR, TEC, TXK and ITK (26, 29, 30). In contrast, ibrutinib irreversibly binds to the kinases EGFR, TEC, ITK and TXK (26, 29), displaying off-target activities towards these kinases (31). Consequently, acalabrutinib has been shown to be associated with low rates of adverse events (AEs), including cardiovascular AEs, whereas the use of ibrutinib is limited by AEs, including major haemorrhage, rash, diarrhoea and atrial fibrillation/flutter.

Table 4 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of adult patients with previously untreated MCL who are inelgibile for ASCT.
ATMP	N/A
Method of administration	Acalabrutinib is taken orally twice daily Bendamustine and Rituximab are administered I.V.
Dosing	• Acalabrutinib 100 mg BID PO until PD or unacceptable toxicity • Bendamustine 90 mg/m2 IV on days 1 and 2 of each cycle for up to 6 cycles • Rituximab 375 mg/m2 IV on day 1 of each cycle for 6 cycles Each cycle consisted of 28 days. Patients completing 6 cycles of acalabrutinib or placebo + BR who achieved a response (PR or better) received RM (375 mg/m2) on Day 1 of every other cycle (starting on the next even-numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses through no later than Cycle 30). Thereafter, patients continued to receive acalabrutinib monotherapy or placebo (100 mg BID or last tolerated dose) until PD or unacceptable toxicity.
Dosing in the health economic model (including relative dose intensity)	For the intervention arm: • Acalabrutinib 100 mg BID PO. RDI of 89%* • Bendamustine 90 mg/m2 IV on days 1 and 2 of each 28-day cycle for up to 6 cycles. RDI of 86%** • Rituximab 375 mg/m2 IV on day 1 of each 28-day cycle for 6 cycles. RDI of 93%*** • Rituximab maintenance 375 mg/m2 IV every 56 days for a maximum of 12 administrations. RDI 77%**** Each cycle consisted of 28 days.

Overview of intervention		
Should the medicine be administered with other medicines?	Bendamustine + rituximab, see dosing above.	
Treatment duration / criteria for end of treatment	Acalabrutinib is administered until progressive disease or unacceptable toxicity. For more information, see dosing above.	
Necessary monitoring, both during administration and during the treatment period	NA	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?		
Package size(s)	Strength	100 mg
	Package	60 stk. tablets

*For acalabrutinib, relative dose intensities were calculated as (total cumulative dose received [mg] / [duration of exposure (days) × 100 (mg) × 2] × 100).

**For bendamustine, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total intended dose per protocol [90 mg/m2 × 100] from cycles 1 to 6 x 100).

***For rituximab, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total intended dose per protocol [375 mg/m2 × 100] from cycles 1 to 6 x 100).

****For rituximab maintenance, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total dose prescribed [375 mg/m2 × 100] from dosed cycles x 100).

3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

If reimbursed, patients are expected to be prescribed acalabrutinib as an add-on therapy to the current standard of care chemo-immune regime bendamustine + rituximab.

3.5 Choice of comparator(s)

According to the Danish clinical treatment guideline for MCL (see section 3.3, (1), the first-line choice of treatment for the relevant patient population is conventional immunochemotherapy. One of the treatment options mentioned is the combination of bendamustine and rituximab. Recent studies have demonstrated that BR is a highly effective treatment option for this patient group. The expert committee have also confirmed that BR is the most appropriate comparator at the dialogue meeting with the secretariate on the 4th March 2025. See Table 7 for more details about the comparator.

Table 5 Overview of the comparator.

Overview of comparator	
Generic name	Bendamustine + rituximab (BR)
ATC code	**Bendamustine:** L01AA09 **Rituximab:** L01FA01
Mechanism of action	**Bendamustine:** Alkylating cytostatic drug **Rituximab:** CD20 antibody
Method of administration	IV
Dosing	• Bendamustine 90 mg/m2 IV on days 1 and 2 of each 28-day cycle for up to 6 cycles. • Rituximab 375 mg/m2 IV on days 1 of each 28-day cycle for up to 6 cycles • Patients completing 6 cycles of placebo + BR who achieved a response (PR or better) received RM (375 mg/m2) on Day 1 of every other cycle (starting on the next even numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses through no later than Cycle 30). Thereafter, patients continued to receive placebo (100 mg BID or last tolerated dose) until PD or unacceptable toxicity.
Dosing in the health economic model (including relative dose intensity)	• Bendamustine 90 mg/m2 IV on days 1 and 2 of each cycle for up to 6 cycles. RDI of 87%* • Rituximab 375 mg/m2 IV on day 1 of each cycle for 6 cycles. RDI of 91%** • Rituximab maintenance 375 mg/m2 IV every 56 days for a maximum of 12 administrations. RDI 77%*** • Each cycle consisted of 28 days.
Should the medicine be administered with other medicines?	Bendamustine and Rituximab are administered together. In most cases, additional anti-cancer agents are not included
Treatment duration/ criteria for end of treatment	See dosing above
Need for diagnostics or other tests (i.e. companion diagnostics)	No

Overview of comparator	
Package size(s)	**Bendamustine:** 5x25 mg powder for conc. for infusion solution, 5x100 mg powder for conc. for infusion solution, **Rituximab** 2x100 mg conc. for infusion solution, opl 1x500 mg conc. for infusion solution, opl
Source: Danish MCL guideline (1)	

*For bendamustine, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total intended dose per protocol [90 mg/m2 × 100] from cycles 1 to 6 x 100).

**For rituximab, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total intended dose per protocol [375 mg/m2 × 100] from cycles 1 to 6 x 100).

*** For rituximab maintenance, relative dose intensities were calculated as (total cumulative dose received [mg/m2] / total dose prescribed [375 mg/m2 × 100] from dosed cycles x 100).

3.6 Cost-effectiveness of the comparator(s)

The DMC has not conducted an assessment of the bendamustine and rituximab combination. However, since both bendamustine and rituximab are off-patent and available at low prices we are confident that BR is a cost-effective treatment (32).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 6 summarizes the efficacy outcomes deemed relevant for evaluating ABR vs. BR for previously untreated MCL. ORR and Additional efficacy outcomes are reported in Appendix B.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
PFS IRC and INV [ECHO]	44.9 months, DCO 15 February 2024	PFS was defined as the time from the date of randomization until PD or death from any cause, whichever occurred first.	PFS was calculated as date of first PD or death (censoring date for censored patients) – randomization date + 1 day

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [ECHO]	44.9 months, DCO 15 February 2024	OS was defined as the time from date of randomization to date of death due to any cause regardless of whether the patient withdrew from randomized therapy or received another anti-MCL therapy.	The OS was calculated as: death date (or censoring date) – randomization date + 1
Overall response rate (ORR) IRC and INV [ECHO]	44.9 months, DCO 15 February 2024	Best overall response was defined as the best response of CR, PR, stable disease, or PD as assessed by IRC per the Lugano Classification for NHL at or before the initiation of subsequent anti-MCL therapy, whichever came first.	Assessment of response and progression was conducted in accordance with the Lugano Classification for NHL using PET, CT and MRI.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

The most clinical relevant outcome to demonstrate efficacy in anticancer trials is PFS, OS and patient-reported outcomes (33). Data on ORR, DoR, time to progression (TTP)/PFS and confirmed ORR are considered suitable markers of anti-tumor activity. Additionally, in DMC´s protocol for the treatment guideline for chronic lymphatic leukemia ((document number 170636)) another hematologic malignancy, the expert committee pre-specified OS, PFS, and QoL (e.g., via the EORTC QLQ-C30) as critical or important efficacy measures. All of these outcome measures were defined as endpoints in the ECHO trial. Further, the cost-utility model was directly based on the key endpoints of the ECHO trial, which represent treatment goals for MCL patients in Denmark: OS, PFS and HRQoL measured via EQ-5D-5L.

4. Health economic analysis

4.1 Model structure

A partitioned survival model (PSM) with three mutually exclusive health states of progression-free (PF), progressed disease (PD), and death was developed in Microsoft Excel. The health states are defined as follows:

- PF – The PF state captures patients who were free of progression according to the Lugano classification for NHL. All patients enter the model in the PF state and are assumed to immediately initiate first-line treatment for MCL. Patients remain in this state until they either experience progression and enter the PD state or experience death without progression and enter the death state.

- PD – The PD state captures patients who have progressed during or after their first-line therapy, according to the Lugano classification for NHL. Patients in this state have R/R MCL and are assumed to remain in this state until death.
- Death – The death state is an absorbing state for deaths from all causes.

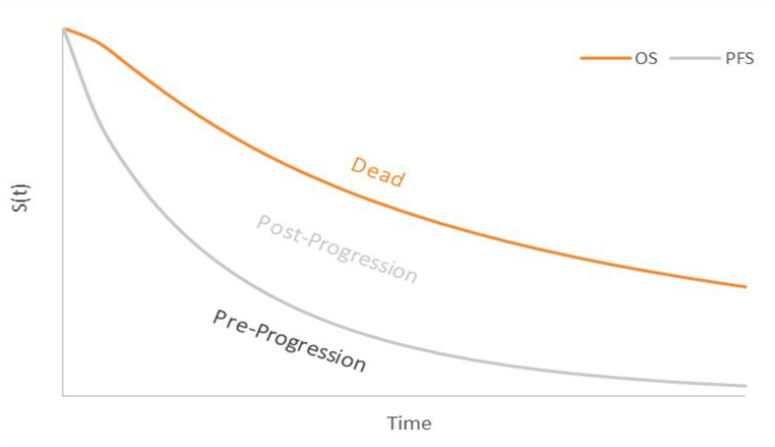
The PF state was further partitioned into periods on and off first-line treatment (ABR or BR) to calculate treatment-related costs (i.e., acquisition, administration and patient time/transport costs), since it is possible that patients discontinue first-line treatment before progression due to tolerability concerns.

As shown in Figure 1, the state occupancy of the model is determined through the lifetime extrapolation of PFS and OS using parametric survival models. The proportions of patients in the PF state over time are directly estimated from the PFS curve, while the proportions in the death state are estimated from one minus the OS curve. State occupancy in the PD state is estimated as the survival probabilities for OS minus PFS. To align with the primary endpoint of ECHO, PFS was modeled using progression as assessed by independent review committee.

The duration of rituximab treatment in the induction and maintenance periods was modelled using Kaplan-Meier data from the ECHO trial. Bendamustine treatment duration was modeled using the mean treatment duration observed in the ECHO trial. For acalabrutinib, the costs of treatment were modeled via parametric survival models fitted to patient-level data on the time to discontinuation of study drug in ECHO. Using time to discontinuation data from ECHO, ensures that the costs of acalabrutinib reflect all reasons for discontinuation including adverse events, progression of disease and death.

To address the costs of progression during R/R MCL treatment, the costs assigned to the PD state included up to 3 lines of treatment. The health state utility decrement for the PD state were sourced from patients with R/R MCL. Additionally, the OS data used to estimate the proportion of patients in the PD state was derived from the ECHO trial and encompassed the survival effects of all subsequent treatment lines in ECHO.

Figure 1 Model structure



4.1.1 Justification for model structure

The choice of model structure (3-states) and extrapolation method (PSM) was informed by the following considerations:

- The approaches accepted in previous health technology assessments for MCL
- The availability of data from the ECHO trial and for external comparators
- The modelling of subsequent treatment for patients who progress after initial treatment for MCL

The PSM approach has been extensively used to model the cost-effectiveness of treatments in advanced cancer and has been accepted for decision making in previous assessments for MCL (34).

4.2 Model features

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Previously untreated MCL patients ineligible for ASCT	Trial population relevant for clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines. Based on mean baseline age (71.6 years) of patients in the ECHO trial.
Cycle length	28 days	Consistent with length of treatment cycle

Model features	Description	Justification
Half-cycle correction	Yes	Applied to the costs assigned to the PF and PD states and to the estimation of QALYs and LYs. The half-cycle correction was not applied to the acquisition and administration costs for first-line therapy (acalabrutinib, bendamustine-rituximab) as these costs are expected to accrue at the start of each cycle. This is justified by the administration schedules of first-line therapies.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Acalabrutinib + bendamustine and rituximab	Intervention in scope for application
Comparator(s)	Bendamustine and rituximab	According to national treatment guideline. Validated by Danish clinical expert
Outcomes	PFS, OS, Time to treatment discontinuation (TTD)	Trial data outcomes to populate the partitioned survival model.

5. Overview of literature

5.1 Literature used for the clinical assessment

No literature search was conducted for the clinical assessment as the application is based on a head-to-head study with a comparator relevant to Danish clinical practice.

Table 8 Overview of literature

Reference	Trial name*	NCT identifier	Dates of study	Used in comparison of*
A Study of BR Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated MCL (35)	ECHO	NCT02972840	Start: 05/04/2017 Completion: 28/10/2025 Data cut-off: 28/10/2025 Future data cut-offs: The final analysis was planned to occur when approximately 268 IRC-assessed PFS events have been observed	Acalabrutinib + bendamustine + rituximab vs placebo bendamustine + rituximab

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

A targeted literature review identified seven studies and submissions reporting utility values for the MCL indication, with three in 1L setting (7, 36-38) and four in 2L+ setting (34, 39-42) . Additionally, an assessment within CLL was identified for disutilities (43). Of these, three sources are used for modelling cost-effectiveness, including the ECHO trial, see table below.

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file: ECHO Clinical Study Report, DCO 15th February 2024	PF, (PD)	Section 10
(7) National Institute for Health and Care Excellence. NICE TA370. Bortezomib for previously untreated mantle cell lymphoma [Internet]. NICE; 2015. Available from: https://www.nice.org.uk/guidance/ta370	Utility decrement from PF to PD Disutility for Anaemia, , Diarrhoea, Fatigue, Febrile neutropenia, , Leukopenia, Lymphopenia, Pneumonia, Thrombocytopenia Neutropenia, Peripheral sensory Neuropathy	Section 10
(43) National Institute for Health and Care Excellence. NICE TA891. Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [Internet]. NICE; 2023. Available from: https://www.nice.org.uk/guidance/ta891	Disutility for Infections and cardiac events	Section 10

5.3 Literature used for inputs for the health economic model

No systematic literature search was carried out for inputs included in the cost-utility analysis. Costs included in the analysis were sourced according to DMC guidelines and a more detailed description can be found in section 11.

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Data on file: ECHO Clinical Study Report, DCO 15th February 2024 (6)	PFS, OS, TTD, adverse events, HRQoL utilities	Clinical trial of interest for comparison	Section 6 Section 9 Section 10
LYM-3002: Bortezomib-Based Therapy for Newly Diagnosed Mantle-Cell Lymphoma (7)	HRQoL decrement for PD	Targeted literature review	Section 10
Eyre TA et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. Br J Haematol. 2024 Jan;204(1):108–26. (44)	Dosing and duration of treatment for Venetoclax as a subsequent treatment	Targeted literature review	Section 11
Foran JM et al. Treatment of mantle-cell lymphoma with Rituximab (chimeric monoclonal anti-CD20 antibody): Analysis of factors associated with response. Ann Oncol. 2000;11:S117–21. (45)	Dosing and duration of treatment for rituximab as a subsequent treatment	Targeted literature review	Section 11
Wang M et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol.	Dosing and duration of treatment for lenalidomide as a subsequent treatment	Targeted literature review	Section 11

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
2012 Jul 1;13(7):716–23. (46)			
R-CHOP administration protocol Available from: https://www.swagcanceralliance.nhs.uk/wp-content/uploads/2020/10/R-CHOP.pdf (47)	Dosing and duration of treatment for R-CHOP as a subsequent treatment	Targeted literature review	Section 11

6. Efficacy

6.1 Efficacy of ABR compared to PBR for ECHO

6.1.1 Relevant studies

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ECHO, NCT: NCT02972840 A Study of BR Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated MCL (35).	ECHO is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating the combination of ABR versus PBR in patients aged 65 years or older and with previously untreated MCL. The study was conducted	Study start: 05/04/2017 Study completion (estimated): 28/10/2025 (48).	Adults aged ≥ 65 years 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	Acalabrutinib 100 mg, day 1-28 in a 28-day cycle, oral twice daily until progression. Bendamustine 90 mg/m2, day 1 and 2 of each 28-day cycle, IV Administered for a max of 6 cycles. Rituximab 375 mg/m2, day 1 of each 28-day cycle, IV Administered for a max off 6 cycles. Patients completing 6 cycles of acalabrutinib or placebo + BR who	Placebo Bendamustine 90 mg/m2, day 1 and 2 of each 28-day cycle, IV Administered for a max of 6 cycles. Rituximab 375 mg/m2, day 1 of each 28-day cycle, IV Administered for a max off 6 cycles. Patients completing 6 cycles of placebo + BR who achieved a response (PR or better) received RM (375 mg/m2) on Day 1	**Primary endpoint:** PFS (IRC) Median follow-up: 44.9 months at 15 Feb 2024 **Key secondary endpoints** OS Median follow-up: 44.9 months, DCO 15 Feb 2024 ORR (IRC) Median follow-up: 44.9 months, DCO 15 Feb 2024. TTR, DOR

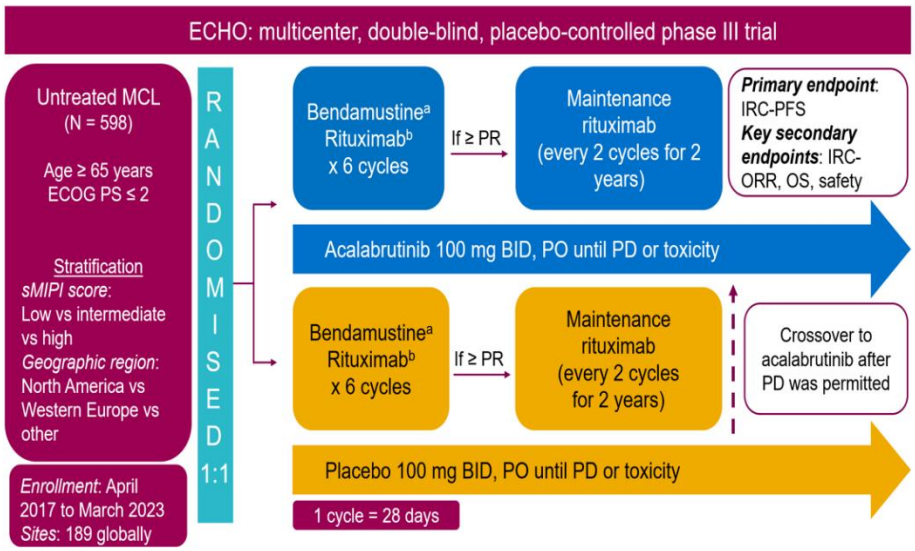
Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
	at 189 study centres in 26 countries globally (5).		which no prior systemic anticancer therapies have been received See ECHO publication.	achieved a response (PR or better) received RM (375 mg/m2) on Day 1 of every other cycle (starting on the next even numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses through no later than Cycle 30). Thereafter, patients continued to receive acalabrutinib monotherapy or placebo (100 mg BID or last tolerated dose) until PD or unacceptable toxicity (5).	of every other cycle (starting on the next even numbered cycle after completion of 6 cycles of BR) for a maximum of 12 additional doses through no later than Cycle 30). Thereafter, patients continued to receive placebo (100 mg BID or last tolerated dose) until PD or unacceptable toxicity (5).	

Table 11 Overview of study design for studies included in the comparison

ECHO study design

The trial design is summarized in Figure 2. Patients randomised to PBR who had disease progression as assessed by the investigator and confirmed by an unblinded physician who was not on the study team but was part of the sponsor's team and was not participating in the study were allowed to cross over and could receive acalabrutinib monotherapy at a dose of 100 mg twice daily (BID) until PD or unacceptable toxicity.

Figure 2. ECHO study design



Source: Data on file (5).

Patient populations and statistical analyses
Sample size

With a 1:1 randomization ratio, ECHO was expected to randomize 546 patients globally, with an additional enrolment in China of approximately 80 patients. The actual total number of randomized patients in the study was 635 patients (Global cohort), including 85 from the China cohort (81 from China mainland + 4 from Taiwan). However, 37 patients (all from China) were excluded from the full analysis set (FAS) due to having < 2 years follow-up at the study DCO (data on file(5)). The 598 patients constituted the FAS population for the interim analysis reported here.

The study was sized to achieve approximately 90% power at the final analysis to detect a HR of 0.67 when evaluating IRC-assessed PFS. Under the model assumptions, this translates to a 49% improvement in median PFS from 52.9 months in the PBR arm to 79 months in the ABR arm with a 2-sided test at alpha level of 0.05 (5).

Populations

The analysis populations used in the ECHO trial are summarized in Table 12.

Table 12. Summary of analysis populations

Analysis set	Description
FAS	• All patients in the global cohort who were randomised to a treatment arm (whether or not they received treatment) • Includes patients from China who were randomised for at least 24 months before DCO[a] • The analysis set follows the principles of intention-to-treat
SAS	All randomised patients who received at least one dose of study treatment during the main study period

[a]Patients from the China population will also be analysed separately; not reported in this document. CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; SAS, safety analysis set. Source: ECHO CSR (5).

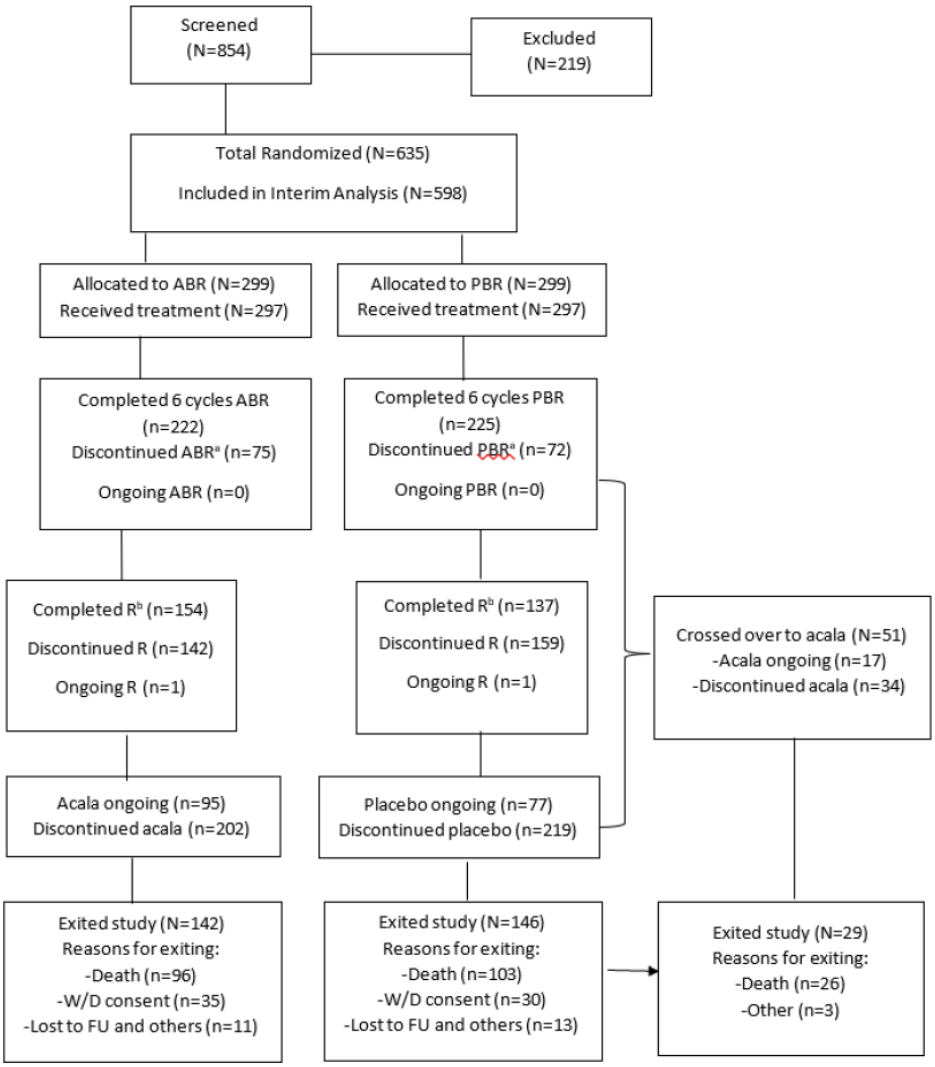
Patient disposition and baseline characteristics

Patient disposition

In total, 594 (99.3%) of 598 patients who were randomised received at least one dose of any study drug (297 of 299 patients per treatment arm) (5).

The 598 patients in the FAS were enrolled across 189 sites in 26 countries. Patients were enrolled in six geographical regions (Asia, Australia and New Zealand, Central and Eastern Europe, Central and South America, North America, and Western Europe), with the US recruiting the highest number of patients (140, 23.4%) across 31 sites (5).

Figure 3 Patient disposition by treatment arm



[a]Discontinued any study drug. [b]Patients who were reported by the investigator to have completed rituximab treatment in line with the protocol. Acala, acalabrutinib; ABR, acalabrutinib plus bendamustine and rituximab; CSR, clinical study report; FU, follow-up; PBR, placebo plus bendamustine and rituximab; R, rituximab; W/D, withdrew.
Source: ECHO CSR, Figure 2.(5)

6.1.2 Comparability of studies

NA

6.1.2.1 Comparability of patients across studies

Baseline- and disease characteristics

Patient demographics, baseline characteristics and disease characteristics were similar between the treatment arms and representative of the target study population.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ECHO		
	ABR (N=299)	PBR (N= 299)	Total (N=598)
Age, years, median (range)	71.0 (65–85)	71.0 (65–86)	71.0 (65–86)
Age group			
< 70 years	123 (41.1)	117 (39.1)	240 (40.1)
≥ 70 years	176 (58.9)	182 (60.9)	358 (59.9)
< 75 years	215 (71.9)	222 (74.2)	437 (73.1)
≥ 75 years	84 (28.1)	77 (25.8)	161 (26.9)
Sex (male)	214 (71.6)	209 (69.9)	423 (70.7)
Race			
White	233 (77.9)	235 (78.6)	468 (78.3)
Asian	44 (14.7)	49 (16.4)	93 (15.6)
American Indian/Alaska Native	2 (0.7)	2 (0.7)	4 (0.7)
Black/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)
ECOG performance status			
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	2 (0.7)	2 (0.3)
Missing	2 (0.7)	2 (0.7)	4 (0.7)
MCL type			
Classic type	238 (79.6)	243 (81.3)	481 (80.4)
Blastoid variant	26 (8.7)	20 (6.7)	46 (7.7)
Pleomorphic variant	15 (5.0)	18 (6.0)	33 (5.5)
Other	0	5 (1.7)	5 (0.8)
Unknown	19 (6.4)	11 (3.7)	30 (5.0)
Not done	1 (0.3)	2 (0.7)	3 (0.5)
Tumour bulk[a]			
< 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)

ECHO			
	ABR (N=299)	PBR (N= 299)	Total (N=598)
≥ 10 cm	20 (6.7)	21 (7.0)	41 (6.9)
Ann Arbor staging for lymphoma			
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)
Ki-67 ≥ 30%	139 (46.5)	147 (49.2)	286 (47.8)
TP53 status			
Known mutation	22 (7.4)	29 (9.7)	51 (8.5)
Simplified MIPI score			
Low risk (0-3)	99 (33.1)	101 (33.8)	200 (33.4)
Intermediate risk (4-5)	128 (42.8)	125 (41.8)	253 (42.3)
High risk (6-11)	72 (24.1)	73 (24.4)	145 (24.2)
Time from randomisation to first dose (months)			
Mean (SD)	2.2 (1.7)	2.2 (2.0)	2.2 (1.8)
Median	2.0	2.0	2.0

Data are *n* (%) unless otherwise stated.
Source: ECHO CSR (5), Dreyling *et al.,* abstract presented at ASH 2024 (49).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

To the best of our knowledge, detailed characteristics of MCL patients in Denmark have not been extensively reported. To ascertain whether the demographic and clinical characteristics of the ECHO study population align with those of Danish patients who are ineligible for high-dose induction therapy followed by ASCT, we consulted a Danish MCL expert. Upon reviewing and discussing Table 13, which presents the baseline characteristics of ECHO study participants, the expert confirmed that the relevant characteristics are indeed comparable to those of the Danish patient cohort that is ineligible for high-dose induction therapy and/or ASCT. Table 14 provides the characteristics of the Danish and ECHO (ABR) study patient characteristics.

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population	Value used in health economic model (reference if relevant)
Age, years, median	71.0	71.6 (mean age in ECHO FAS)
Sex (% of male)	71.6	71% (ECHO FAS)

ECOG performance status (%)		
0	52.2	52.2
1	43.1	43.1
2	4.0	4.0
3	0	0
MCL-type (%)		
Classic type	79.6	79.6
Blastoid variant	8.7	8.7
Pleomorphic variant	5.0	5.0

Source: ECHO CSR, Table 14 and 15 (5).

Comparability of study and Danish clinical practice

The ECHO study design closely resembles current Danish clinical practice in the treatment of MCL. In Denmark, patients with previously untreated MCL are currently typically treated with BR as first-line therapy. Upon disease progression, these patients are commonly switched to BTKi as second-line treatment (1).

In the ECHO study, this is reflected by the use of crossover from the PBR arm to ABR arm and the patterns of subsequent therapy. Among patients receiving subsequent therapy, 43.3% of patients in the ABR arm and 86.4% of patients in the PBR arm received a BTKi.

Crossover design

The use of crossover was a design feature of the ECHO study and was permitted for patients randomized to the PBR arm after PD. Crossover was considered ethically desirable because acalabrutinib has already proven beneficial in subsequent lines of therapy and the ECHO study is evaluating the benefits of advancing acalabrutinib to the first-line setting. In the PBR arm, a total of 51 patients crossed over to acalabrutinib monotherapy during the study after experiencing PD.

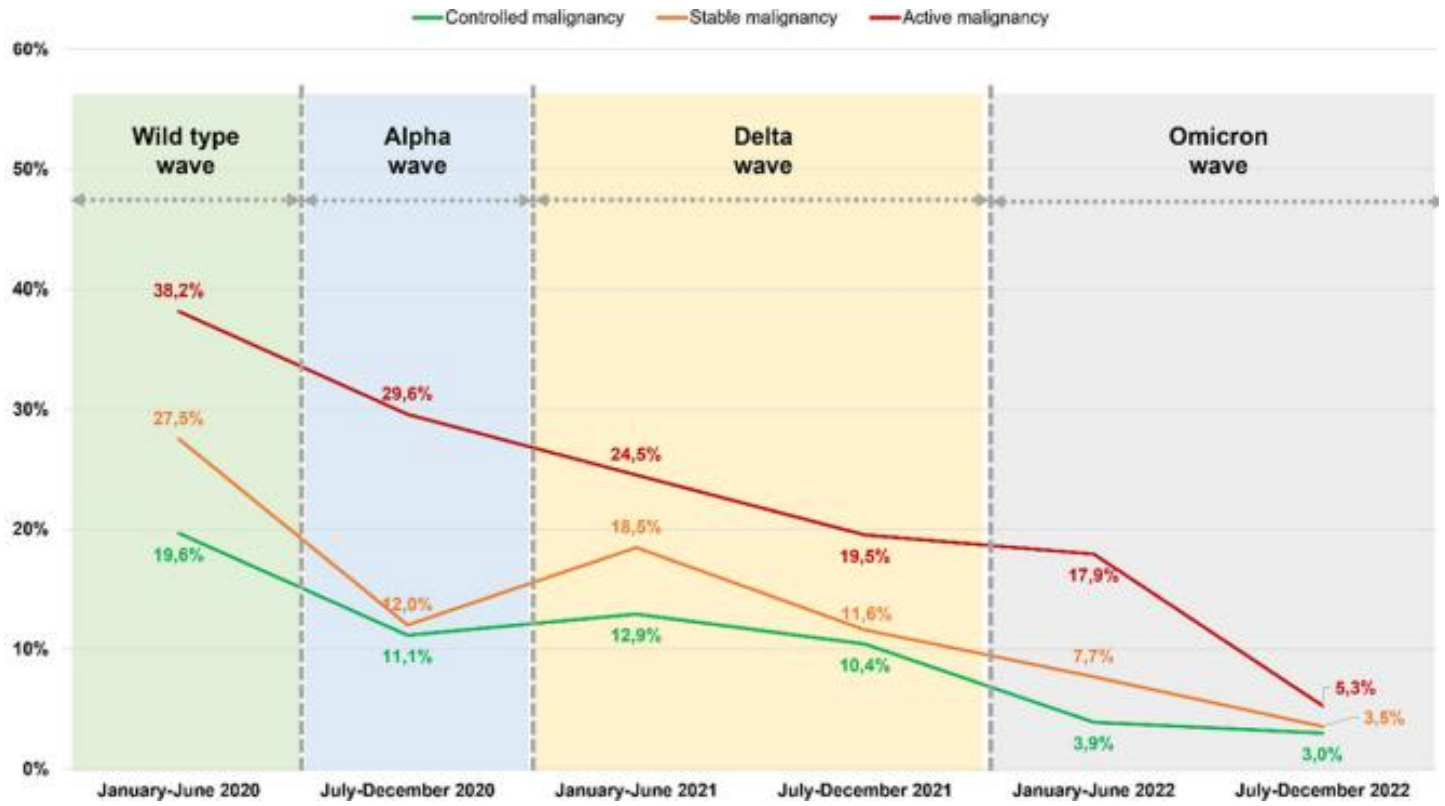
COVID-19 death censored population analysis of PFS and OS

The ECHO study enrolled patients between May 2017 and March 2023, and was in active recruitment throughout the 2020-2023 COVID-19 pandemic. The study follow-up included the initial stages of the pandemic when COVID-19 management guidelines, including vaccination and monoclonal antibodies, were not available. As a result, fatal COVID-19 events were substantial during the study period, occurring in 9.4% and 6.7% of patients in the ABR and PBR arms(SAS population), respectively.

Over the course of the pandemic, the availability of vaccines and advancements in treatment led to a sustained decrease in the risk of COVID-19 mortality in patients with haematological cancers. According to findings from the EPICOVIDEHA study (50), the

mortality rate among patients with active malignancy decreased from 38.2% during the first wave in 2020 to 5.3% during the Omicron Wave in 2022 (see below). When projecting forward to patients treated for MCL after the pandemic, these trends indicate that the rate of mortality from COVID-19 is likely to be significantly lower than during the pandemic and for periods of the ECHO trial.

Figure 4 Mortality rate (y-axis) over time in patients with haematological cancer (50)



In response to the pandemic, the ECHO trial protocol was amended to include a prespecified sensitivity analysis of PFS and OS with censoring of COVID-19 deaths. The aim of the analysis was to assess the impact of the pandemic on trial results.

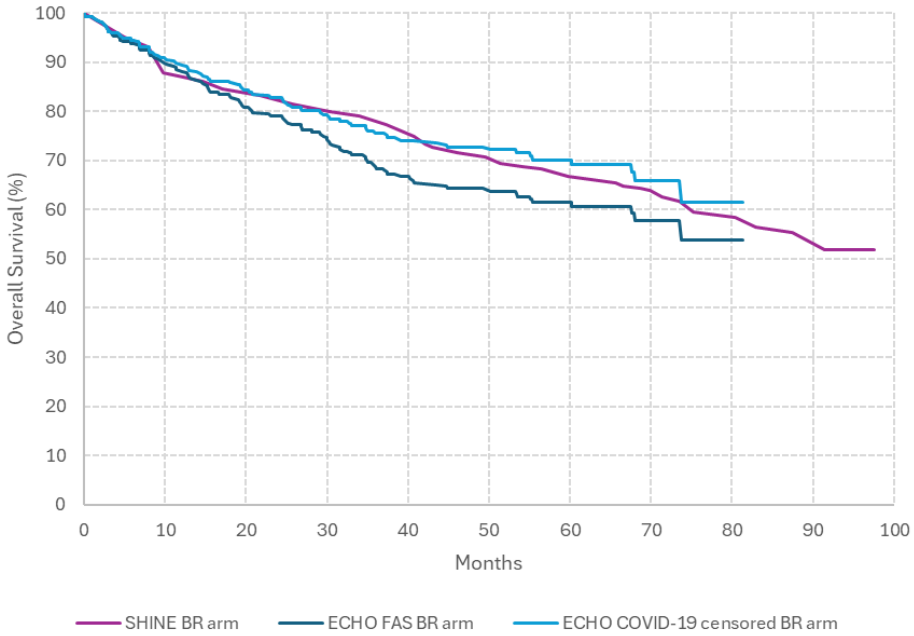
In addition to clinical outcomes, the pandemic impacted the duration of treatment in ECHO, with 31 patients discontinuing acalabrutinib due to a COVID-19 adverse event. To estimate the impact of COVID-19 on treatment duration, a post-hoc analysis of TTD with censoring of COVID-19 related discontinuations was conducted. Following the censoring of COVID-19, the median TTD for acalabrutinib increased from 30.0 months in the intention to treat group to 35.3 months. In the cost-effectiveness model, the TTD for acalabrutinib is based on the post-hoc analysis with censoring of COVID-19 discontinuations to not underestimate the cost of the treatment.

The impact of COVID-19 on other aspects of trial conduct, such as deviations from planned visits at treating centres, was also assessed. Overall, there were very few instances of missed visits (2 and 4 patients in the ABR and PBR arms, respectively). The results of COVID-19 censoring for missed visits indicates that there was no significant impact of the pandemic on the performance of planned visits of efficacy assessment.

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.

The fact that the pandemic impacted the results can be observed in Figure 5, where the ECHO OS data for the PBR arm has been compared with the BR comparator arm from the recent international, randomised, double-blind, Phase 3 SHINE trial. SHINE, which compared the combination of ibrutinib (a first generation BTKi) and BR versus BR alone, is a similar study to ECHO that was otherwise conducted pre-pandemic (51) 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 (BR with the same dosing and treatment regimens), and study population of interest (i.e. transplant unsuitable patients).

Figure 5 Comparison of ECHO OS and SHINE OS comparator arms



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 (see Table 15). The comparator (BR) arms across the SHINE and ECHO studies would therefore be expected to demonstrate consistent survival outcomes in clinical trial settings. This assumption was supported by a Danish external clinical expert. However, when the BR 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 (light blue line in in Figure 5) was more closely aligned with the SHINE OS KM (purple line in Figure 5). Given the study designs, comparator arms and patient populations across both trials were well matched, this illustrates that the outcomes from the ECHO study were impacted by the COVID-19 pandemic.

Table 15 Demographics and baseline characteristics of ECHO and SHINE comparator arms

Characteristic	ECHO FAS BR arm (N = 299) (6)	SHINE BR arm (N = 262) (51)
Age		
Median, yrs (range)	71 (65 – 86)	71 (65 – 87)
≥ 70, yrs (%)	182 (60.9)	154 (58.8)
≥ 75, yrs (%)	77 (25.8)	82 (31.3)
Sex		
Male, n (%)	209 (69.9)	186 (71.0)
Race, n (%)		
White	235 (78.6)	206 (78.6)
Asian	49 (16.4)	42 (16.0)

Black or African American	2 (0.7)	1 (0.4)
ECOG status, n (%)		
0	140 (46.8)	141 (53.8)
1 or 2	155 (51.8)	121 (46.2)
Disease stage, n (%)		
II	11 (3.7)	14 (5.3)
III	24 (8.0)	22 (8.4)
IV	263 (88.0)	226 (86.3)
sMIPI score, n (%)		
Low risk	101 (33.8)	46 (17.6)
Intermediate risk	125 (41.8)	129 (49.2)
High risk	73 (24.4)	87 (33.2)
Extranodal disease, n (%)		
Yes	277 (92.6)	226 (86.3)
No	22 (7.4)	36 (13.7)
Bone marrow involvement, n (%)		
Yes	218 (72.9)	200 (76.3)
No	75 (25.1)	62 (23.7)
Tumour bulk, n (%)		
< 5 cm	186 (62.2)	163 (62.2)
≥ 5 cm	113 (37.8)	98 (37.4)

*not all values sum to 100 as missing and unknown not reported here, can on request.

The PFS and overall OS results of the COVID-19 censored population from ECHO are shown in Table 16.

Table 16 Summary efficacy statistics ECHO COVID-19 censored

	ABR (N = 299)	BR (N = 299)
IRC PFS		
Total number of events, n (maturity)	83 (27.8)	117 (39.1)
Median, months (95% CI)	NR (66.4, NR)	61.6 (49.6, 68.9)
HR, (95% CI)	0.64 (0.48, 0.84)	
p-value	0.0017	
OS		
Total number of events, n (maturity)	64 (21.4)	80 (26.8)
Median, months (95% CI)	NR (NR, NR)	NR (73.8, NR)
HR, (95% CI)	0.75 (0.53, 1.04)	
p-value	0.0797	

HR: Hazard ratio, NR: Not reached

The section below presents the interim outcomes for the ITT population and an analysis of PFS and OS in a population that excluded patients who died of COVID-19. Due to the extraordinary circumstances during the pandemic the PFS and OS outcomes of the ITT population are only presented in 6.1.4 and section 6.1.4.1 respectively for transparency.

The comparative analysis and the cost-utility analysis will be based on PFS and OS in the population that excluded patients who died of COVID-19 of PFS and OS.

6.1.4 Efficacy – results per ECHO

PFS IRC – results per ECHO

The addition of acalabrutinib to BR demonstrated a statistically significant 27% reduction in risk of disease progression or death (p = 0.0160) which corresponds to an approximate 17-month increase in median PFS.

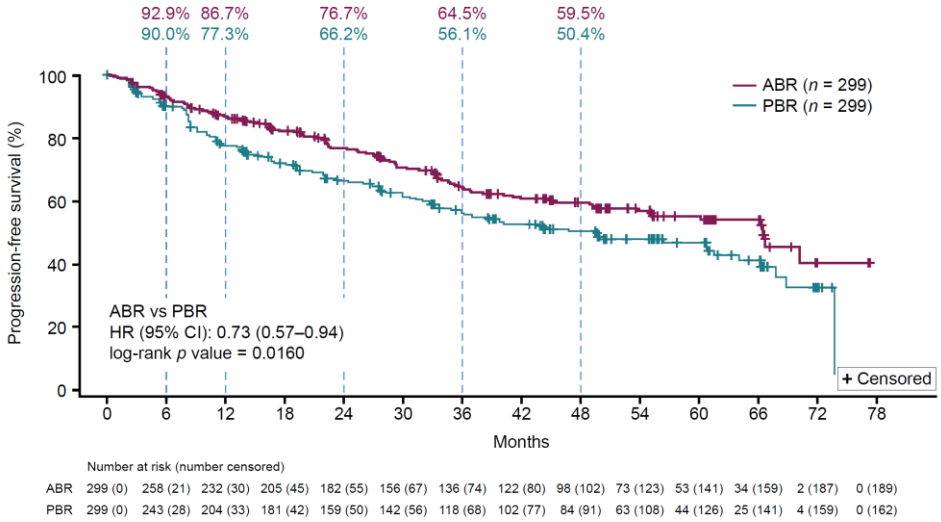
After a median follow-up time of 46.1 months in the ABR arm and 44.4 months in the PBR arm, the estimated median PFS for ABR was 66.4 months (95% CI: 55.1–NE) and 49.6 months for PBR (95% CI: 36.0–64.1) (Table 17).

Table 17. Analysis of PFS by IRC assessment (FAS)

	ABR (*n* = 299)	PBR (*n* = 299)
Patient status		
Events, *n* (%)	110 (36.8%)	137 (45.8%)
Death[a]	53 (17.7%)	38 (12.7%)
Disease progression	57 (19.1%)	99 (33.1%)
PFS (months)		
Median (95% CI)	66.4 (55.1–NE)	49.6 (36.0–64.1)
Stratified analysis[b] (vs PBR)		
Hazard ratio[c] (95% CI)	0.73 (0.57–0.94)	–
***p* value[c]**	0.0160	–
Unstratified analysis[b] (vs PBR)		
Hazard ratio[c] (95% CI)	0.72 (0.56–0.93)	–
***p* value[d]**	0.0112	–
KM estimates of PFS[d] probability by time point		
24 months (95% CI), number by risk	76.7 (71.1–81.3), 182	66.2 (60.1–71.6), 159
36 months (95% CI), number by risk	64.5 (58.1–70.2), 136	56.1 (49.7–62.0), 118
48 months (95% CI), number by risk	59.5 (52.8–65.5), 98	50.4 (43.8–56.6), 84

[a]Only includes deaths prior to progression. [b]Stratified/unstratified by randomisation stratification factors: geographic region (North America, Western Europe, Other) and simplified MIPI Score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11]) as collected via IXRS. [c]Estimated based on stratified or unstratified Cox proportional hazards model for hazard ratio (95% CI), respectively. [d]Estimated based on stratified or unstratified log-rank test for p-value.
Source: ECHO CSR, Table 17 (5).

Figure 6 KM plot for PFS by IRC assessment (FAS)



"+" indicates a value from a censored patient. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; KM, Kaplan–Meier; PBR, placebo plus bendamustine and rituximab; PFS, progression-free survival.
Source: ECHO CSR, Figure 3.(5)

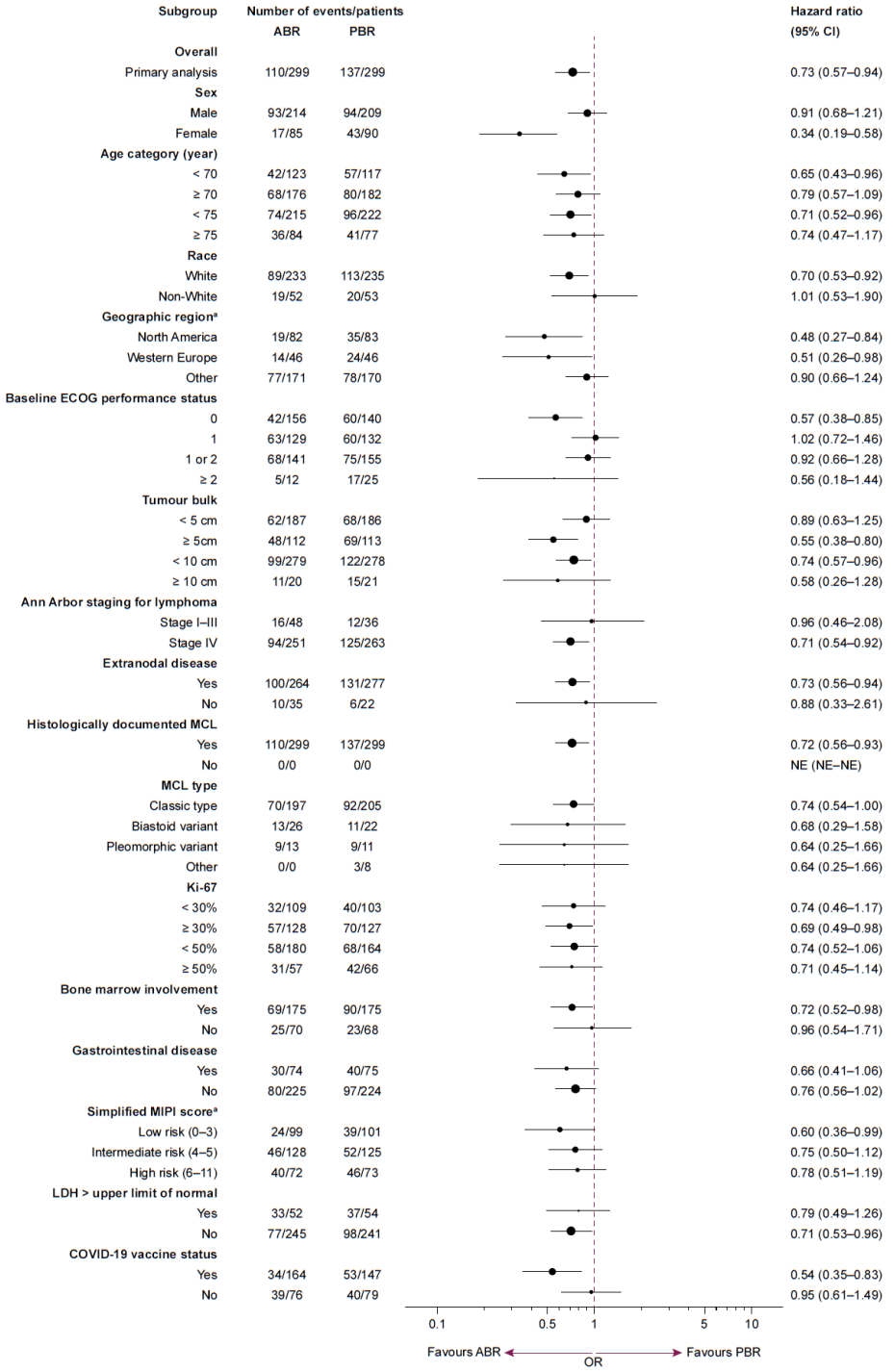
Patient subgroups of the IRC-assessed PFS analyses

PFS benefit with ABR compared with PBR was consistent across the majority of subgroups analysed

A subgroup analysis of patients with biological high-risk factors is presented in Appendix K, the analysis was presented at EHA 2025 the analysis includes patients with biological risk factors such as blastoid and pleomorphic variants as well as high KI-67.

The results of the subgroup analyses of IRC-assessed PFS were consistent with those of the main PFS analysis. The results demonstrated no evidence of significant heterogeneity in the effect of ABR on PFS in the majority of subgroups examined, including for age, geographic region, advanced (Stage IV) disease, highly proliferative disease (Ki-67 > 30%) and patients with an intermediate/high simplified MIPI score. Patients with features of high-risk disease, including blastoid and pleomorphic morphology, high-risk simplified MIPI score, and highly proliferative disease (indicated by high Ki-67 index), all demonstrated a similar trend of improved PFS with the addition of acalabrutinib to BR (Figure 7).

Figure 7. Forest plot for subgroup analysis of PFS by IRC assessment



The size of the circle indicates the sample size, with larger circles indicating a larger sample size. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; Ki-67, marker of proliferation Kiel 67; LDH, lactate dehydrogenase; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimated; PBR, placebo plus bendamustine and rituximab; PFS, progression-free survival.

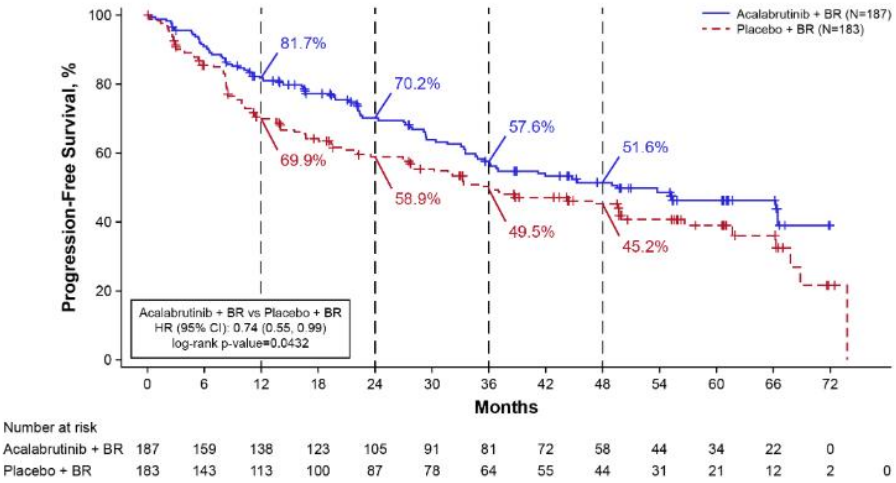
Source: ECHO CSR, Figure 4.(5)

Subgroup of patients with high-risk disease

A subgroup analysis of patients with biological high-risk factors is presented in Appendix K, the analysis was presented at EHA 2025 the analysis includes patients with biological risk factors such as blastoid and pleomorphic variants as well as high KI-67. In a post hoc analysis, efficacy outcomes were analyzed in the subgroup of patients with high-risk disease defined as any of the following: high-risk MIPI (6-11), *TP53* mutation, Ki-67 index ≥30%, and/or blastoid/pleomorphic histology (52). As of February 15, 2024, 62.5% (n=187) and 61.2% (n=183) had high-risk disease in the ABR and PBR arms, respectively. Among them, 24.1% and 24.4% of pts had high-risk MIPI, 7.4% and 9.7% had TP53 mutation, 46.5% and 49.2% had Ki-67 index ≥30%, and 13.7% and 12.7% had blastoid/pleomorphic histology. In pts with high-risk disease status, ORR was 89.8% with ABR vs 84.7% with PBR; best overall response of CR was observed in 67.9% with ABR vs 47.5% of pts with PBR. At a median follow-up of 44.9 months, median PFS was significantly longer with ABR (49.5 mo) vs PBR (36.0 mo; HR 0.74; 95% CI 0.55-0.99; P=0.0432; Figure 7). After disease progression, 38 pts with high-risk disease who received placebo crossed over to acalabrutinib. With an OS maturity rate of 42%, there was a positive OS trend in favor of ABR (HR 0.87; 95% CI 0.64-1.19; P=0.3913) (53).

When considering only patients with either *TP53* mutation (n=22 vs n=29), Ki-67 index ≥30% (n=139 vs n=147), and/or blastoid/pleomorphic histology (n=41 vs n=38), ABR also demonstrated longer PFS vs PBR (HR 0.66; 95% CI 0.48-0.91; *P*=0.0119). Similarly, when only patients with Ki-67 index ≥30% and/or blastoid/pleomorphic histology were evaluated, PFS was longer with ABR vs PBR (HR 0.64; 95% CI 0.46-0.90; *P*=0.0092) (52).

Figure 8 PFS by IRC in patients with high-risk MCL in the ECHO trial (52).



Analysis that excluded patients who died of COVID-19

As the COVID-19 pandemic occurred during the ECHO study when enrolment was active, the FDA provided guidance on clinical trial protocols during the COVID-19 pandemic and

to AstraZeneca for ECHO. Based on the FDA feedback, the ECHO protocol was amended and included a pre-planned analysis reporting data with censoring of COVID-19 related deaths to evaluate the impact of COVID-19 deaths.

The results from this analysis (Table 18) confirmed the robustness of the primary analysis and indicated an increased clinical benefit of ABR versus PBR for the target population (HR: 0.64; 95% CI: 0.48–0.84; *p* = 0.0017; Figure 9).

After censoring for COVID-19 deaths, median PFS improved in both arms and PFS was not reached with ABR compared with 61.6 months with PBR (HR: 0.64; 95% CI: 0.48–0.84; *p* = 0.0017) and was 69.9% (95% CI: 63.5–75.4) and 57.3% (95% CI: 50.5–63.5) at 48 months. (Table 18).

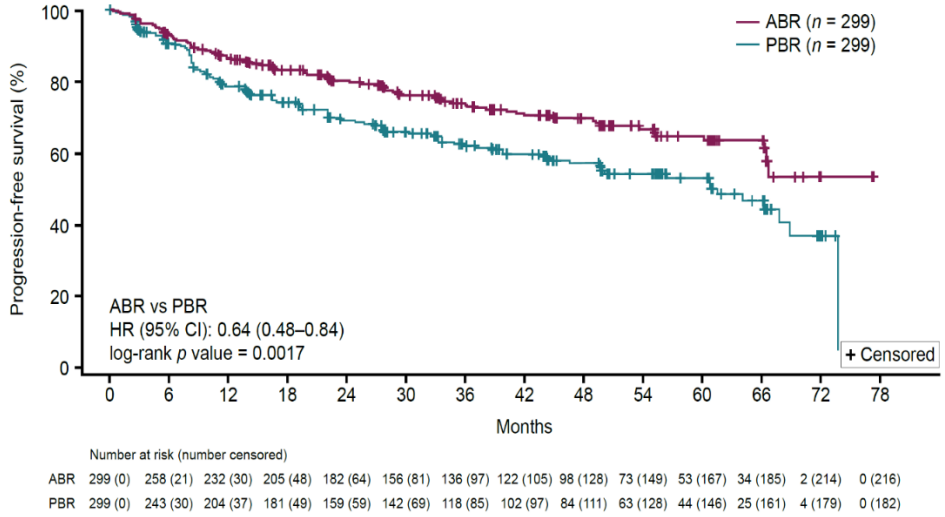
Table 18. Analysis of PFS by IRC assessment (FAS: censoring the confirmed/suspected COVID-19-related deaths)

	ABR (n = 299)	PBR (n = 299)
Patient status		
Events, *n* (%)	83 (27.8%)	117 (39.1%)
Death[a]	26 (8.7%)	18 (6.0%)
Disease progression	57 (19.1%)	99 (33.1%)
PFS (months)		
Median (95% CI)	NE (66.4–NE)	61.6 (49.6–68.9)
Stratified analysis[b] (vs PBR)		
Hazard ratio[c] (95% CI)	0.64 (0.48–0.84)	–
***p* value[d]**	0.0017	–
Unstratified analysis[b] (vs PBR)		
Hazard ratio[c] (95% CI)	0.64 (0.48–0.85)	–
***p* value[d]**	0.0018	–
KM estimates of PFS[c] probability by time point (%)		
24 months (95% CI), number by risk	80.3 (74.9–84.6), 182	69.2 (63.2–74.4), 159
36 months (95% CI), number by risk	74.0 (68.0–79.0), 136	62.1 (55.7–67.8), 118
48 months (95% CI), number by risk	69.9 (63.5–75.4), 98	57.3 (50.5–63.5), 84

[a]Only includes deaths prior to progression. [b]Stratified/unstratified by randomisation stratification factors: geographic region (North America, Western Europe, Other) and simplified MIPI Score (low risk [0 to 3], intermediate risk [4 to 5], high risk [6 to 11]) as collected via IXRS. [c]Estimated based on a stratified or unstratified Cox proportional hazards model for HR (95% CI), respectively. [d]Estimated based on a stratified or unstratified log-rank test for *p* value, respectively. Time to event (or time to censoring for censored patients) was calculated as the date of disease progression or death (censoring date for censored patients)– randomisation date + 1. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; MCL, mantle cell lymphoma; MIPI, Mantle Cell Lymphoma International Prognostic Index; PBR, placebo plus bendamustine and rituximab; PFS, progression-free survival.

Source: ECHO CSR, Table 18.(5)

Figure 9. Analysis of KM plot for PFS by IRC assessment (FAS: censoring the confirmed/suspected COVID-19-related deaths)



HRs (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 a stratified log-rank test, stratified by randomisation stratification factor as recorded in IXRS. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PBR, placebo plus bendamustine and rituximab.

Source: ECHO CSR, Figure 5 (5).

6.1.4.1 OS – results per ECHO

Overall survival

The median OS in this study was not reached in either arm. However, there was a trend towards a prolonged OS with ABR compared with PBR despite the crossover design and recruitment during the COVID epidemic.

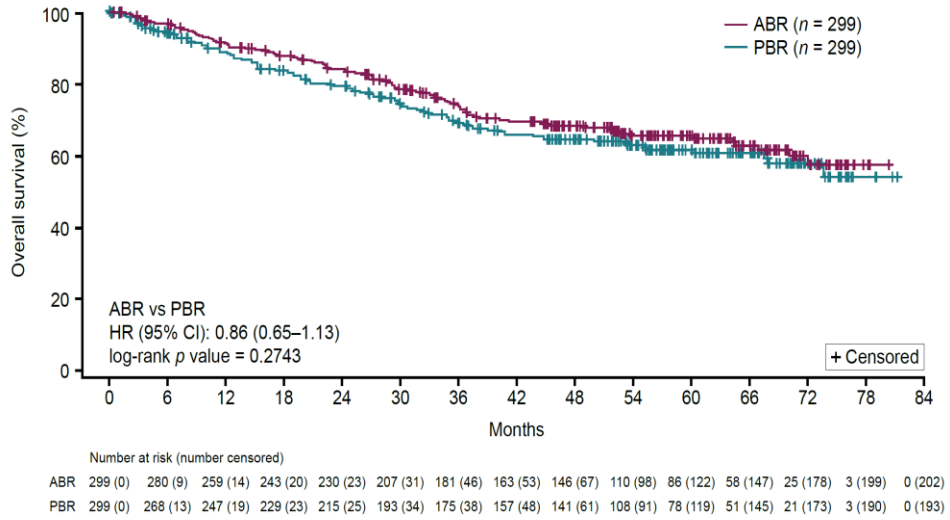
In the FAS population, there was a positive OS trend in favour of ABR compared with PBR (maturity rate = 34%; HR: 0.86; 95% CI: 0.65–1.13; *p* = 0.2743). After a median follow-up time of 46.1 months in the ABR arm and 44.4 months in the PBR arm, 97 patients (32.4%) and 106 patients (35.5%) in the ABR and PBR arm, respectively, had died. Median OS in this study was not reached in either arm. OS results are reported in Table 19. The KM curves of OS per treatment arm show that at 48 months, the estimated survival rate was higher with ABR (68.0%) than PBR (64.3%)(Table 19). The OS benefit was demonstrated despite the crossover of patients from the PBR arm to acalabrutinib monotherapy following PD, which was part of the trial design and is in line with clinical practice because patients in the PBR arm would be expected to receive a BTKi as second-line therapy.

Table 19. Overall survival (FAS)

	ABR (*n* = 299)	PBR (*n* = 299)
Patient status		
Total deaths,[a] *n* (%)	97 (32.4%)	106 (35.5%)
OS (months)		
Median (95% CI)	NE (72.1–NE)	NE (73.8–NE)
Stratified analysis[b] (vs PBR)		
Hazard ratio (95% CI)[c]	0.86 (0.65–1.13)	–
***p* value[d]**	0.2743	–
Unstratified analysis[b] (vs PBR)		
Hazard ratio (95% CI)[c]	0.87 (0.66–1.15)	–
***p* value[d]**	0.3248	–
KM estimates of OS by time point (%)		
24-month OS rate (95% CI)	83.8 (79.0–87.6), 230	79.1 (73.9–83.4), 215
36-month OS rate (95% CI)	73.8 (68.2–78.7), 181	68.8 (62.9–73.9), 175
48-month OS rate (95% CI)	68.0 (62.0–73.3), 146	64.3 (58.2–69.7), 141

[a]Death from any cause. [b]Based on a stratified or unstratified Cox proportional hazards model, by randomisation stratification factors as recorded in IXRS if stratified. [c]Based on a stratified or unstratified log-rank test, by randomisation stratification factors as recorded in IXRS if stratified.
[d]Estimated based on a stratified or unstratified log-rank test for *p* value. Months are derived as days/30.4375. Time to event (or time to censoring for censored patients) was calculated as date of disease progression or death (censoring date for censored patients)–randomisation date + 1. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IXRS, Interactive Voice/Web Response System; KM, Kaplan–Meier; NE, not estimable; OS, overall survival; PBR, placebo plus bendamustine and rituximab.
Source: ECHO CSR, Table 21.(5)

Figure 10. KM curve for OS per treatment arm (FAS)



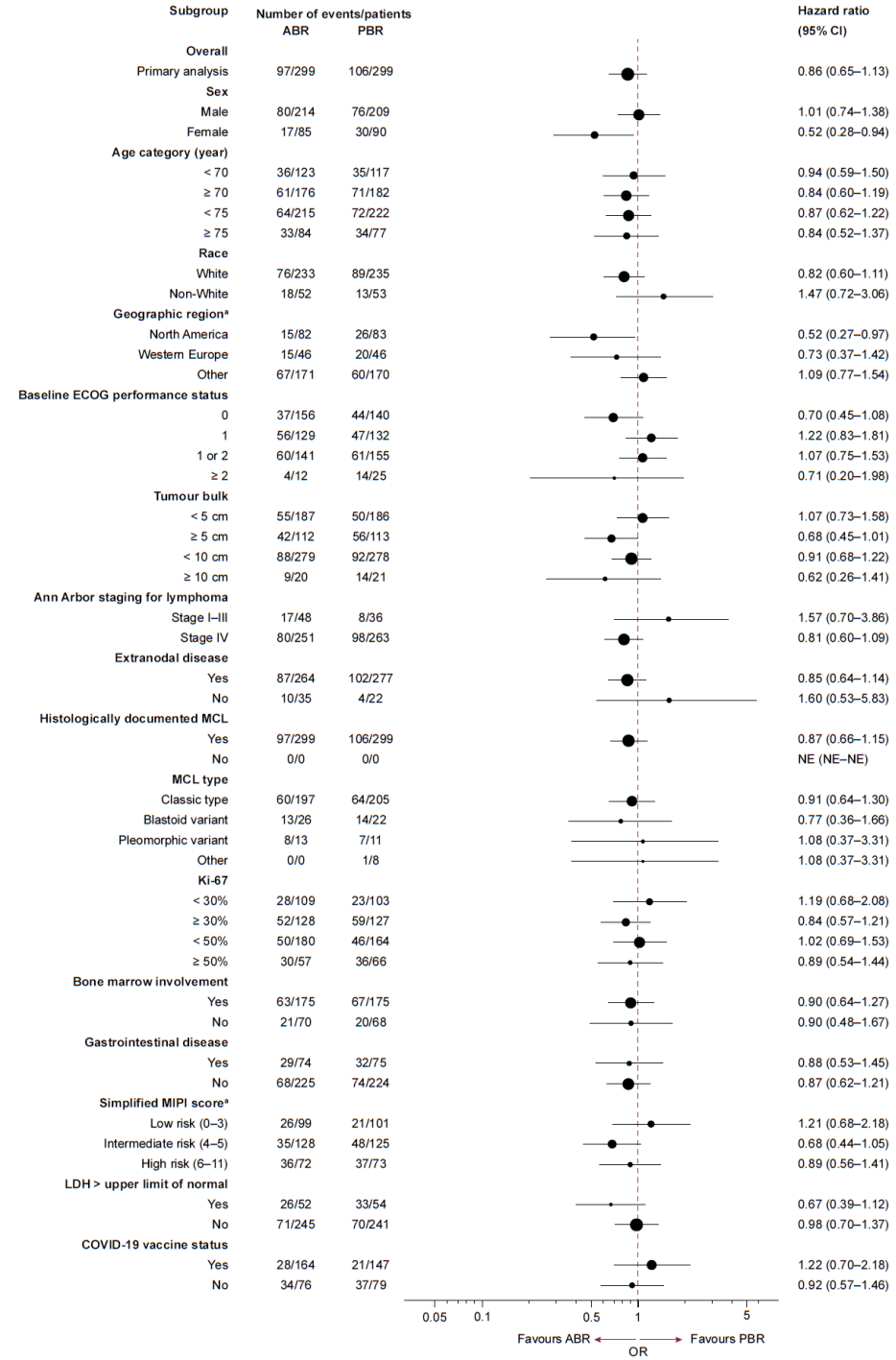
ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; IRC, independent review committee; KM, Kaplan–Meier; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PBR, placebo plus bendamustine and rituximab.
Source: ECHO CSR, Figure 7.(5)

Patient subgroups of the OS analyses

Subgroup analyses of OS (FAS including the crossover period) demonstrated no evidence of significant heterogeneity of treatment effect on OS in the majority of subgroups examined(

Figure 11).

Figure 11. Forest plot of subgroup analysis for OS (FAS)



ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IXRS, interactive voice/web response system; MCL, mantle cell lymphoma; OS, overall survival; PBR, placebo plus bendamustine and rituximab. [a]According to the IXRS record. Hazard ratios (95% CI) are based on a unstratified Cox proportional hazards model.
Source: ECHO CSR Appendix, Figure 14.2.5.8.(5)

Analysis of OS that excluded patients who died of COVID-19

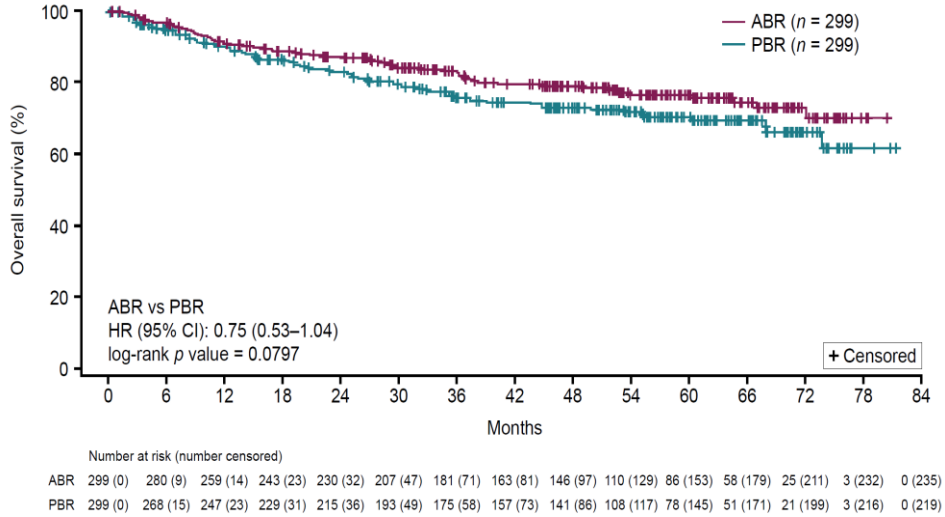
Any patient who was known to have died of COVID-19 was censored at their death date. After censoring patients who died of COVID-19, the treatment effect on OS became more pronounced with an HR of 0.75 (95% CI: 0.53–1.04; $p = 0.0797$) in favour of ABR over PBR Table 20 and Figure 11.

Table 20 Analysis of OS (FAS: censoring the confirmed/suspected COVID-19-related deaths)

Patient status	ABR (*N* = 299)	PBR (*N* = 299)
Events[a], *n* (%)	64 (21.4%)	80 (26.8%)
Deaths	64 (21.4%)	80 (26.8%)
Censored, *n* (%)	235 (78.6%)	219 (73.2%)
COVID-19 deaths[e]	33 (11.0%)	26 (8.7%)
OS (months) (95% CI)		
Median (95% CI)	NE (NE–NE)	NE (73.8–NE)
Stratified analysis[b] (ABR vs PBR) HR (95% CI)[c]	0.75 (0.53–1.04)	–
***p* value**	0.0797	–
Unstratified analysis[b] (ABR vs PBR) HR (95% CI)[c]	0.76 (0.55–1.06)	–
***p* value**	0.1042	–

Months are derived as days/30.4375. Time to event (or time to censoring for censored patients) is calculated as the date of death (or censoring date for censored patients) - randomisation date + 1. [a]Death from any cause. [b]Based on a stratified or unstratified Cox proportional hazards model, by randomisation stratification factor simplified MIPI score as recorded in IXRS if stratified. [c]Based on a stratified or unstratified log-rank test, by randomisation stratification factor simplified MIPI score as recorded in IXRS if stratified. [d]Estimated based on stratified or unstratified log-rank test for *p* value. [e]COVID-19 deaths include all grade 5 confirmed/suspected COVID-19 infection AEs and deaths from a reason specified as COVID-19. ABR, acalabrutinib plus bendamustine and rituximab; AE, adverse event; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; IXRS, interactive voice/web response system; MIPI, Mantle Cell Lymphoma International Prognostic Index; NE, not estimable; OS, overall survival; PBR, placebo plus bendamustine and rituximab.
Source: ECHO CSR Appendix, Table 14.2.5.3.(5)

Figure 12 Analysis of the KM plot for OS by IRC assessment (FAS: censoring the confirmed/suspected COVID-19-related deaths)



HRs (95% CI) are based on a stratified Cox proportional hazards model, stratified by randomisation stratification factors simplified MIPI score as recorded in IXRS. *p* value is based on a stratified log-rank test, stratified by randomisation stratification factor as recorded in IXRS. ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; IXRS, interactive voice/web response system; KM, Kaplan–Meier; MIPI, Mantle Cell Lymphoma International Prognostic Index; OS, overall survival; PBR, placebo plus bendamustine and rituximab.
Source: ECHO CSR, Figure 8.(5)

7. Comparative analyses of efficacy

NA

7.1.1 Differences in definitions of outcomes between studies

NA

7.1.2 Method of synthesis : NA

7.1.3 Results from the comparative analysis

Table 21 Results from the comparative analysis of ABR vs. PBR for ECHO

Outcome measure	ABR (N=299)	PBR (N=299)	Result
Median PFS, Population that excluded patients who died of COVID-19,	NE (66.4–NE)	61.6 (49.6–68.9)	0.64 (0.48–0.84); p = 0.0017

Outcome measure	ABR (N=299)	PBR (N=299)	Result
time point: 44.9 months at 15 February 2024			
Median OS, Population that excluded patients who died of COVID-19, **time point:** 44.9 months at 15 February 2024	NE (NE–NE)	NE (73.8–NE)	0.75 (0.53–1.04); p = 0.0797
IRC-assessed ORR (CR+PR) **time point:** 44.9 months at 15 February 2024	273 (87.7–94.1)	266 (85.0–92.2)	Difference: 2.3% (-2,5%, 7,2%) p= 0.3239
KM estimates of PFS, From population that excluded patients who died of COVID-19, probability by timepoint (%)			
24 months (95% CI), number at risk	80.3 (74.9–84.6), 182	69.2 (63.2–74.4), 159	
36 months (95% CI), number at risk	74.0 (68.0–79.0), 136	62.1 (55.7–67.8), 118	
48 months (95% CI), number at risk	69.9 (63.5–75.4), 98	57.3 (50.5–63.5), 84	

7.1.4 Efficacy – results per PFS

In the population that censored COVID-19 deaths, median PFS in the ABR and PBR arms was (not reached vs 61.6 months) and the treatment benefit seen with ABR was (HR: 0.64; 95% CI: 0.48–0.84, p = 0.0017), indicating that the clinical benefit of ABR is superior to PBR.

7.1.5 Efficacy – results per OS

The addition of acalabrutinib to BR was associated with a trend towards increased OS at this interim FAS despite 51 patients crossing over from the PBR arm at disease progression. In the population that censored for patients who died because of COVID-19 showed a positive OS trend, with an improvement in the stratified HR of 0.75 (95% CI: 0.53–1.04).[33]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The primary source of clinical data for the model is the ECHO trial DCO 15th February 2024. The ECHO trial provides data on the outcomes of treatment with ABR and PBR in the model. The PSM used PFS, OS, and general population mortality to model state occupancy in the PF, PD and dead health states. Parametric survival modelling was used to extrapolate these results after the trial follow-up period and over the lifetime horizon (30 years).

8.1.1 Extrapolation of efficacy data

All time-to-event outcomes for use in the model were extrapolated from the patient-level data from the ECHO trial following the guidance from the NICE Decision Support Unit's Technical Support Document 14, updated guidance on selecting survival models from Palmer et al. and DMC's guidelines with consideration to the statistical and visual fit to the trial data and the plausibility of the long-term extrapolations (54-56). All extrapolations are based on the DCO1 of the COVID-19 censored ECHO trial, dated 15 February 2024. Please see section 0 for a description of the COVID-19 censored data. For each endpoint the following steps were followed:

1. Generate Kaplan-Meier plots and diagnostic plots (log cumulative hazards, log odds, log normal, quantile-quantile, and Schoenfeld residual) to assess whether the proportional hazards assumption has been violated and if measures of relative treatment effect are appropriate for modelling on each endpoint separately.
2. Generate empirical and smoothed hazards plots to assess and compare across endpoints for clinically plausibility of relationships between functional forms on different endpoints.
3. Fit parametric survival models using standard distributions (exponential, Weibull, Gompertz, gamma, lognormal, loglogistic, and generalised gamma) to the individual arms of the trial or joint models, as appropriate.
4. Evaluate the best fitting parametric curve(s) to each arm on the basis of statistical fit to the trial data (Akaike's Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual fit of the extrapolated curve to the trial Kaplan-Meier curve, visual fit of the hazard function of the extrapolated curve to the smoothed hazards and external data, comparison of the extrapolated portion of the curves to empirical longer term survival data, and feedback from AstraZeneca medical advisors and external clinical experts on the plausibility of long-term survival.

AstraZeneca consulted a Danish external clinical expert concerning the long-term survival outcomes for patients with MCL patients in Denmark. For each endpoint a preferred

parametric fit was selected based on the above criteria and clinical plausibility. Additionally, alternative distributions were explored in scenario analyses. All supplementary figures can be found in Appendix D.

8.1.1.1 Extrapolation of progression free survival (PFS)

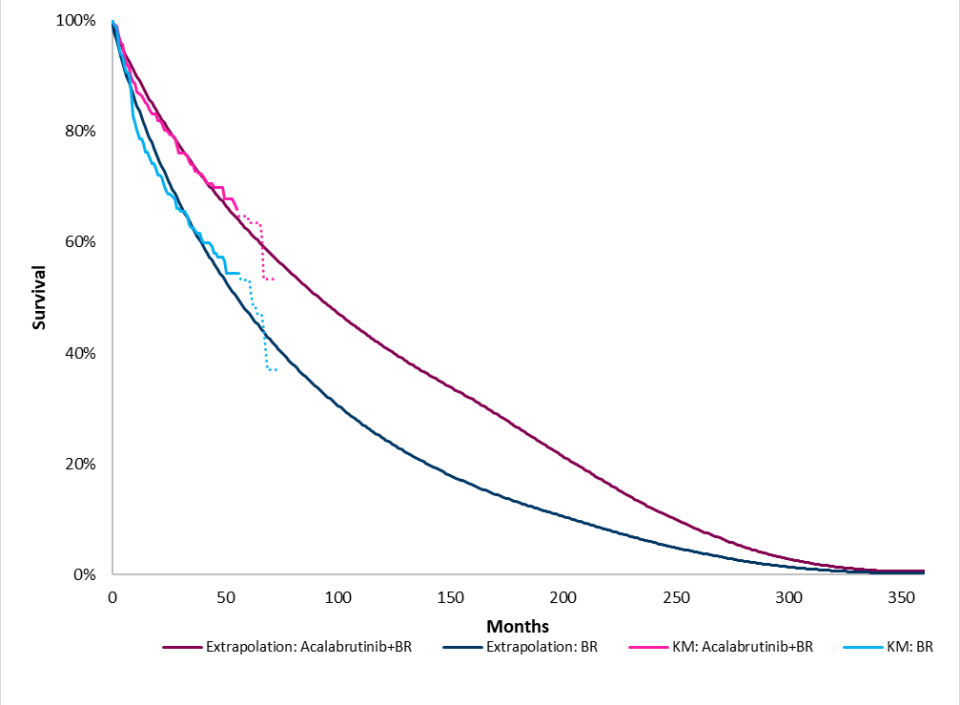
Summary of extrapolation of PFS is presented in Table 22. Please refer to D.2 for full description of extrapolation choice.

Table 22 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	ECHO trial, COVID-19 censored population
Model	- Exponential - Weibull - Log-normal - Log-logistic - Gompertz - Generalized Gamma - Gamma - Generalized F
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	ABR: Log-normal PBR: Log-logistic
Function with best BIC fit	ABR: Exponential PBR: Exponential
Function with best visual fit	ABR: All except exponential PBR: All except exponential
Function with best fit according to evaluation of smoothed hazard assumptions	ABR: Gamma, Weibull PBR: Gamma, Weibull
Validation of selected extrapolated curves (external evidence)	Clinical expert's opinion
Function with the best fit according to external evidence	Intervention: N/A Comparator: Gompertz, Log-normal, Log-logistic
Selected parametric function in base case analysis	ABR: Gamma PBR: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No

Method/approach	Description/assumption
Assumptions of cure point	No

Figure 13 Base case extrapolations of PFS overlayed with observed data for PFS in ECHO.



Dotted lines represent KM-data where <20 % of patients are at risk.

8.1.1.2 Extrapolation of overall survival (OS)

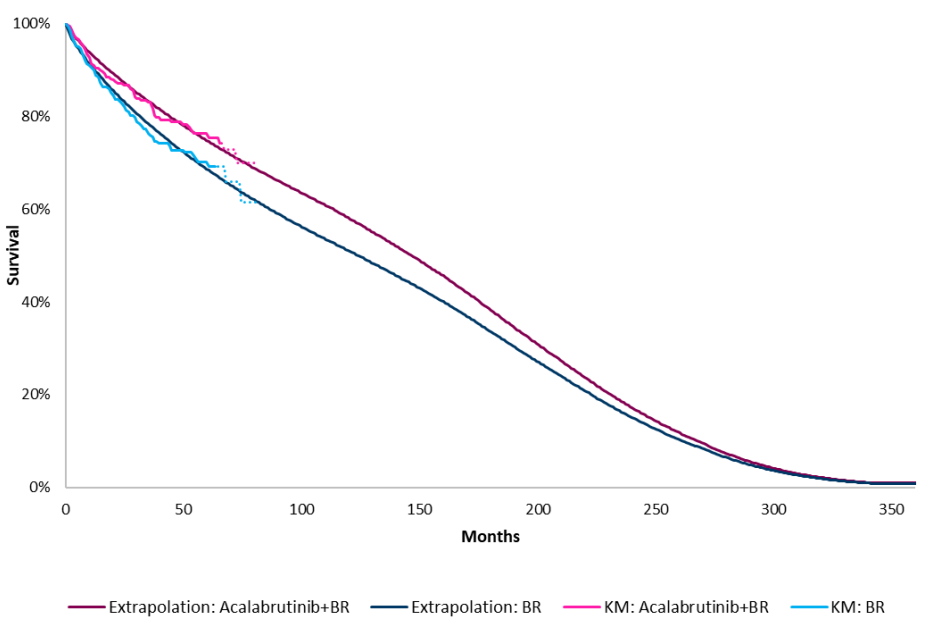
Summary of extrapolation of OS is presented in Table 23. Please refer to Appendix D for full description of extrapolation choice.

Table 23 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	ECHO trial, COVID-19 censored population
Model	Exponential, Weibull, Log-normal, Log-logistic , Gompertz, Generalized Gamma, Gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	ABR: Gompertz PBR: Log-normal
Function with best BIC fit	ABR: Gompertz PBR: Exponential

Method/approach	Description/assumption
Function with best visual fit	ABR: All except exponential PBR: All except exponential
Function with best fit according to evaluation of smoothed hazard assumptions	ABR: Gamma, Weibull PBR: Gamma, Weibull
Validation of selected extrapolated curves (external evidence)	Clinical expert opinion
Function with the best fit according to external evidence	Intervention: N/A Comparator: Gamma, Weibull or exponential
Selected parametric function in base case analysis	ABR: Gamma PBR: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes, age- and gender-matched background mortality is used to cap OS of patients in all treatment arms in model.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 14 Base case extrapolations of OS overlayed with observed data for OS in ECHO



Dotted lines represent KM-data where <20 % of patients are at risk.

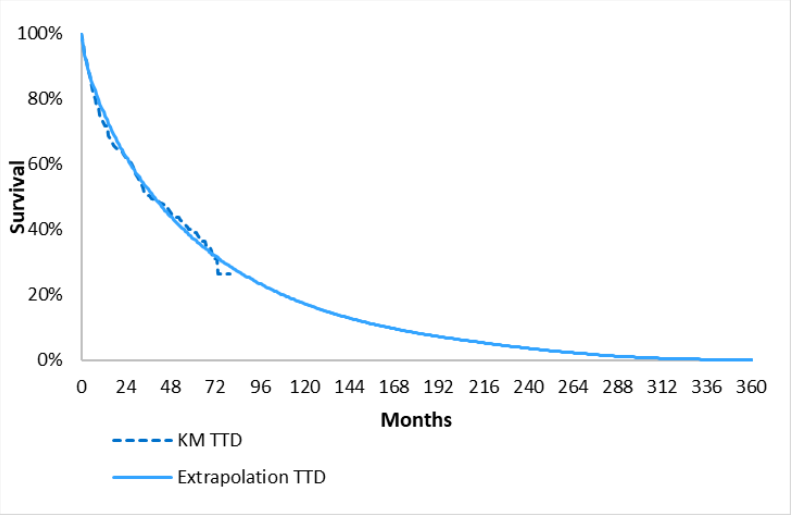
8.1.1.3 Extrapolation of time to treatment discontinuation (TTD)

Summary of extrapolation of TTD is presented in Table 24. Please refer to Appendix D for full description of extrapolation choice.

Table 24 Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	ECHO trial, COVID-19 censored population
Model	Exponential, Weibull, Log-normal, Log-logistic, Gompertz, Generalized Gamma, Gamma, Generalized F
Assumption of proportional hazards between intervention and comparator	NA
Function with best AIC fit	ABR: Log-normal PBR: NA
Function with best BIC fit	ABR: Log-normal PBR: NA
Function with best visual fit	ABR: All except exponential PBR: NA
Function with best fit according to evaluation of smoothed hazard assumptions	ABR: Gamma, Weibull PBR: Gamma, Weibull
Validation of selected extrapolated curves (external evidence)	Clinical expert opinion
Function with the best fit according to external evidence	Intervention: Gamma, Weibull Comparator: N/A
Selected parametric function in base case analysis	ABR: Gamma PBR: NA
Adjustment of background mortality with data from Statistics Denmark	Yes, through overall survival
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	NA
Assumptions of cure point	NA

Figure 15 Base case extrapolations of TTD for acalabrutinib overlayed with observed data for TTD in ECHO.



8.1.2 Calculation of transition probabilities

NA

Table 25 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
NA	NA	NA	NA

8.2 Presentation of efficacy data from [additional documentation]

NA.

8.3 Modelling effects of subsequent treatments

Costs of subsequent treatments were included in the model with no impact on efficacy other than what has been captured in the ECHO trial.

8.4 Other assumptions regarding efficacy in the model

NA

8.5 Overview of modelled average treatment length and time in model health state

An overview of modelled average treatment length and time in model health states is shown in Table 26. Estimates that are undiscounted and not half cycle corrected can be found in Table 27.

Table 26 Estimates in the model

	Modelled average (reference in Excel)	Modelled median (reference in Excel)	Observed median from relevant study
PFS			
ABR	7.6 years (=Results!J86)	7.7 years (=Results!K86)	Not reached
PBR	5.6 years (=Results!J88)	4.6 Years (=Results!K88)	5.1 years (61.6 months)
OS			
ABR	9.3 years (=Results!J91)	12.2 years (=Results!K91)	Not reached
PBR	8.5 years (=Results!J93)	10.3 years (=Results!K93)	Not reached
TTD			
ABR	5.4 years (=Results!J96)	3.3 years (=Results!K96)	3.1 years
PBR	1.5 years (=Results!J98)	2.0 years (=Results!K98)	1.9 years

Note: Modelled outcomes have been adjusted for background mortality as per DMC guidance. Modelled outcomes are discounted and half cycle corrected.

Table 27 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	Progression-free [months]	Progressed disease [months]
ABR	64.5	114.7	29.6
PBR	18.3	81.6	49.6

9. Safety

9.1 Safety data from the clinical documentation

Safety data was reported for the SAS, which included all randomized patients who received at least one dose of the study treatment during the main study period.

As of the DCO on 15 February 2024, the median follow-up was 44.9 months (46.1 months in the ABR arm and 44.4 months in the PBR arm). The median treatment exposure for acalabrutinib in the ABR arm was 28.6 months, compared to 24.6 months for placebo in the PBR arm. At the DCO, 95 patients (31.9%) in the ABR arm and 77 patients (25.9%) in the PBR arm were still receiving treatment.

Additional safety analyses can be seen in Appendix A.

Table 28 Overview of safety events reported in the ECHO study at the interim analysis with data cut-off on 15 February 2024, in the safety analysis set.

	ABR (N=297) (5)	PBR (N=297) (5)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	NA
Number and proportion of patients with ≥1 adverse events, n (%)	296 (99.7)	294 (99.0)	1% (-1%;2%)
Number of serious adverse events*, n	NA	NA	NA
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	205 (69.0)	184 (62.0)	7% (-1%;15%)
Number of CTCAE grade ≥ 3 events, n	NA	NA	NA
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	264 (88.9)	262 (88.2)	1% (-4%;6%)
Number of adverse reactions, n	NA	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions (treatment-related TEAE), n (%)	281 (94.6)	274 (92.3)	2% (-2%;6%)
Number and proportion of patients who had a dose reduction, n (%)	94 (31.6)	77 (25.9)	6% (-2%;13%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%) **	202 (67.6)	220 (73.6)	-6% (-13%;1%)
Number and proportion of patients who discontinue treatment due to adverse events, n (%) **	127 (42.5)	103 (34.4)	8% (0%;16%)

* A serious adverse event% is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect § CTCAE v. 5.0 must be used if available. **

Discontinuation of acalabrutinib/placebo at DCO reported from the full analysis set, intention to treat population (N=299). Source: ECHO CSR, Table 10 and 37 (5).

Treatment-emergent serious adverse events

Treatment-emergent SAEs of any grade occurred in 69.0% and 62.0% of patients in the ABR and PBR arms, respectively. Table 29 summarizes the frequency of all treatment-emergent serious adverse events (SAEs) with frequency of ≥ 5% recorded in the SAS of the ECHO trial (5).

Table 29 Serious adverse events reported in 5% or more patients in either treatment arm of the ECHO study (preferred term) at interim analysis (data cut-off on 15 February 2024) in the SAS(5)

Adverse events	ABR (N=297)(5)		PBR (N=297)(5)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
COVID-19 pneumonia	41 (13.8)	NA	34 (11.4)	NA
Pneumonia	28 (9.4)	NA	21 (7.1)	NA
COVID-19	26 (8.8)	NA	19 (6.4)	NA
Pyrexia	17 (5.7)	NA	15 (5.1)	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Source: ECHO CSR, Table 56 (5).

For the health economic model, any grade 3 or higher AEs that occurred in at least 1.5% of the patients in ECHO trial evaluating the ABR and PBR were included. See Table 30.

Table 30 Adverse events used in the health economic model

Adverse events	ABR	PBR		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
Anaemia	5.4%	5.7%	ECHO (SAS)	Rates of adverse events grade ≥3 from ECHO, table includes adverse events that occurred in at least 1.5% of patients in either treatment arm.
Cardiac events	2.0%	1.0%		
Diarrhoea	1.7%	2.0%		
Fatigue	2.4%	3.0%		
Febrile neutropenia	4.0%	1.3%		
Infections	0.7%	0.0%		

Leukopenia	5.4%	5.4%
Lymphopenia	2.4%	5.1%
Neutropenia	34.0%	35.4%
Pneumonia	5.1%	4.0%
Thrombocytopenia	5.4%	5.1%

9.2 Safety data from external literature applied in the health economic model

N/A, no safety data was sourced from external literature has been applied in health economic model.

Table 31 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA	NA	NA	NA	NA	NA	NA	NA

10. Documentation of health-related quality of life (HRQoL)

Table 32 present the included HRQOL instrument for the assessment.

Table 32 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-VAS	ECHO (6)	Clinical effectiveness In FAS
EQ-5D-5L	ECHO (6)	Clinical effectiveness IN FAS
EORTC QLQ-C30	ECHO (6)	Clinical effectiveness in FAS

10.1 Presentation of the health-related quality of life EQ-VAS

10.1.1 Study design and measuring instrument

One of the tools measuring HRQoL in ECHO is the EQ-VAS, which is well known and will not be described in more detail here here.

10.1.2 Data collection

Patient-reported outcome assessments were to be performed at screening, on Day 1 of Cycles 3, 5, and 8, then every 4 cycles until discontinuation of study treatment, and then every 12 weeks thereafter until PD or use of alternative anti-MCL therapy. (5)

Pattern of missing data is presented in Table 33.

Table 33 Pattern of missing data and completion (5)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Screening	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 28 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 36 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 44 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 48 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 52 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 56 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 60 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 64 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 68 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 72 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 76 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 80 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 84 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 88 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

10.1.3 HRQoL results

Findings show no difference in quality of life between either treatment arm

(5)

Figure 16 Mean change from baseline in EQ-5D-5L VAS (95% CI)(5)

Table 34 HRQoL EQ-5D VAS summary statistics. Baseline and change from baseline (CHFBL)(5)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 36 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention		Comparator		Intervention vs. comparator	
Cycle 44 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 48 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 52 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 56 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 60 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 64 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 68 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 72 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 76 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 80 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	
Cycle 84 Day 1 CHFBL	[redacted]		[redacted]		[redacted]	

10.2 Presentation of the health-related quality of life EQ-5D-5L

Study design and measuring instrument

One of the tools measuring HRQoL in ECHO is the EQ-5D-5L, which is well known and will not be described in more detail here here.

Data collection

Patient-reported outcome assessments were to be performed at screening, on Day 1 of Cycles 3, 5, and 8, then every 4 cycles until discontinuation of study treatment, and then every 12 weeks thereafter until PD or use of alternative anti-MCL therapy. (5)

Pattern of missing data is presented below.

Table 35 Pattern of missing data and completion (5)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Screening	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 36 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 44 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 48 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 52 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 56 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 60 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 64 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 68 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 72 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 76 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 80 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 84 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 88 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

HRQoL results

Findings show no difference in quality of life between either treatment arm

(5)

Figure 17 Mean change from baseline in EQ-5D-5L INDEX (95% CI)(5)

Table 36 HRQoL summary of EQ-5D-5L index(5)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 36 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 44 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 48 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 52 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 56 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 60 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention		Comparator		Intervention vs. comparator	
Cycle 64 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 68 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 72 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 76 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 80 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Cycle 84 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

10.3 Presentation of the health-related quality of life EORTC QLQ-C30

10.3.1 Study design and measuring instrument

One of the tools measuring HRQoL in ECHO is the EORTC-QLQ-C30, which is well known and will not be described in more detail here here.

10.3.2 Data collection

Patient-reported outcome assessments were to be performed at screening, on Day 1 of Cycles 3, 5, and 8, then every 4 cycles until discontinuation of study treatment, and then every 12 weeks thereafter until PD or use of alternative anti-MCL therapy. (5)

Pattern of missing data is presented in.

Table 37 Pattern of missing data and completion(5)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Screening	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 36 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 44 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 48 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 52 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 56 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 60 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 64 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 68 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 72 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 76 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 80 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 84 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]
Cycle 88 Day 1	ABR = 299 PBR = 299	[redacted]	[redacted]	[redacted]

10.3.3 HRQoL results

Findings show no difference in quality of life between either treatment arm

Figure 18 Mean change from baseline in EORTC-QLQ-C30 (95% CI)

(5)

Table 38 EORTC-QLQ-C30 summary statistics. Baseline and change from baseline (CHFBL)(5)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 3 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 5 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 8 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 12 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 16 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 20 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 24 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 28 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 32 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 36 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 40 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Intervention		Comparator		Intervention vs. comparator	
Cycle 44 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 48 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 52 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 56 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 60 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 64 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 68 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 72 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 76 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 80 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 84 Day 1 CHFBL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.4 Health state utility values (HSUVs) used in the health economic model

10.4.1 HSUV calculation

Utility values in the model were obtained from the ECHO trial using the health-state based utility approach. HRQoL data were collected in the ECHO trial using the EQ-5D-5L questionnaires. EQ-5D-5L data was collected according to the following schedule:

- During patient screening (i.e., within 30 days before the first administration of study drug)
- At cycles 3 and 5 of the treatment phase
- At cycle 8 and then every 4 cycles during treatment phase
- During post-treatment disease follow-up, i.e. after 12 weeks from last visit until disease progression, withdrawal by subject, lost to follow-up, or study terminated by sponsor, whichever comes first after last.

The data collection schedule for EQ-5D-5L in ECHO had included the routine measurement of data up to progression only. Only a small number of utility scores were available after progression of disease (n=43), and not all patients who progressed (n=57 for ABR and n=99 for PBR) in ECHO had provided a utility score after progression(5). As a result, the estimates of utility for PD, based on the ECHO trial, are highly uncertain leading to the implausible outcome that the utility for patients who progress is the same as the utility for patients who are progression-free. Hence, the available literature was used to estimate the decrement in utility associated with PD. The base case scenario used the PFS HSUV from the ECHO trial and used a PD decrement relative to PFS estimated from the LYM-3002 trial.

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression by ICR status (pre-progression by ICR, post-progression by ICR)
- Treatment + Progression by ICR status
- Treatment + Progression by ICR status + Treatment * Progression by ICR status (Both terms and their interaction included)

The values from the EQ-5D-5L profiles in ECHO were subsequently mapped using the Danish preference weight set (57). Utilities in the model are subsequently age-adjusted. Please refer to Appendix A for further information on the analysis.

10.4.1.1 Mapping

NA.

10.4.2 Disutility calculation

Adverse event disutility was included to reflect the impact of treatment safety and tolerability health-related quality of life. Utility decrements due to AEs were applied in the model for AEs grade ≥3 that occurred in at least 1.5% of the patients in pivotal trials. Disutility was applied as a one-off decrements in the first model cycle, calculated as $DisutilityAE \times IncidenceAE$ and then summed across all adverse events.

The disutilities and durations of AEs has been sourced from previous HTA submissions (7, 43), see section 10.5.

10.4.3 HSUV results

Table 39 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs base case				
Progression free	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease with LYM-3002 decrement applied	[redacted]	[redacted]	[redacted]	[redacted]
HSUVs scenario analyses				
Progressed disease with ECHO data	[redacted]	[redacted]	[redacted]	[redacted]

10.5 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Due to the fact that only a small number of utility scores were available after progression of disease in the ECHO trial (see 10.4.1), a utility decrement from the PF state to the PD state was sourced from NICE appraisal TA370(7), see section 5.2 . Other than that, the model only uses external utility sources for disutilities.

10.5.1 Study design

NA. Only used for disutilities.

[See description in 10.1.1.]

10.5.2 Data collection

NA. Only used for disutilities.

[See description in 10.1.3.]

10.5.3 HRQoL Results

NA. Only used for disutilities.

[See description in 10.1.3.]

10.5.4 HSUV and disutility results

[See description in 0 and fill out relevant tables below.]

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

Disutilities for adverse events used in the model can be found in Table 41.

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Duration (days)	Instrument	Tariff (value set) used	Comments
Anaemia	-0.007	9.73	EQ-5D	UK	TA370(7)
Diarrhoea	-0.102	6.23			
Fatigue	-0.038	23.03			
Febrile neutropenia	-0.014	8.33			
Leukopenia	-0.042	9.45			
Lymphopenia	-0.065	16.73			
Neutropenia	-0.032	9.10			

	Results [95% CI]	Duration (days)	Instrument	Tariff (value set) used	Comments
Peripheral sensory Neuropathy	-0.087	148.68			
Pneumonia	-0.058	16.03			
Thrombocytopenia	-0.038	10.08			
Cardiac events	-0.220	14.00	NA	NA	TA891(43)
Infections	-0.220	14.00			Assumed duration

11. Resource use and associated costs

Included costs are reported in 2025 Danish kroner (DKK). The model includes the following costs, which are discussed in detail below:

- Pharmaceutical costs
- Administration costs
- Disease management costs
- Adverse events related costs
- Subsequent treatments costs
- Patient costs

11.1 Medicines - intervention and comparator

The medicine cost for intervention and comparator is outlined in Table 42, and were based on prices from medicinpriser.dk (AIP). The model also allows specification of simple percentages discounts for all included medicines, including subsequent treatments. Several options for strength/package size were included because they are used in the calculation of drug costs when no vial sharing is used.

Table 42 Unit cost of medicines used for the intervention and comparator in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Acalabrutinib	100 mg	60	40 994.30
Bendamustine	2.5 mg/ml	5x10ml	300.00
Bendamustine	2.5 mg/ml	5x40ml	1 100.00

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Rituximab	100 mg	2	2 675.80
Rituximab	500 mg	1	6 687.00

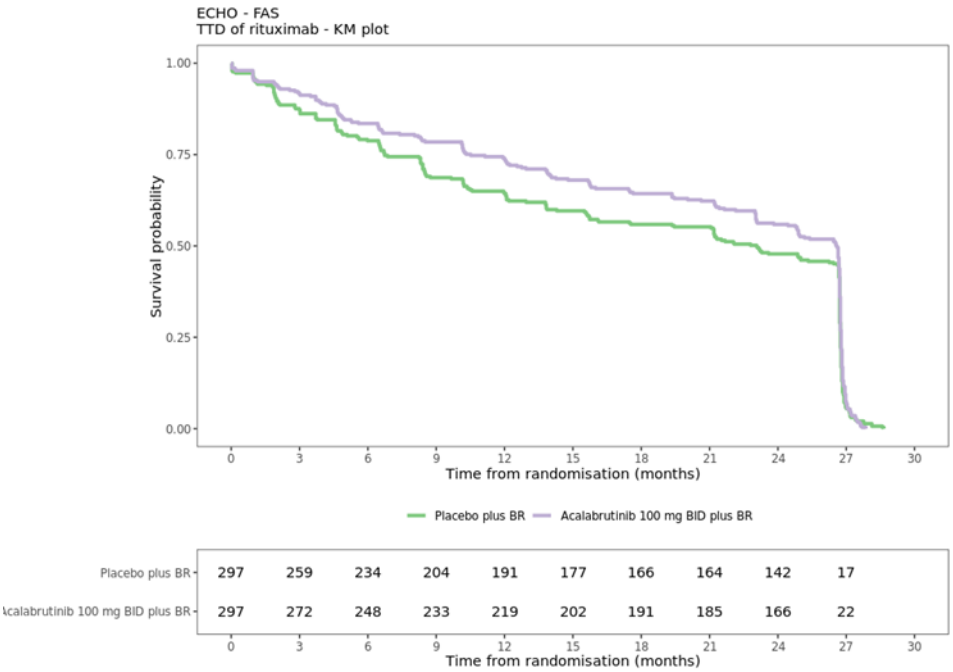
The dosing assumptions for medicines used for the intervention and comparator in the model can be found in the table below. The relative dose intensity was sourced from the ECHO trial (6)).

Table 43 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Acalabrutinib	100 mg	89 %	Day 1-28 in a 28-day cycle. Two times daily	No wastage included
Bendamustine (intervention)	90 mg/m^2	86 %	Day 1 and 2 of each 28-day cycle	No
Rituximab (intervention)	375 mg/m^2	93 %	Day 1 of each 28-day cycle	No
Bendamustine (comparator)	90 mg/m^2	87%	Day 1 and 2 of each 28-day cycle	No
Rituximab (comparator)	375 mg/m^2	91 %	Day 1 of each 28-day cycle	No

Time-to-event data from ECHO was used to model treatment discontinuation for both acalabrutinib and rituximab, see appendix. Given the high maturity of rituximab data and fixed end of dosing, the Kaplan-Meier data were directly used in the model, and no extrapolations were needed, see Figure 19. For rituximab, data from FAS were used.

Figure 19 Time to treatment discontinuation for rituximab in ECHO



11.2 Medicines– co-administration

NA

11.3 Administration costs

In the model it is assumed that regimens are administered in an outpatient setting, and that if a patient required more than one IV chemotherapy per day, only a single administration cost is applied. Oral drugs are assumed to incur no administration costs.

Administration costs for bendamustine are modeled as a one-off cost in the first cycle of the model, based on the mean time on treatment from the ECHO trial (5.4 cycles). For rituximab, the administration costs are applied as long as the patient is on treatment according to the time-on-treatment data from ECHO (both for induction and for maintenance). Administration costs are also applied to subsequent treatments (11.6).

Table 44 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Day 1 and 2 of every 28 day cycle (induction) Day 1 of every other 28 cycle (maintenance)	2 136	17MA98	17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år. Diagnosis code: (DC831) Mantle celle lymfom (MCL). Duration: <12 hours. Age: 71 years

11.4 Disease management costs

Disease management costs were applied to each cycle in the model for the proportion of patients in the PF and PD health states. These costs were independent of the treatment assigned in 1L and represent routine tests and visits associated with disease management. Disease management costs for the PF and PD health states were estimated by multiplying resource use per model cycle in the PF and PD states with relevant unit costs. Health care resource use type and frequency was estimated through an interview with a Danish clinician. Disease management resource use for the PF and PD health states are presented in Table 45 and Table 46 respectively.

Table 45 Progression-free survival disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Full blood count	4 times per year	55.72	NA	HONORARTABEL DAGTID Overenskomst om almen praksis. 2101 Blodtagning fra blodåre pr. Forsendelse
Lactate dehydrogenase	4 times per year	55.72	NA	Assumed same cost as full blood count.
Haematologist visit	4 times per year	2 136	17MA98	17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år. Diagnosis code: (DC831) Mantle celle lymfom (MCL). Duration: <12 hours. Age: 71 years

Table 46 Progressed disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Full blood count	8 times per year	55.72	NA	HONORARTABEL DAGTID Overenskomst om almen praksis. 2101 Blodtagning fra blodåre pr. Forsendelse
X-ray	2 times per year	1 731	30PR18	30PR18 Røntgenundersøgelse (alm), ukompliceret - Diagnosis code: (DC831)Mantle celle lymfom (MCL). Treatment code: UXRC00, Røntgenundersøgelse af thorax
Lactate dehydrogenase	8 times per year	55.72	NA	Assumed same cost as full blood count.
Haematologist visit	6 times per year	2 136	17MA98	17MA98, MDC17 1-dagsgruppe, pat. mindst 7 år. Diagnosis code: (DC831) Mantle celle lymfom (MCL). Duration: <12 hours. Age: 71 years

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Inpatient visit (medical)	2 times per year	51 697	17MA01	Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år. Diagnosis code:(DC831) Mantle celle lymfom (MCL). Duration: >=12 hours. Age: 71 years
Blood transfusion	10 times per year	4 221	16PR02	Transfusion af blod, øvrig. Diagnosis code: (DC831)Mantle celle lymfom (MCL). Treatment code: BOQA0 Blodtransfusion

11.5 Costs associated with management of adverse events

The model includes costs for grade 3+ AEs. It is assumed that AEs will require a hospital stay for more than 12 hours, and a stay above 12 hours was used in the Danish Health Data Authority's Interactive DRG tool when estimating costs. To adhere to DMC's guidelines there is assumed to be an overlap between leukopenia, lymphopenia and neutropenia. The model only includes the cost for neutropenia, which is the AE that is most frequent of the three.

The costs of AE management were included as a one-off cost in the first model cycle for the proportion of patients experiencing each AE. The total cost was calculated as the product of the AE incidence and its respective unit cost. The unit costs for AE management used in the model are presented in Table 47.

Table 47 Cost associated with management of adverse events

	DRG code	Unit cost/ DRG tariff
Anaemia	16MA10, øvrige sygdomme i blod og bloddannende organer. Diagnosis code: DD649, Anæmi UNS	28 342
Cardiac events	05MA01, Akut myokardieinfarkt med ST-segment elevation Diagnosis code: DI219, Akut myokardieinfarkt UNS	23 209
Diarrhoea	06MA11, Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år,u. kompl. bidiag. - Diagnosis code: DK529B, Ikke-infektiøs diarré UNS	4 977
Fatigue	21MA07 Andre skader, forgiftning og toksiske virkninger. Diagnosis code: DT983D5, Følgetilstand med træthed efter kræftbehandling	19 963
Febrile neutropenia	16MA03 Granulo- og trombocytopeni. Diagnosis code: DD709 Neutropeni UNS	37 482
Infections	04MA13 Lungebetændelse og pleuritis, pat. mindst 60 år Diagnosis code: DJ189 Pneumoni UNS	44 614

	DRG code	Unit cost/ DRG tariff
Neutropenia	16MA03 Granulo- og trombocytopeni. Diagnosis code: DD709 Neutropeni UNS	37 482
Peripheral sensory Neuropathy	01MA04 Sygdomme I hjernenerver og perifere nerver. Diagnosis code: DG589 Mononeuropati UNS	33 208
Pneumonia	04MA13 Lungebetændelse og pleuritis, pat. mindst 60 år Diagnosis code: DJ189 Pneumoni UNS	44 614
Thrombocytopenia	16MA03 Granulo- og trombocytopeni. Diagnosis code: DD696 Trombocytopeni UNS	37 482

11.6 Subsequent treatment costs

Subsequent treatment costs were estimated according to the distribution of progressed patients across different subsequent treatment options and considering the duration of each subsequent therapy. These costs are modelled as a one-time cost applied to patients who experience a non-fatal PFS event. The impact of subsequent treatments on survival was assumed to be incorporated within the extrapolated OS curves.

The unit costs for subsequent treatments can be found in Table 48 (excluding costs for rituximab in R-CHOP, which have already been shown in Table 43). For medicines where vial sharing is not applicable in the model, only the lowest cost/mg pack is included (venetoclax, lenalidomide, ibrutinib, prednisolone). For other medicines several pack sizes are included.

Table 48 Medicine costs for subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Cyclophosphamide	1000 mg	1	335.00
Cyclophosphamide	500 mg	1	192.00
Doxorubicin	2 mg/ml	100 ml	350.00
Doxorubicin	2 mg/ml	25 ml	120.00
Vincristine	1 mg/ml	2 ml	660.28
Vincristine	1 mg/ml	1 ml	404.64
Prednisolone	25 mg	100	79.00
Ibrutinib	560 mg	28	50 902.94
Lenalidomide	25 mg	21	11 450
Venetoclax	100 mg	14	4 533,5

In alignment with ECHO trial data, three lines of subsequent treatment were incorporated into the model. For each line, the total cost of subsequent treatments was calculated based on the proportion of patients receiving subsequent therapies, see Table 49 which shows the proportion of patients in ECHO who received any treatment in each subsequent line of therapy after progressing. Note that this proportion was determined by the number of patients in the ECHO trial who received subsequent treatment in each line, out of the total number who had progressed. This is different from calculating the proportion who have received a subsequent treatment during follow-up out of all patients included in the trial. According to a Danish clinical expert, the proportion seen in the PBR arm is in line with what is expected in Danish clinical practice. For this reason, the proportion who receive subsequent lines of treatment from ECHO was kept in the model base case.

Table 49 Proportion of patients in ECHO who received any treatment in each subsequent line of therapy after progression

Treatment line	ECHO trial	
	ABR (n = 299)	PBR (n = 299)
2L	52.6%	88.9%
3L	17.5%	32.3%
4L	5.3%	13.1%

Additionally, the model accounted for the distribution of specific subsequent treatments and the duration of these treatments. First, utilisation of subsequent therapy for ABR and PBR was sourced from the ECHO trial data. The subsequent treatments from the ECHO trial data was shown to a Danish clinical expert who then provided his own estimates of what the subsequent treatment use could be in Danish clinical practice (Table 50). It was assumed that patients will receive 3L and 4L treatments approximately one and two years after 2L treatment, respectively. Thus, in the model base case, 1 year of discounting was applied for 3L subsequent treatment one-off costs, and 2 years of discounting was applied for 4L subsequent treatment one-off costs.

Table 50 Subsequent treatment regimens by first-line treatment option used in the model (estimates provided by clinical expert)

	2L		3L		4L	
	ABR	PBR	ABR	PBR	ABR	PBR
Ibrutinib/covalent BTKi	0%	80%	20%	21%	0%	0%
Lenalidomide + Rituximab	20%	10%	20%	10.5%	6%	6%
Rituximab	20%	5%	5%	5%	6%	6%
Lenalidomide	0%	0%	10%	10.5%	6%	6%
Venetoclax	60%	5%	45%	53%	82%	82%
Total	100%	100%	100%	100%	100%	100%

Efficacy from ECHO is used regardless of choice of subsequent treatments. Dosing and frequency of subsequent therapies are listed in Table 51.

Table 51 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Ibrutinib	560 mg	94 %	Once per day	No wastage included
Rituximab	375 mg/m2	100 %	R-CHOP: Day 0 or 1 of each 21-day cycle Monotherapy or in combination with lenalidomide: Once a week for one 28-day cycle	No
Doxorubicin	50 mg/m2	100 %	Day 1 of each 21-day cycle	No
Vincristine	1.4 mg/m2	100 %	Day 1 of each 21-day cycle	No
Cyclophosphamide	750 mg/m2	100 %	Day 1 of each 21-day cycle	No
Prednisolone	50 mg/m2	100 %	Day 1-5 of each 21-day cycle	Yes
Lenalidomide	20 mg/m2	100 %	Day 1-21 of 28-day cycle	Yes
Venetoclax	400 mg/m2	100 %	Once per day	Yes

Administration costs were applied to the patients who receive subsequent treatments. The administration costs used in 1L were also applied to 2L and beyond.

The mean time on subsequent treatments can be found in Table 52. For ibrutinib, the mean exposure for patients who crossed over to acalabrutinib in ECHO was used. R-CHOP is not included in the base case (see Table 50).

Table 52 Time on subsequent treatment

Treatment	Months	Source
Ibrutinib	22,00	ECHO Trial cross-over, RMST
R-CHOP	5,52	Maximum treatment duration from LYM-3002 (7)
R-Lenalidomide	11,10	Wang et al. (2012) (46)
Rituximab	1,00	Foran et al. (2000) (45)
Lenalidomide	11,10	Wang et al. (2012) (46)
Venetoclax	3,20	Eyre et al. (2019) (58)

11.7 Patient costs

Patient time costs and transport costs were included in the model in line with DMC's guidelines. Cost per patient hour was set to 188 DKK, see Table 53. In line with the guidelines, it is assumed that the patient travels 40 kilometers round trip for each hospital visit. The cost per kilometer is set to 140 DKK per round trip. In the model it is assumed that the patient spends 60 minutes on transportation per hospital visit.

Table 53 Unit costs used in the model for patient cost

Activity	Cost [DKK]
Cost per patient hour	DKK 188.00
Cost per transport	DKK 140.00

No patient costs have been included for the management of adverse events, as the impact of these is deemed neglectable due to the low frequencies adverse events observed. This is also evident in the impact of adverse events on the incremental cost in the health economic analysis.

Patient disease management costs can be found in Table 54. For the patient costs related to disease management it was assumed that the costs of full blood count, x-ray, lactate dehydrogenase were part of the other visits to the hospital, primarily the outpatient visit, incurring no additional time costs. In the model each of these disease management items requires a roundtrip to the hospital, incurring time and transport cost for the patient.

Table 54 Patient disease management costs used in the model

Activity	Time spent [minutes, hours, days]
Haematologist visit	1 hour
Inpatient visit (medical)	72 hours
Blood transfusion	2 hours
Full blood count, x-ray, lactate dehydrogenase	Assumed covered as part of other visits

Patient time costs for administration of drugs can be found in Table 55. Bendamustine is administered over 30-60 minutes. The model assumes 45 minutes. For rituximab it was the time cost were calculated based on a dosing of rituximab which starts at 100 mg per hour, increasing by 100 mg per hour (resulting in 2.5 hours up to the target dose being reached. In the model each administration requires a roundtrip to the hospital, incurring time and transport cost for the patient.

Table 55 Patient administration costs used in the model

Activity	Time spent [minutes, hours, days]
Administration of bendamustine (BR) day 1 of each cycle	45 minutes
Administration of bendamustine (BR) day 2 of each cycle	45 minutes
Administration of rituximab (BR) day 1 of each cycle	150 minutes

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

NA

12. Results

12.1 Base case overview

Table 56 Base case overview

Feature	Description
Comparator	Bendamustine+rituximab
Type of model	Partitioned survival model
Time horizon	30 years (life time)
Treatment line	1st line treatment
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in ECHO and utility decrement in PD from TA370. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Administration costs Disease management costs Costs of adverse events Subsequent treatment costs Patient costs
Dosage of medicine	Fixed dose (acalabrutinib) and body surface area (rituximab and bendamustine)
Average time on treatment	Intervention: 5.4 years

Feature	Description
	Comparator: 1.5 years
Parametric function for PFS	Intervention: Gamma Comparator: Gamma
Parametric function for OS	Intervention: Gamma Comparator: Gamma
Inclusion of waste	Yes, for non-oral treatments
Average time in model health state Progression-free	ABR: 7.6 years (discounted) PBR: 5.6 years (discounted)
Average time in model health state Progressed disease	ABR: 1.7 years (discounted) PBR: 2.9 years (discounted)
Average time in model health state Alive	ABR: 9.3 years (discounted) PBR: 8.5 years (discounted)

12.1.1 Base case results

Table 57 Base case results, discounted estimates

	ABR	PBR	Difference
Medicine costs	2 154 128	125 754	2 028 374
Administration	23 595	23 243	352
Disease management costs	351 852	524 665	-172 813
Costs associated with management of adverse events	20 926	19 886	1 040
Subsequent treatment costs	82 057	634 378	-552 321
Patient costs	92 652	128 580	-35 928
Palliative care costs	0	0	0
Total costs	**2 725 211**	**1 456 506**	**1 268 705**
Life years gained (PFS)	7,55	5,59	1,96
Life years gained (PD)	1,74	2,91	-1,17
Total life years	**9,30**	**8,51**	**0,79**
QALYs (PFS)	6,52	4,88	1,65
QALYs (PD)	1,35	2,25	-0,90
QALYs (adverse reactions)	-0,0009	-0,0009	-0,0001
Total QALYs	**7,87**	**7,12**	**0,74**
Incremental costs per life year gained		**1 610 485**	

	ABR	PBR	Difference
Incremental cost per QALY gained (ICER)	**1 706 836**		

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Deterministic sensitivity analyses (DSA) are shown in Figure 20 and Table 58, which show a tornado diagram and a table with selected sensitivity analyses respectively. Uncertainty was tested on parameters such as patient characteristics, cost inputs, health care resource use, safety data, subsequent treatment lines distributions, discount rates and utilities. DSAs were conducted by varying parameters by their upper and lower confidence interval bounds when available, or by ±10% when confidence intervals are not available, except for discount rates which were changed to 0 % or 6 %. The default estimation of standard error of 10% is chosen as a conservative approach that allows for a broad, yet plausible range of parameter values, when applied.

The top three parameters which had the greatest impact on the ICER were the discount rates, treatment duration of ibrutinib as a subsequent treatment, and HSUV in progressed health state.

Figure 20 Tornado diagram of ICER

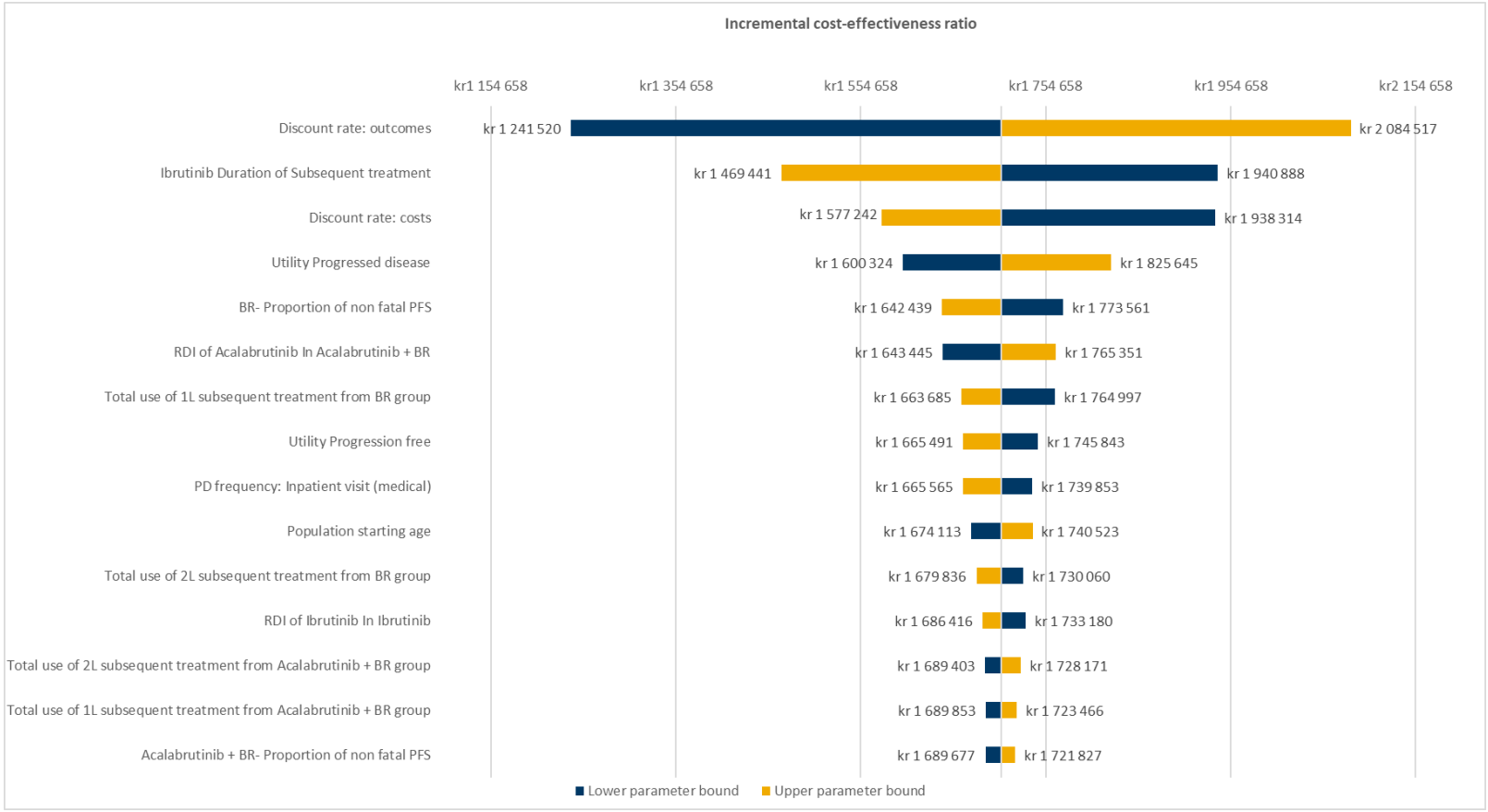


Table 58 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	1 268 705	0,743	1 706 836
Ibrutinib Duration of Subsequent treatment	15.0	CI from ECHO	1 442 677	0,743	1 940 888
	29.1		1 092 247	0,743	1 469 441
Utility Progressed disease	0.78	CI (calculated)	1 268 705	0,793	1 600 324
	0.87		1 268 705	0,695	1 825 645
Utility Progression free	0.88	CI from ECHO	1 268 705	0,727	1 745 843
	0.90		1 268 705	0,762	1 665 491
Discount rate: costs	0.000	Assumption	1 440 764	0,743	1 938 314
	0.060		1 172 377	0,743	1 577 242
Discount rate: outcomes	0.000	Assumption	1 268 705	1,022	1 241 520
	0.060		1 268 705	0,609	2 084 517
RDI of Acalabrutinib In Acalabrutinib + BR	0.870	+/- 10 % (rounded)	1 221 586	0,743	1 643 445
	0.910		1 312 199	0,743	1 765 351
All AE disutilities	+50%	Assumption	1 268 705	0,743	1 706 915
	-50%		1 268 705	0,743	1 706 758

Scenario analyses, including changing source of utilities, excluding AE disutility and changing parametric models for time to treatment discontinuation (TTD), PFS and OS are shown in Table 59. When changing parametric models, the same model was used for both arms. In terms of OS, the base case model with Gamma is in line with Weibull and Generalised Gamma, while the Exponential reduces the ICER and Log-normal and Gompertz increases the ICER substantially. For TTD Weibull results in an ICER slightly above the base case, the Exponential reduces the ICER substantially, and the other models increase the ICER. The results are less sensitive to choice of PFS model. Changing utility sources increases the ICER and excluding patient costs increases the ICER slightly. Adverse event disutilities have almost no impact on results.

Table 59 Results of scenario analyses

Scenario	ICER
Base case	1 706 836
Weibull OS ABR and PBR	1 743 500
Log-logistic OS ABR and PBR	1 831 339
Gompertz OS ABR and PBR	1 928 986
Generalised Gamma OS ABR and PBR	1 792 544
Log-normal OS ABR and PBR	1 973 814

Exponential OS ABR and PBR	1 482 395
Weibull PFS ABR and PBR	1 723 181
Log-logistic PFS ABR and PBR	1 835 274
Gompertz PFS ABR and PBR	1 823 804
Generalised Gamma PFS ABR and PBR	1 742 687
Log-normal PFS ABR and PBR	1 864 675
Exponential PFS ABR and PBR	1 707 479
TTD Weibull ABR	1 797 740
TTD Log-logistic ABR	2 094 241
TTD Gompertz ABR	2 148 374
TTD Generalised Gamma ABR	2 035 630
TTD Log-normal ABR	2 155 652
TTD Exponential ABR	1 468 253
TTD Generalised F ABR	2 035 980
Utility: Utility from ECHO for both PFS and PD	1 916 607
Utility: UK utility values with utility decrement from TA370	1 820 070
Costs: Patient costs excluded	1 755 172
Disutility: Exclude AE disutility	1 706 680

12.2.2 Probabilistic sensitivity analyses

The mean results of the probabilistic sensitivity analysis are presented in Table 60 for ABR and PBR using 1000 Monte Carlo simulations. Over the lifetime time horizon, the total discounted costs and QALYs associated with ABR were DKK 2 683 357 and 7.53, respectively. For PBR, total costs were DKK 1 414 148 and total QALYs were 6.83. Consistent with the deterministic base case, ABR had higher total costs and QALYs than PBR. Overall, the probabilistic results gave a slightly higher ICER than the deterministic results.

Figure 21, Figure 22 and Figure 23 display the PSA scatter plot, cost-effectiveness acceptability curves and convergence plot for the ICER, respectively. The scatter plot shows the majority of iterations being in the north-eastern quadrant of the cost-effectiveness plane, meaning higher costs and more QALYs than the comparator. The iterations are mostly located in the area around the deterministic estimate. Some extreme values exist, both positive and negative values, particularly for incremental QALYs. The iterations The ICER converged in under 100 iterations.

Table 60 Results of the probabilistic sensitivity analysis

Regimen	Mean Total Costs	Mean Total QALYs	ΔCosts vs PBR	ΔQALYs vs PBR	Incremental cost per QALY (vs. PBR)
ABR	2 683 357	7.53	1 269 209	0.70	1 805 503 per QALY
PBR	1 414 148	6.83	-	-	-

Figure 21 Scatter plot for the probabilistic sensitivity analysis

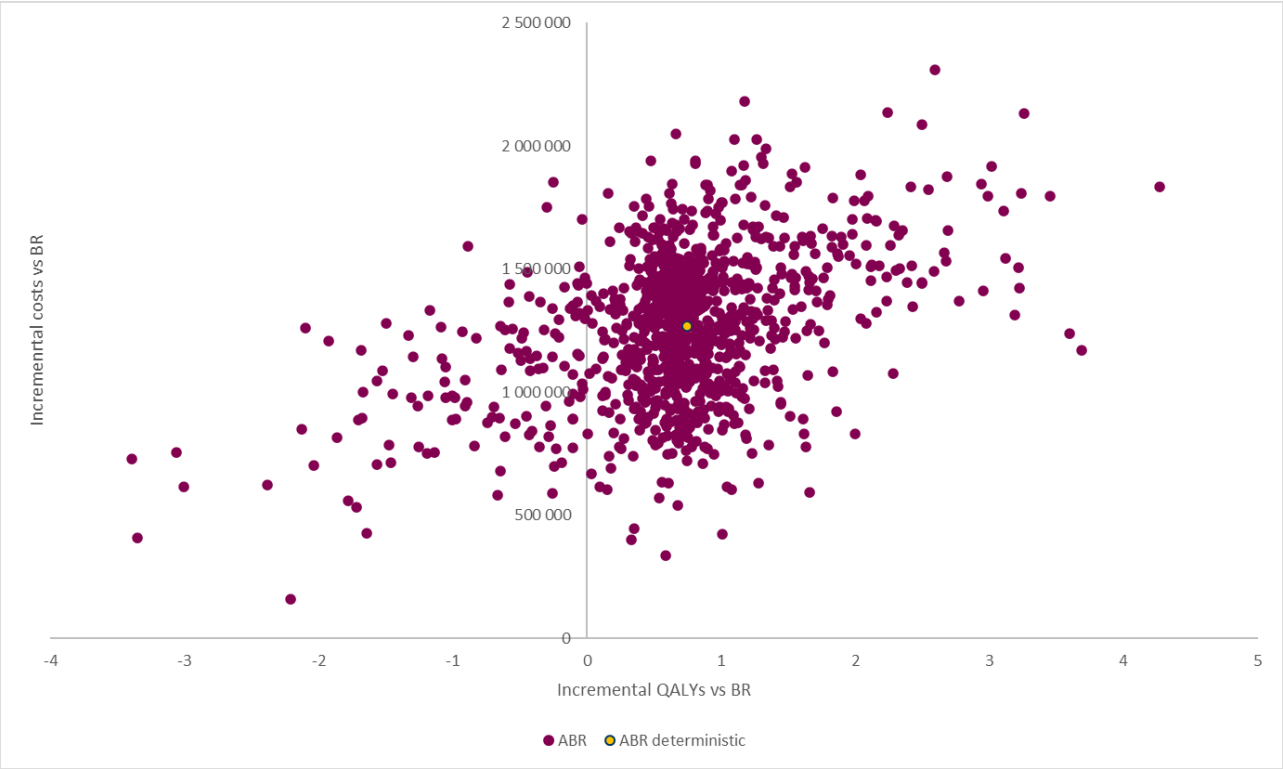


Figure 22 Cost-effectiveness acceptability curve

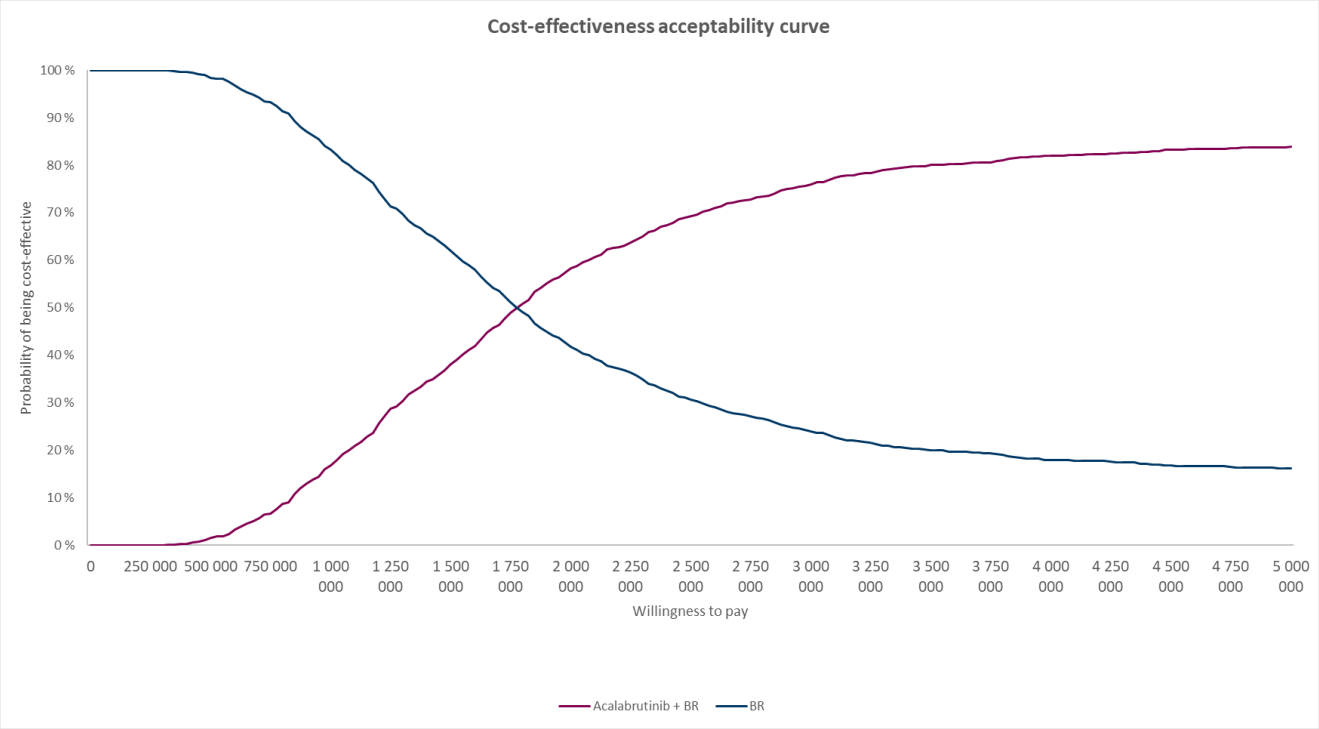
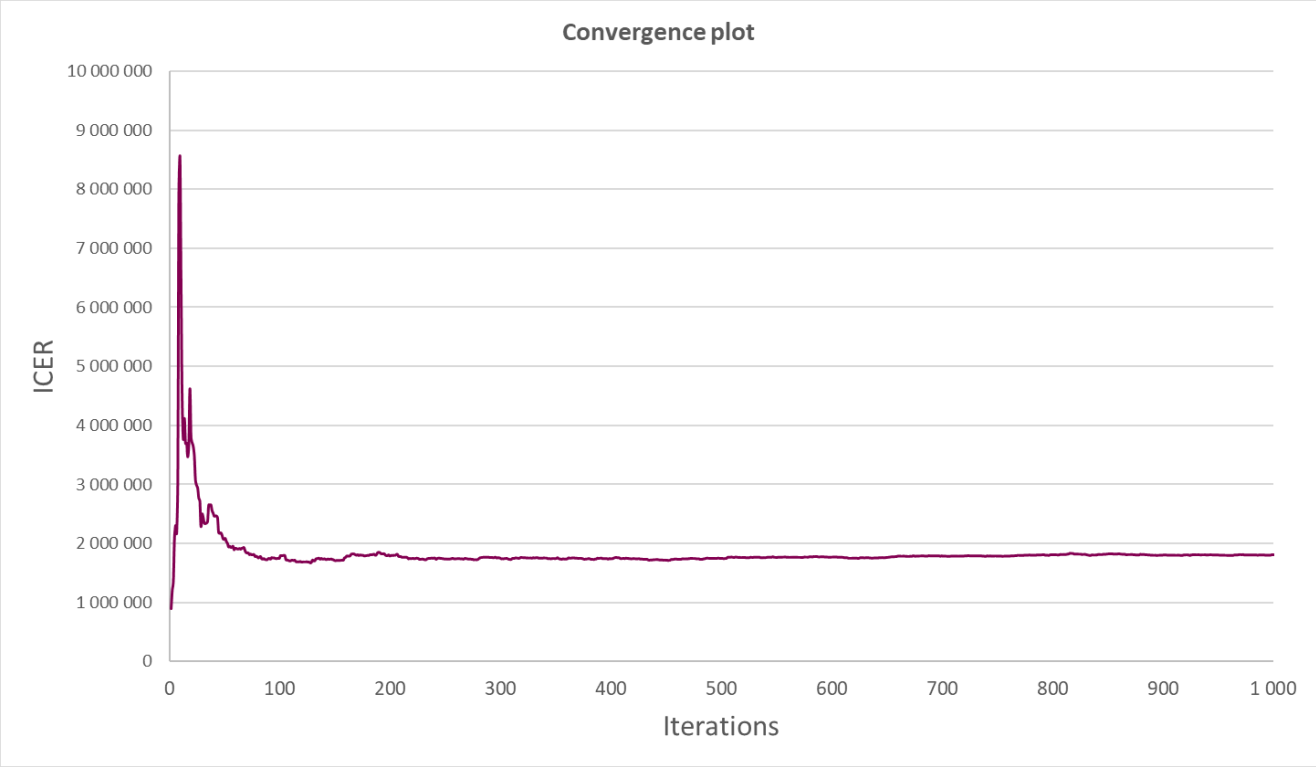


Figure 23 Convergence plot for the ICER



13. Budget impact analysis

Assumptions on patient numbers are explained in 3.2. The same patient numbers are used in the budget impact analysis. 80% of newly diagnosed patients start systemic therapy at diagnosis, with about 60% of this group comprising of those ineligible for ASCT. An incidence of 88 patients yearly, results in 42 new patients in each (see Table 61 and Table 12 in chapter 3.2). In the budget impact analysis, it is assumed that all of these eligible patients will receive ABR if ABR is implemented (100 % market share). If ABR is not implemented, it is assumed that 0 % of these 42 patients will receive ABR. Costs for the budget impact analysis are taken from the cost-effectiveness model with the base case assumptions as described previously in this application, without discounting.

Table 61 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
ABR	42	42	42	42	42
BR	0	0	0	0	0
			Non-recommendation		
ABR	0	0	0	0	0
BR	42	42	42	42	42

Table 62 Expected budget impact of recommending the medicine for the indication (in millions)

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	DKK 24.0	DKK 39.5	DKK 51.7	DKK 61.9	DKK 70.8
The medicine under consideration is NOT recommended	DKK 11.6	DKK 17.7	DKK 22.4	DKK 26.4	DKK 30.2
Budget impact of the recommendation	DKK 12.4	DKK 21.8	DKK 29.3	DKK 35.5	DKK 40.6

14. List of experts

[redacted]

15. References

1. Bentzen H, Poulsen CB, Haaber J, Tholstrup DM, Gjerdrum LRM, Hutchings M, et al. DLG, Mantle Celle Lymfom,

behandling, diagnostik. 2022.
2. Lindberg A, Eskelund CW, Albertsson-Lindblad A, Kolstad A, Laurell A, Raty R, et al. Pre-treatment health-related quality of life parameters have prognostic impact in patients >65 years with newly diagnosed mantle cell lymphoma: The Nordic Lymphoma Group MCL4 (LENA-BERIT) experience. Hematol Oncol. 2022;40(1):22-30.
3. Jerkeman M, Ekberg S, Glimelius I, Albertsson-Lindblad A, Entrop JP, Ellin F, et al. Nationwide Assessment of Patient Trajectories in Mantle Cell Lymphoma: The Swedish MCLcomplete Project. Hemasphere. 2023;7(8):e928.
4. Lewis DJ, Jerkeman M, Sorrell L, Wright D, Glimelius I, Pasanen A, et al. Ibrutinib-Rituximab Is Superior to Rituximab-Chemotherapy in Previously Untreated Older Mantle Cell Lymphoma Patients: Results from the International Randomised Controlled Trial, Enrich. Blood. 2024;144:235.
5. AstraZeneca Data on File. Interim CSR - A 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). 2024.
6. AstraZeneca Data on File. Interim CSR - A 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). 2024.
7. NICE TA370. Bortezomib for previously untreated mantle cell lymphoma: National Institute for Health and Care Excellence; 2015 [Available from: https://www.nice.org.uk/guidance/ta370.
8. NORD. Mantle Cell Lymphoma. Available from: https://rarediseases.org/rare-diseases/mantle-cell-lymphoma/. (Accessed 13 February 2025). 2025.
9. Navarro A, Beà S, Jares P, Campo E. Molecular pathogenesis of mantle cell lymphoma. Hematology/oncology clinics of North America. 2020;34(5):795.
10. Sethi S, Epstein-Peterson Z, Kumar A, Ho C. Current Knowledge in Genetics, Molecular Diagnostic Tools, and Treatments for Mantle Cell Lymphomas. Front Oncol. 2021;11:739441.
11. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.
12. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022;140(11):1229-53.
13. Aukema SM, Hoster E, Rosenwald A, Canoni D, Delfau-Larue MH, Rymkiewicz G, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. Blood. 2018;131(4):417-20.
14. Hoster E, Rosenwald A, Berger F, Bernd HW, Hartmann S, Loddenkemper C, et al. Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network. J Clin Oncol. 2016;34(12):1386-94.
15. Leukemia & Lymphoma Society L. NHL Subtypes. Available from: https://www.lls.org/sites/default/files/2024-05/PS58_NHL_2024.pdf Accessed February 18th 2025
16. Kallam A, Vose J. Current Treatments in Mantle Cell Lymphoma. Oncology (08909091). 2023;37(8).
17. Jain P, Wang ML. Mantle cell lymphoma in 2022—A comprehensive update on molecular pathogenesis, risk stratification, clinical approach, and current and novel treatments. American journal of hematology. 2022;97(5):638-56.
18. 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. J Clin Oncol. 2014;32(27):3059-68.
19. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-65.
20. Afdeling_for_Cancer_og_Cancerscreening L, Dansk_CLL_Database National årsrapport 2023 - Malignt Lymfom og CLL. lymphoma.dk; 2023.
21. Andersen NS, Jensen MK, de Nully Brown P, Geisler CH. A Danish population-based analysis of 105 mantle cell lymphoma patients: incidences, clinical features, response, survival and prognostic factors. Eur J Cancer. 2002;38(3):401-8.
22. Befolkningstal [Internet]. Accessed 25/02/2025 Available from: Accessible through: https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal.
23. Jerkeman M, Wader KF, Glimelius I, Pasanen A, Kim WS, Hansen LK, et al. Acalabrutinib and Rituximab in Elderly Patients with Newly Diagnosed Mantle Cell Lymphoma Including a Matched Population-Based External Comparator-the Nordic Lymphoma Group NLG-MCL8 (ALTAMIRA) Phase II Trial. Blood. 2024;144:747.
24. EMA. Imbruvica - withdrawal of application for variation to marketing authorisation ema.europa.eu: European Medicines Agency 2023 [Available from: https://www.ema.europa.eu/en/medicines/human/variation/imbruvica.
25. Trab T, Chanchiri I, Al-Mashhadi A, Dall EB, Rasch S, Johansen M, et al. Real-World Outcomes for Patients Treated with Ibrutinib for Relapsed/Refractory Mantle Cell Lymphoma in Denmark. Blood. 2024;144:6325.
26. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, et al. Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2016;374(4):323-32.
27. AstraZeneca F. Prescribing informaition, Calquence accessdata.fda.gov; 2025.
28. Herman SEM, Montraveta A, Niemann CU, Mora-Jensen H, Gulrajani M, Krantz F, et al. The Bruton Tyrosine Kinase (BTK) Inhibitor Acalabrutinib Demonstrates Potent On-Target Effects and Efficacy in Two Mouse Models of Chronic Lymphocytic Leukemia. Clin Cancer Res. 2017;23(11):2831-41.
29. Barf T, Covey T, Izumi R, van de Kar B, Gulrajani M, van Lith B, et al. Acalabrutinib (ACP-196): A Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. J Pharmacol Exp Ther. 2017;363(2):240-52.
30. Covey T, Gulranjani M, Cheung J, Bibikova E, Clevenger T, Krantz F, et al. Pharmacodynamic Evaluation of Acalabrutinib in Relapsed/Refractory and Treatment-Naive Patients with Chronic Lymphocytic Leukemia (CLL) in the Phase 1/2 ACE-CL-001 Study. Blood. 2017;130(Supplement 1):1741-.
31. Guo Y, Liu Y, Hu N, Yu D, Zhou C, Shi G, et al. Discovery of Zanubrutinib (BGB-3111), a Novel, Potent, and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase. J Med Chem. 2019;62(17):7923-40.
32. Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. N Engl J Med. 2022;386(26):2482-94.
33. EMA. Evaluation of anticancer medicinal products in man - Scientific guideline.; 2020.
34. TA502 Ibrutinib for treating relapsed or refractory mantle cell lymphoma: National Institute for Health and Care Excellence; 2018 [Available from: https://www.nice.org.uk/guidance/ta502.
35. Wang M, Salek D, Belada D, Song Y, Jurczak W, Kahl BS, et al. Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma. Journal of Clinical Oncology. 2025:10.1200/JCO-25-00690.
36. Bendamustine; powder for injection 100 mg vial, 1: The Pharmaceutical Benefits Agency; 2015 [Available from:

https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-07/bendamustine-psd-july-2015.
37. van Keep M, Gairy K, Seshagiri D, Thilakarathne P, Lee D. Cost-effectiveness analysis of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (VR-CAP) in patients with previously untreated mantle cell lymphoma. BMC cancer. 2016;16:1-11.
38. Meeting PSDPMP. Public Summary Document (PSD) March 2015 PBAC Meeting 2015 [Available from: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-03/bendamustine-hydrochloride-ribomustin-psd-03-2015.
39. Ibrutinib (CLL/SLL): The Pharmaceutical Benefits Scheme; 2016 [Available from: https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2016-11/ibrutinib-cll-sll-psd-november-2016.
40. TA677 Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma: National Institute for Health and Care Excellence; 2021 [Available from: https://www.nice.org.uk/guidance/ta677.
41. Zanubrutinib: Canada's Drug Agency; 2022 [Available from: https://www.cda-amc.ca/zanubrutinib-0.
42. Meeting PSDPNP. Public Summary Document (PSD) November 2016 PBAC Meeting 2016 [Available from: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2016-11/ibrutinib-mcl-psd-november-2016.
43. TA891 Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia: National Institute for Health and Care Excellence; 2023 [Available from: https://www.nice.org.uk/guidance/ta891.
44. Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Menon G, Iyengar S, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. British Journal of Haematology. 2024;204(1).
45. Foran J, Cunningham D, Coiffier B, Solal-Celigny P, Reyes F, Ghielmini M, et al. Treatment of mantle-cell lymphoma with Rituximab (chimeric monoclonal anti-CD20 antibody): analysis of factors associated with response. Annals of oncology. 2000;11:S117-S21.
46. Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, Neelapu SS, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. The lancet oncology. 2012;13(7):716-23.
47.
48. Clinicaltrials.gov. A Study of BR Alone Versus in Combination With Acalabrutinib in Subjects With Previously Untreated MCL Last updated in 2025 [Available from: https://clinicaltrials.gov/study/NCT02972840.
49. Dreyling M, Mayer J, Belada D, Song Y, Jurczak W, Paludo J, et al. 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 1626 presented at the 66th ASH Annual Meeting, December 7-10, 2024, San Diego, California, USA. Available from: https://ash.confex.com/ash/2024/webprogram/Paper200290.html. (Accessed 03 December 2024). 2024.
50. Salmanton-García J, Marchesi F, Farina F, Weinbergerová B, Itri F, Dávila-Valls J, et al. Decoding the historical tale: COVID-19 impact on haematological malignancy patients—EPICOVIDEHA insights from 2020 to 2022. EClinicalMedicine. 2024;71.
51. Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. New England Journal of Medicine. 2022;386(26):2482-94.
52. Martin Dreyling PLZ, Miguel A. Pavlovsky, Kamal Bouabdallah, Mariana Bastos-Oreiro, Ellie John, Victoria Otero, Andre Henri Goy. EFFICACY OF RITUXIMAB-

BENDAMUSTINE WITH OR WITHOUT ACALABRUTINIB IN PATIENTS WITH UNTREATED, HIGH-RISK MANTLE CELL LYMPHOMA: AN ANALYSIS OF THE PHASE 3 ECHO TRIAL. Abstract Presented at EHA 2025. 2025.
53. Dreyling M, Zinzani P, Pavlovsky M, Bouabdallah K, Bastos-Oreiro M, John E, et al. EFFICACY OF RITUXIMAB-BENDAMUSTINE WITH OR WITHOUT ACALABRUTINIB IN PATIENTS WITH UNTREATED, HIGH-RISK MANTLE CELL LYMPHOMA: AN ANALYSIS OF THE PHASE 3 ECHO TRIAL. Hematological Oncology. 2025;43:e46_70093.
54. Anvendelse af forløbsdata i sundhedsøkonomiske analyser.: Medicinrådet; 2020 [Available from: https://medicinraadet.dk/media/ickpupwo/anvendelse_af_forl%C3%B8bsdata_i_sundheds%C3%B8konomiske_analyser-vers-_1-1_adlegacy.pdf.
55. Latimer NR. Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Medical Decision Making. 2013;33(6):743-54.
56. Palmer S, Borget I, Friede T, Husereau D, Karnon J, Kearns B, et al. A guide to selecting flexible survival models to inform economic evaluations of cancer immunotherapies. Value in Health. 2022.
57. Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L value set: a hybrid model using cTTO and DCE data. Applied Health Economics and Health Policy. 2021;19:579-91.
58. Eyre TA, Walter HS, Iyengar S, Follows G, Cross M, Fox CP, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica. 2019;104(2):e68.
59. AstraZeneca. ECHO CSR-tables-and-figures. 2024.
60. Mallinckrod CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. Drug Information Journal. 2008;42(4):303-19.

Appendix A. Main characteristics of studies included

Table 63 Table 63 Main characteristic of studies included

Trial name: ECHO	**NCT number: NCT02972840**
Objective	The ECHO trial evaluated the combination of acalabrutinib plus bendamustine and rituximab (ABR) compared with placebo plus bendamustine and rituximab (PBR) in patients aged 65 years or older with previously untreated MCL. The primary objective was to evaluate the efficacy of ABR compared with PBR based on an IRC assessment of PFS in accordance with the Lugano classification for non-Hodgkin lymphoma (NHL) in these patients (5).
Publications – title, author, journal, year	Wang, Michael, et al. "Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma." *Journal of Clinical Oncology* (2025): 10-1200 (35). Dreyling, Martin, et al. "Efficacy of Rituximab-Bendamusine with or without Acalabrutinib in patients with untreated, high-risk mantle cell lymphoma: an analysis of the phase 3 ECHO trial." Abstract presented at EHA (2025) (52).
Study type and design	The ECHO study is an ongoing global, phase III, randomized, double-blind, placebo-controlled, multicenter study assessing ABR compared with PBR in patients aged 65 years or older with previously untreated MCL (5). **Randomization** Patients were randomized in a 1:1 ratio into two treatment arms using an Interactive Voice/Web Response System to receive double-blind treatment with either: 1. Arm A: Acalabrutinib + 6 cycles of BR 2. Arm B: Placebo + 6 cycles of BR Randomisation was stratified according to: Geographical location (North America vs Western Europe vs Other) Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk [0 to 3] vs intermediate risk [4 to 5] vs high risk [6 to 11]) (5). **Crossover** Patients randomized to PBR who had disease progression as assessed by the investigator and confirmed by an unblinded physician who was

Trial name: ECHO	NCT number: NCT02972840
	not on the study team but was part of the sponsor's team and was not participating in the study were allowed to cross over and could receive acalabrutinib monotherapy at a dose of 100 mg twice daily (BID) until PD or unacceptable toxicity (5).
Sample size (n)	In total, 598 patients were randomised, 299 per treatment arm. 297 patients in each of the treatment arms received treatment (5).
Main inclusion criteria	Men and women aged ≥ 65 years 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 performance status of ≤ 2 (5)
Main exclusion criteria	Patients for whom the goal of therapy was tumour debulking before SCT History of prior malignancy (with some exclusions) History of CNS lymphoma or leptomeningeal disease Uncontrolled autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura Significant cardiovascular disease Malabsorption syndrome Ongoing immunosuppressive therapy Required or received anticoagulation therapy with warfarin or other equivalent vitamin K antagonists within 7 days of first dose of study drug (5).
Intervention	**297 patients received at least one dose of study drug** **ABR** Acalabrutinib 100 mg BID PO until PD or unacceptable toxicity Bendamustine 90 mg/m2 IV on days 1 and 2 of each cycle for up to 6 cycles Rituximab 375 mg/m2 IV on day 1 of each cycle for 6 cycles

Trial name: ECHO		NCT number: NCT02972840
	Rituximab maintenance Rituximab 375 mg/m2 IV on day 1 of every other cycle, starting on the next even-numbered cycle after completion of BR for a maximum of 12 additional doses until no later than cycle 30 (5).	
Comparator(s)	**297 patients received at least one dose of study drug** **PBR** Placebo 100 mg BID PO until PD or unacceptable toxicity Bendamustine 90 mg/m2 IV on days 1 and 2 of each cycle for up to 6 cycles Rituximab 375 mg/m2 IV on day 1 of each cycle for 6 cycles **Rituximab maintenance** Rituximab 375 mg/m2 IV on day 1 of every other cycle, starting on the next even-numbered cycle after completion of BR for a maximum of 12 additional doses until no later than cycle 30 (5).	
Follow-up time	As of the DCO (15 February 2024), the median follow-up was 44.9 months: 46.1 months in the ABR arm (rage 0.0-80.1) and 44.4 months in the PBR arm (rage 0.0-80.3) (5).	
Is the study used in the health economic model?	Yes	

Trial name: ECHO	NCT number: NCT02972840

Primary, secondary and exploratory endpoints

Primary endpoint

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

Key secondary endpoints

To evaluate ABR compared with PBR in terms of:

IRC-assessed ORR (CR + PR) per the Lugano Classification for NHL

Overall survival

Other secondary endpoints

To evaluate ABR compared with PBR in terms of:

Investigator-assessed PFS per the Lugano Classification for NHL

Investigator-assessed ORR (CR + PR) per the Lugano Classification for NHL

IRC-assessed and investigator-assessed DOR per the Lugano Classification for NHL

IRC-assessed and investigator-assessed TTR per the Lugano Classification for NHL

PK characteristics of acalabrutinib and its active metabolite (ACP-5862), alone and when given in combination with bendamustine

Safety endpoints

Incidence of AEs, SAEs, AEs leading to study drug dose modification or treatment discontinuation

Exploratory endpoints

To evaluate ABR compared with PBR in terms of:

MRD.

MRD was assessed in bone marrow at CR and in peripheral blood at CR, at every 24-week intervals, and at PD.

Potential predictive biomarkers and mechanisms of resistance for the disease

Patient reported outcome (PRO)

PRO by FACT-Lym subscale scores, TOI, FACT-G, and FACT-Lymphoma total score and the scores change from baselines

PRO by EQ-5D-5L index score and EQ-VAS score and the scores change from baselines

PRO by EORTC QLQ-C30 scores and the scores change from baselines

Medical resource utilization (MRU)

[State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results must be provided in Appendix D.]

Endpoints included in this application:

PFS IRC and INV

Overall survival

Overall response rate IRC and INV

Duration of response IRC and INV

Time to response IRC and INV

MRD

Patient reported outcome (PRO)

PRO by FACT-Lym subscale scores, TOI, FACT-G, and FACT-Lymphoma total score and the scores change from baselines

PRO by EQ-5D-5L index score and EQ-VAS score and the scores change from baselines

PRO by EORTC QLQ-C30 scores and the scores change from baselines

Incidence of AEs, SAEs, AEs leading to study drug dose modification or treatment discontinuation

Method of analysis	Most efficacy analyses were performed on the full analysis set (FAS) (ITT) population as randomized and included data from the main study. Exceptions were the OS analysis, which was based on the FAS population during the entire study, including the crossover period for

	the PBR arm, and the DOR and TTR analyses, which were performed for the responders (CR or PR) in the FAS population (5). PFS (IRC and INV) and OS of ABR vs. PBR was estimated using the Kaplan-Meier method with a stratified log-rank test adjusting for for the stratification factors geographic region (North America; Western Europe; Other) and the Simplified Mantle Cell Lymphoma International Prognostic Index (MIPI). Hazard ratios and the corresponding confidence intervals (CI) were estimated with Cox proportional hazards regression (5). ORR (IRC and INV) was analyzed using the mid-p method for 95% CI for each arm, while the treatment difference in ORR was evaluated using the stratified Cochran-Mantel-Haenszel test for the P-value and the Miettinen and Nurminen method for the 95% CI (5). DOR (IRC and INV) and TTR (IRC and INV) were summarized with descriptive statistics (5).
Subgroup analyses	Prespecified subgroup analysis of IRC-assessed PFS and OS were performed using potential prognostic variables at screening or baseline to investigate the consistency and robustness of PFS and OS between ABR and PBR (5): Sex (male vs. female) Age category (year) (< 70 vs. ≥ 70; < 75 vs. ≥ 75) Race (White vs. Non-White) Geographic Region (North America vs. Western Europe vs. Other) Baseline ECOC performance status (0 vs. 1 vs. 1 or 2 vs. ≥ 2) Tumor bulk (largest diameter, cm): (< 5 cm versus ≥ 5; < 10 cm versus ≥ 10 cm) Ann Arbor staging for lymphoma (Stage I-III vs. Stage IV) Extranodal disease (Yes vs. No) Historically Documented MCL (Yes vs. No) MCL type (Classical type vs. Blastoid variant vs. Pleomorphic variant vs. Other) Ki-67 (%) (< 30 versus ≥ 30; < 50 versus ≥ 50) Bone marrow involvement (Yes vs. No) Gastrointestinal disease (Yes. vs. No) Simplified MIPI score (Low risk [0-3], Intermediate risk [4-5] or High risk [6-11])

Trial name: ECHO	NCT number: NCT02972840
	LDH > upper limit of normal (Yes vs. No) COVID-19 vaccine status (Yes vs. No) The hazard ratio (ABR arm and PBR arm) and its corresponding 95% CI for each subgroup were calculated based on an unstratified Cox regression model and displayed graphically in a forest plot (5).
Other relevant information	Sensitivity analysis excluding patients that died of COVID-19 was performed. As the COVID-19 pandemic occurred during the ECHO study when enrolment was active, the FDA provided guidance on clinical trial protocols during the COVID-19 pandemic and to AstraZeneca for ECHO. Based on the FDA feedback, the ECHO protocol was amended and included a pre-planned sensitivity analysis reporting data with censoring of COVID-19 related deaths to evaluate the impact of COVID-19 deaths (5).

Appendix B. Efficacy results per study

Results per study

[Complete the table for all studies included, regardless of whether they have been used in the health economic model. Explain how all estimates, such as CIs and p-values, have been estimated, this includes the method used, adjustment variables, stratification variables, weights, corrections (in cases with 0 counts), correlation structure (mixed effects model for repeated measurements) and methods used for imputation. Specify how assumptions were checked. Survival rates: state at which time point these are reported for.]

Table 64 Results per study

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS, Covid censored.	ABR	299	NE (66.4–NE) months	NE	NA	NA	HR: 0.64	0.48–0.84	0.0017	HRs (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisation stratification factors simplified MIPI score as	ECHO CSR, Table 18 (5).
	PBR	299	61.6 (49.6–68.9) months								

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										recorded in IXRS.	
PFS probability by 48 months (%) Covid censored.	ABR	299	69.9% (63.5–75.4)	12.6%	NA	NA	NA	NA	NA		ECHO CSR, Table 18 (5)
	PBR	299	57.3% (50.5–63.5)								
Median OS, Covid censored.	ABR	299	NE (NE–NE) months	NE	NA	NA	HR: 0.75	0.53–1.04	0.0797	The median OS is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the	ECHO CSR Appendix, Table 14.2.5.3 (59).
	PBR	299	NE(73.8-NE) months								

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										variables used for stratification for randomizatio n, and study arm.	
Median PFS, ITT	ABR	299	66.4 (55.1-–NE) months	16.8	NA	NA	HR: 0.73	0.57–0.94	0.016	HRs (95% CI) are based on stratified Cox proportional hazards model, stratified by randomisatio n stratification factors simplified MIPI score as recorded in IXRS.	ECHO CSR (5).

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	PBR	299	49.6 (36.0–64.1) months								
PFS probability by 48 months (%) ITT	ABR	299	59.5% (52.8–65.5)	9.1%	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	ECHO CSR (5)
	PBR	299	50.4% (43.8–56.6)								
Median OS, ITT	ABR	299	NE (72.1–NE) months	NE	NA	NA	HR: 0.86	0.65–1.13	0.2743	The median OS is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with	ECHO CSR (5)

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										adjustment for the variables used for stratification for randomizatio n, and study arm.	
	PBR	299	NE(73.8-NE) months								
ORR (CR+PR) IRC.	ABR	299	91% (87.3%-93.8%)	3%	-2%-8.1%	0.2196				Best overall response was defined as the best response of CR, PR, stable disease, or PD as assessed by IRC per the Lugano	ECHO CSR, (5).
	PBR	299	88% (83.9%–91.3%)								

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										Classification for NHL.	
CR by IRC	ABR	299	66.6%	NA	NA	NA				Best overall response was defined as the best response of CR, PR, stable disease, or PD as assessed by IRC per the Lugano Classification for NHL.	
	PBR	299	53.5%								
Time to initial respons, PR or better, IRC	ABR	272	2.8 (2.8-2.8) months	NE	NA	NA	NA	NA	NA	TTR was defined as the time from the date of randomisation until the date of first	ECHO CSR, Table 27 (5)
	PBR	263	2.8 (NE-NE) months								

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										documented response CR or PR (assessed by the investigator and IRC, respectively) per the Lugano Classification for NHL.	
Time to initial respons, CR, IRC	ABR	199	5.5 (3.2-5.6) months	NE	NA	NA	NA	NA	NA	TTR was defined as the time from the date of randomisation until the date of first documented response CR or PR	ECHO CSR, Table 27 (5)
	PBR	160	5.5 (5.3-5.6) months								

Results of [ECHO NCT02972840] (6)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										(assessed by the investigator and IRC, respectively) per the Lugano Classification for NHL.	

B.1.1 ORR IRC and INV – results per ECHO

The ORR was similar between ABR and PBR, although ABR showed a numerically higher CR rate

Over the follow-up period, the ORR (CR + PR) was similar in the ABR and PBR arms (91.0% [95% CI: 87.3–93.8] and 88.0% [95% CI; 83.9–91.3], respectively; Table 65). The CR rate was numerically higher in the ABR arm than in the PBR arm, with an additional 13% of patients achieving a CR with ABR compared with PBR (66.6% vs 53.5%). ORR based on INV assessment was consistent with the IRC-assessed ORR.

Table 65. Analysis of ORR (IRC and INV assessments)

	IRC assessment		INV assessment	
	ABR (*n* = 299)	**PBR (*n* = 299)**	**ABR (*n* = 299)**	**PBR (*n* = 299)**
Best overall response, *n* (%)				
CR	199 (66.6%)	160 (53.5%)	223 (74.6%)	196 (65.6%)
PR	73 (24.4%)	103 (34.4%)	50 (16.7%)	70 (23.4%)
Stable disease	3 (1.0%)	5 (1.7%)	4 (1.3%)	7 (2.3%)
Disease progression	8 (2.7%)	13 (4.3%)	7 (2.3%)	14 (4.7%)
Unknown	1 (0.3%)	5 (1.7%)	–	–
Missing	15 (5.0%)	13 (4.3%)	15 (5.0%)	12 (4.0%)
ORR (CR + PR), *n* (%)	272 (91.0%)	263 (88.0%)	273 (91.3%)	266 (89.0%)
95% CI[a]	(87.3%–93.8%)	(83.9%–91.3%)	(87.7%–94.1%)	(85.0%–92.2%)
ORR difference (vs PBR)	3.0%	–	2.3%	–
95% CI[b]	(−2.0%, 8.1%)	–	(−2.5%, 7.2%)	–
***p* value**	0.2196	–	0.3239	–

'Missing' category includes patients without any post-baseline response assessment.

[a]95% CIs were based on the mid-p method.

[b]95% CI for the ORR difference was based on Miettinen-Nurminen method (Miettinen and Nurminen 1985).

ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CR, complete response; CSR, clinical study report; IRC, independent review committee; ORR, overall response rate; PBR, placebo plus bendamustine and rituximab; PR, partial response.

Source: ECHO CSR, Tables 20 and 24 .(5)

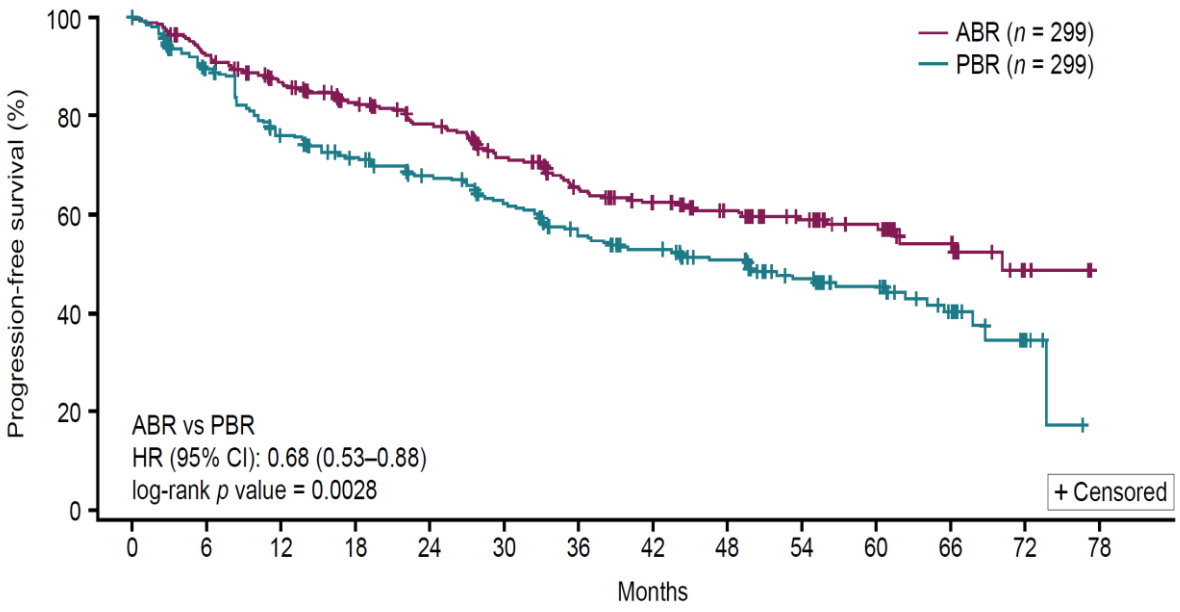
B.1.2 PFS INV – results per ECHO

[Complete a section for each study in the comparison according to the description in 0.]

Investigator-assessed PFS (INV-PFS) supported the results of the primary analyses, showing a 32% reduction in risk of disease progression or death (HR ABR vs PBR: 0.68 [95% CI: 0.53–0.88]; *p* = 0.0028)

The results of INV-assessed PFS were similar to those of IRC-assessed PFS. 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 70.2 months (95% CI: 61.7–NE) in the ABR arm and 49.7 months (95% CI: 36.0–62.4) in the PBR arm. ABR demonstrated an improvement in INV-assessed PFS compared with PBR, with a 32% reduction in risk of PD or death (HR: 0.68; 95% CI: 0.53–0.88; *p* = 0.0028). The KM curves of PFS per treatment arm showed that at 24 months, estimated INV-assessed PFS was higher with ABR than with PBR; 78.3% and 67.9% of patients who received ABR and PBR, respectively, were estimated to be alive and progression-free. At 36 months, these percentages were 65.7% and 56.1%, respectively, and were 60.8% and 50.8% at 48 months (Figure 24). The overall concordance rates between IRC-assessed PFS and INV-assessed PFS for ABR and PBR were 94.3% and 95.7%, respectively (Table 66).

Figure 24. KM plot for PFS (INV-assessment)



Number at risk (number censored)

ABR	299 (0)	261 (16)	236 (26)	211 (40)	192 (48)	164 (60)	143 (68)	129 (75)	105 (96)	82 (116)	59 (138)	37 (157)	3 (189)	0 (192)
PBR	299 (0)	247 (22)	205 (27)	185 (35)	168 (43)	149 (48)	123 (60)	111 (65)	92 (80)	67 (99)	48 (116)	28 (132)	5 (153)	0 (157)

ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CSR, clinical study report; HR, hazard ratio; INV, investigator; KM, Kaplan–Meier; PBR, placebo plus bendamustine and rituximab; PFS, progression-free survival.

Source: ECHO CSR, Figure 9.(5)

Table 66. Concordance between IRC-assessed and INV-assessed PD (FAS)

Determined as PD by IRC	Determined as PD by investigator		
	Yes	No	Total
ABR (*n* = 299)			
Yes	47 (15.7%)	10 (3.3%)	57 (19.1%)
No	9 (3.0%)	233 (77.9%)	242 (80.9%)
Total	56 (18.7%)	243 (81.3%)	299 (100%)
Overall concordance rate	93.6%	–	–
PBR (*n* = 299)			
Yes	95 (31.8%)	4 (1.3%)	99 (33.1%)
No	10 (3.3%)	190 (63.5%)	200 (66.9%)
Total	105 (35.1%)	194 (64.9%)	299 (100%)
Overall concordance rate	95.3%	–	–

ABR, acalabrutinib plus bendamustine and rituximab; CSR, clinical study report; INV, investigator; IRC, independent review committee; PBR, placebo plus bendamustine and rituximab; PD, progressive disease.

Source: ECHO CSR, Table 23.(5)

B.1.3 DOR IRC and INV– results per ECHO

[Complete a section for each study in the comparison according to the description in 0.]

Patients who received ABR experienced a longer DOR than patients who received PBR

DOR by IRC assessment demonstrated a longer time from first CR or PR to disease progression or death among patients who received ABR compared with PBR. The estimated median IRC-assessed DOR was 63.5 months (95% CI: 52.5–NE) with ABR compared with 53.8 months (95% CI: 37.6–66.1) with PBR. The estimated median IRC-assessed DOR rate at 24 months in the ABR and PBR arms was 77.1% (95% CI: 71.3–81.8) and 68.6% (95% CI: 62.3–74.1), respectively. The estimated median IRC-assessed DOR rate at 36 months was 64.6% (95% CI: 58.0–70.4) and 58.5% (95% CI: 51.8–64.6) in the ABR and PBR arms, respectively. The estimated median IRC-assessed DOR rate at 48 months was higher for ABR than PBR (59.9% [95% CI: 53.0–66.1] and 51.1% [95% CI: 44.0–57.7], respectively). DOR based on investigator assessments was consistent with the IRC-assessed DOR

Table 67. Analysis of DOR (IRC and INV assessment)

	IRC assessment		Investigator assessment	
	ABR (*n* = 272)	PBR (*n* = 263)	ABR (*n* = 273)	PBR (*n* = 266)
Patient status				
Events, *n* (%)	99 (36.4%)	117 (44.5%)	94 (34.4%)	121 (45.5%)
Death	52 (19.1%)	34 (12.9%)	49 (17.9%)	33 (12.4%)
Disease progression	47 (17.3%)	83 (31.6%)	45 (16.5%)	88 (33.1%)
DOR (months)				
Median (95% CI)	63.5 (52.5–NE)	53.8 (37.6–66.1)	NE (59.0–NE)	53.1 (40.7–65.2)
KM estimates of DOR probability by time point (%)				

24 months (95% CI), number at risk	77.1 (71.3–81.8), 175	68.6 (62.3–74.1), 151	79.8 (74.3–84.3), 186	71.5 (65.5–76.7), 163
36 months (95% CI), number at risk	64.6 (58.0–70.4), 127	58.5 (51.8–64.6), 112	66.4 (59.9–72.1), 135	58.1 (51.4–64.1), 116
48 months (95% CI), number at risk	59.9 (53.0–66.1), 77	51.1 (44.0–57.7), 64	62.4 (55.7–68.5), 86	52.4 (45.5–58.8), 73

Months are derived as days/30.4375. DOR was calculated as date of disease progression or death (censoring date for censored patients) – (date of achieving the first CR or PR) + 1.

ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CR, complete response; CSR, clinical study report; DOR, duration of response; INV, investigator; IRC, independent review committee; KM, Kaplan–Meier; NE, not estimable; PBR, placebo plus bendamustine and rituximab; PR, partial response.

Source: ECHO CSR, Tables 25 and 26.(5)

B.1.4 TTR IRC – results per ECHO

[Complete a section for each study in the comparison according to the description in 0.]

The TTR was similar between ABR and PBR

Median TTR of CR + PR was similar among patients who received ABR and PBR (2.8 months in both arms). Median time to CR was also similar among treatment arms (5.5 months in both arms). TTR of CR + PR based on investigator assessment was similar to that for IRC-assessed TTR of CR + PR.

Table 68. Time to response (CR + PR) by IRC assessment

	IRC assessment	Investigator assessment

	ABR (*n* = 272)	PBR (*n* = 263)	ABR (*n* = 273)	PBR (*n* = 266)
Time to initial CR (months)				
n	199	160	223	196
Median (95% CI)	5.5 (3.2–5.6)	5.5 (5.3–5.6)	5.4 (3.8–5.6)	5.6 (5.6–5.8)
Time to initial response of PR or better (months)				
n	272	263	273	266
Median (95% CI)	2.8 (2.8–2.8)	2.8 (NE–NE)	2.8 (2.8–2.9)	2.8 (2.8–2.9)

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.

ABR, acalabrutinib plus bendamustine and rituximab; CI, confidence interval; CR, complete response; CSR, clinical study report; IRC, independent review committee; NE, not estimable; PBR, placebo plus bendamustine and rituximab; PR, partial response.

Source: ECHO CSR, Tables 27 and 28.(5)

Appendix C. Comparative analysis of efficacy

NA

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 69 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

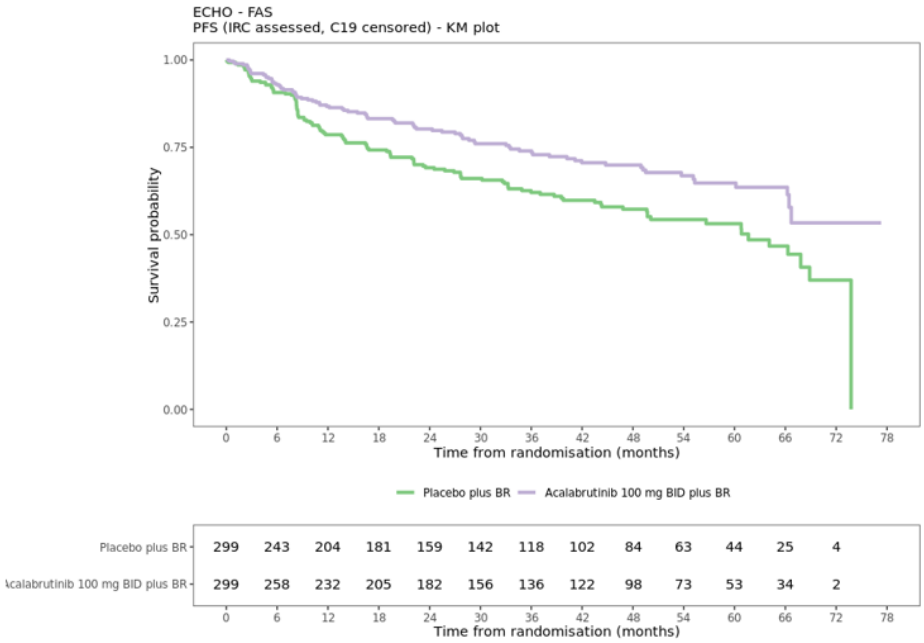
Appendix D. Extrapolation

D.1 Extrapolation of progression-free survival

D.1.1 Data input

Data from the ECHO trial is used to inform the extrapolation of PFS beyond the follow-up in the clinical trial. Figure 25 displays the KM for PFS for the covid-19 censored population in ECHO, including numbers at risk.

Figure 25 KM for PFS for the covid-19 censored population in ECHO



D.1.2 Model

Standard parametric models were used to extrapolate PFS from ECHO data, the following distributions are options in the model:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma
- Gamma
- Generalised F

D.1.3 Proportional hazards

The results of the Schoenfeld residuals test and Log-cumulative hazards plot for the COVID-19 population are presented in Figure 26 Figure 27 Log-cumulative hazards vs. and Figure 27, respectively.

The Schoenfeld residual test reports a p-value of 0.8814 and suggests that there is no statistically significant evidence (p>0.05) to reject proportional hazards. However, the scaled Schoenfeld residual plot, which depicts the effect of treatment as a function of time, shows a non-horizontal line and a non-zero slope for treatment effect over time.

The log-cumulative hazard plots cross at an early stage, and merge at other points.

Based on the assessments above it was concluded that the proportional hazards assumption was likely breached. Curves were therefore fitted separately to each arm of ECHO.

Figure 26 Schoenfeld residual plot for PFS

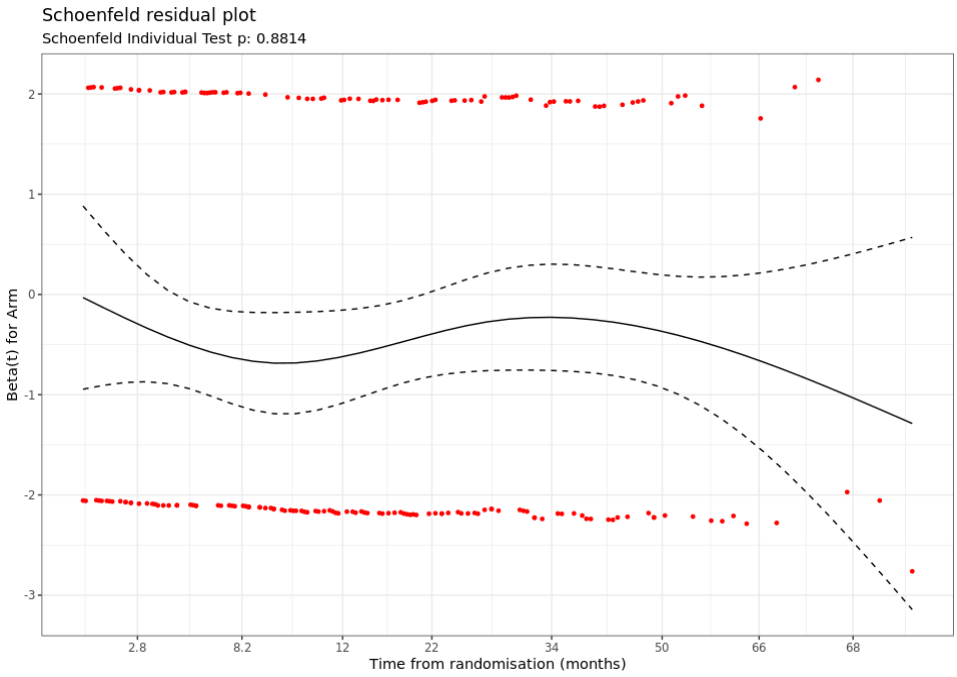
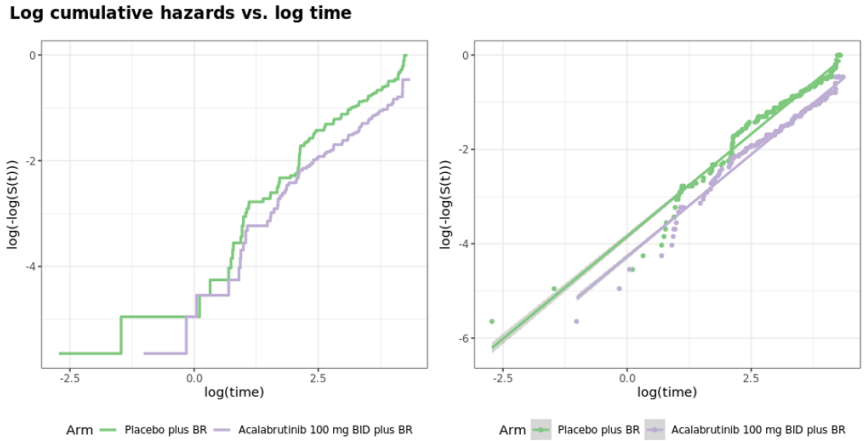


Figure 27 Log-cumulative hazards vs. log time plots for PFS



D.1.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC values for each distribution as fitted to each arm are shown in Table 70. In terms of AIC, the lognormal distribution has the best statistical fit to the ABR arm, whereas the loglogistic has the best fit to the PBR arm. All distributions have reasonable statistical fits in both arms (ΔAIC < 5).

Table 70 AIC and BIC for PFS

Distribution	AIC (rank)		BIC (rank)	
	ABR	PBR	ABR	PBR
Exponential	964.4 (7)	1251.9 (8)	968.1 (1)	1255.6 (1)
Weibull	964.0 (5)	1250.5 (5)	971.4 (5)	1257.9 (5)
Log-normal	961.1 (1)	1249.1 (2)	968.5 (2)	1256.5 (3)
Log-logistic	963.2 (3)	1248.7 (1)	970.6 (3)	1256.1 (2)
Gompertz	963.5 (4)	1249.7 (4)	970.9 (4)	1257.1 (4)
Generalised Gamma	963.1 (2)	1249.7 (3)	974.2 (7)	1260.8 (7)
Gamma	964.4 (6)	1251.1 (6)	971.8 (6)	1258.5 (6)
Generalised F	965.1 (8)	1251.6 (7)	979.9 (8)	1266.4 (8)

D.1.5 Evaluation of visual fit

The extrapolated PFS curves were plotted together with the KM data for ABR and PBR from the ECHO trial using standard parametric functions (see figures below). Note that in the model, unlike in the figures below, all time-to-event outcomes are adjusted with general population mortality, making the long-term difference between extrapolation methods smaller than depicted in the figures.

From visual inspection of both arms, most models fit the observed data reasonably well. All models slightly overestimate PFS approximately between year 1 and 2, while underestimating during the last part of follow-up, although some of the underestimation could be explained by lower numbers of patients at risk (see Figure 13 shown in the main section of the dossier).

The lognormal, Gompertz, generalised F and generalised gamma curves seem to provide optimistic long-term estimates in comparison to the other statistical models.

For PBR, the different models are similar in terms of median PFS, with PFS capped by general mortality and OS ranging from 4.4 years (exponential) to 5.1 years (log-normal).

For ABR on the other hand, the log-normal, generalized gamma, Gompertz and Generalised F are far more optimistic than other distributions, with a median PFS around 9.5 years, in contrast to around 7.8 for Weibull and Gamma respectively, or 7.1 for the exponential.

For long term PFS at 20 years, capped by general mortality and OS, the Log-normal, Generalised Gamma, Gompertz and Generalised F are more optimistic than other distributions, particularly for ABR, with a proportion still in PFS of around 14.5%.

Figure 28 Standard parametric extrapolations and Kaplan-Meier of PFS for PBR

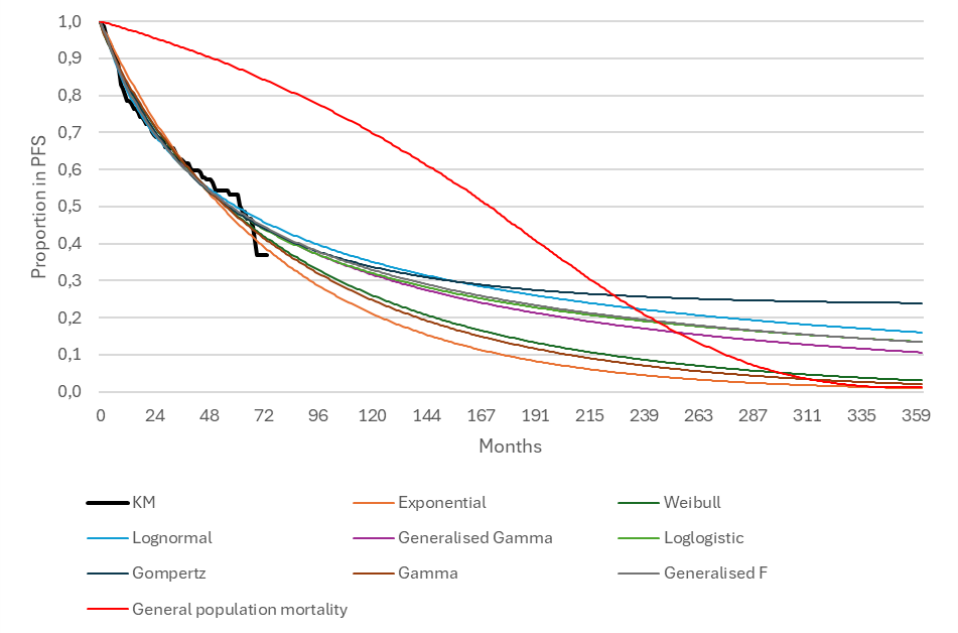


Figure 29 Standard parametric extrapolations and Kaplan-Meier of PFS for PBR for 120 months

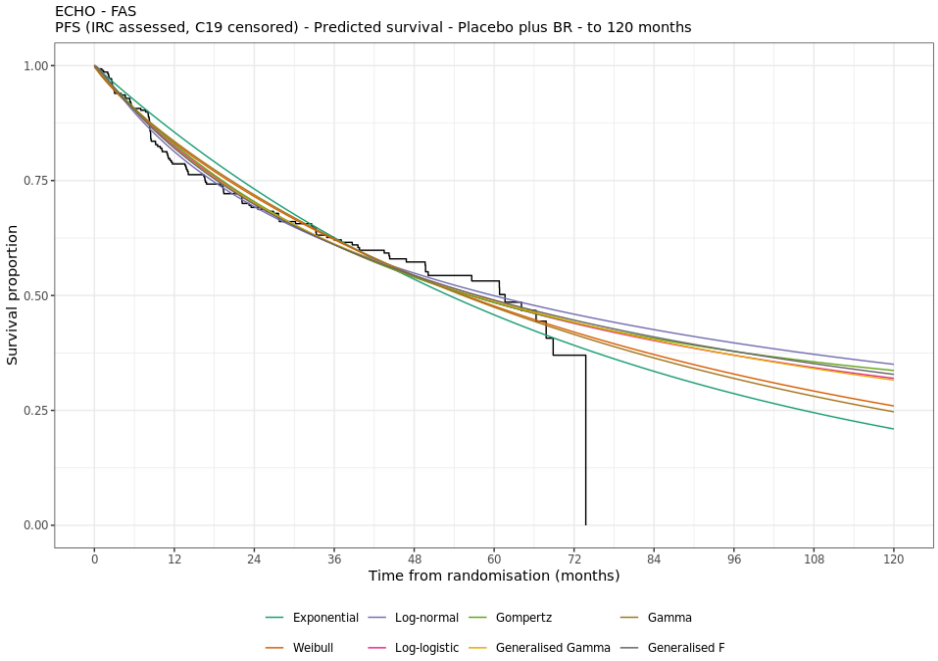


Figure 30 Standard parametric extrapolations and Kaplan-Meier of PFS for ABR for the entire model time horizon

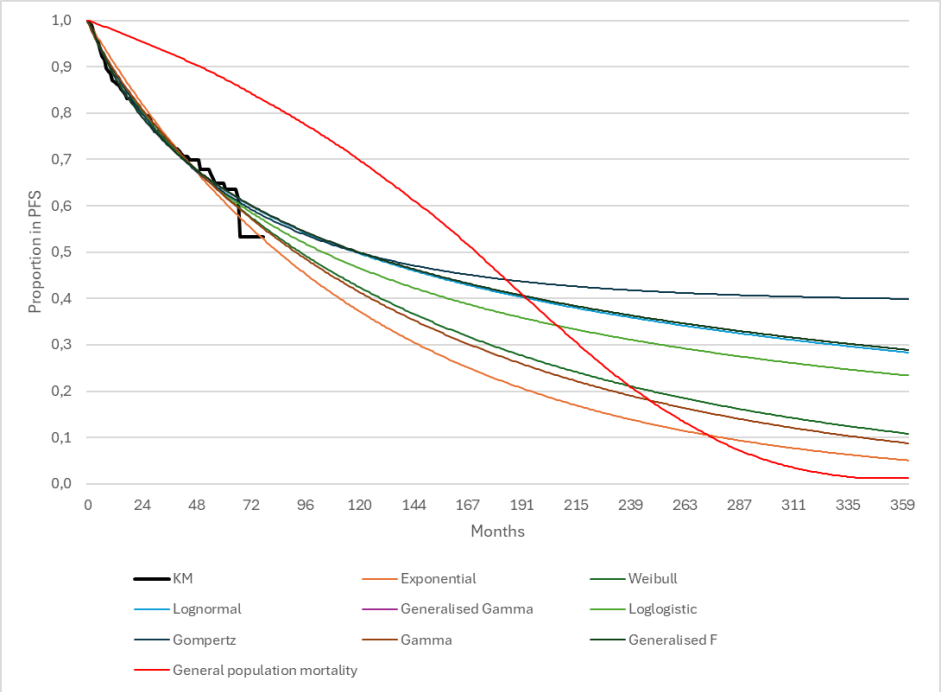
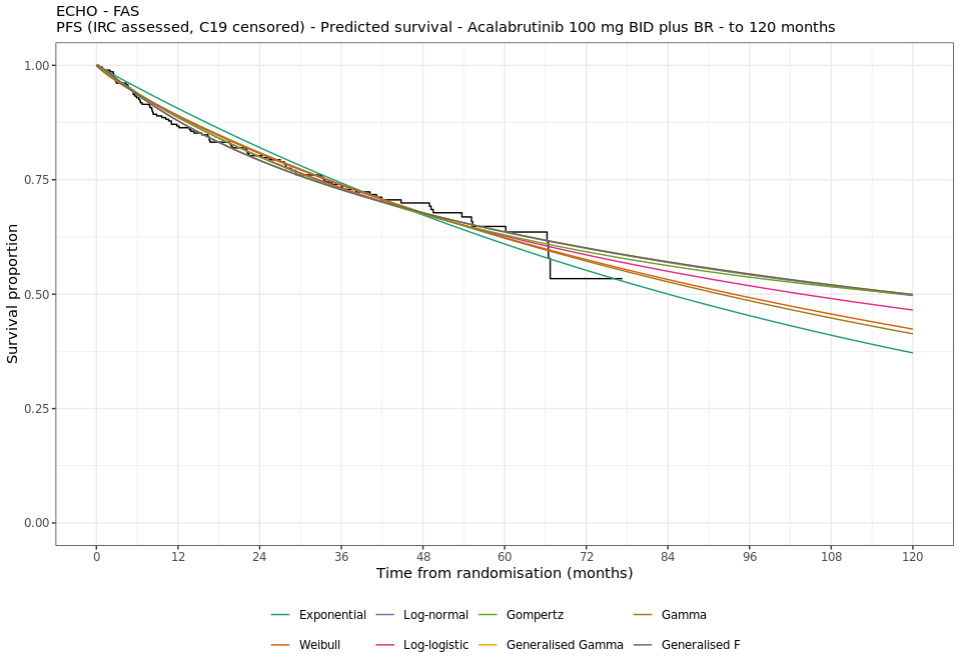


Figure 31 Standard parametric extrapolations and Kaplan-Meier of PFS for ABR for 120 months



D.1.6 Evaluation of hazard functions

Figure 32 and Figure 33 show empirical smoothed hazards and modelled hazards for PBR (first figure) and ABR (second figure). Both the ABR and PBR arm show decreasing hazards throughout the trial, before an increase at about 42 to 48 months. After month 66 the number at risk starts to become small and therefore the sharp increase in the hazards are unreliable. Despite the uncertainty, a constant hazard is unlikely to be representative of the empirical hazards. This is supported by the goodness-of-fit statistics where the exponential is ranked 7th and 8th in AIC and BIC, respectively. The initial high and thereafter gradually decreasing hazard seen using Weibull, Gamma, log-logistic and Gompertz reflect the empirical hazard for the first part of follow-up. However, the Gompertz and Log-logistic show more rapidly declining hazards over time than Weibull or Gamma.

Figure 32 Smoothed empirical hazards and modelled hazards for PBR

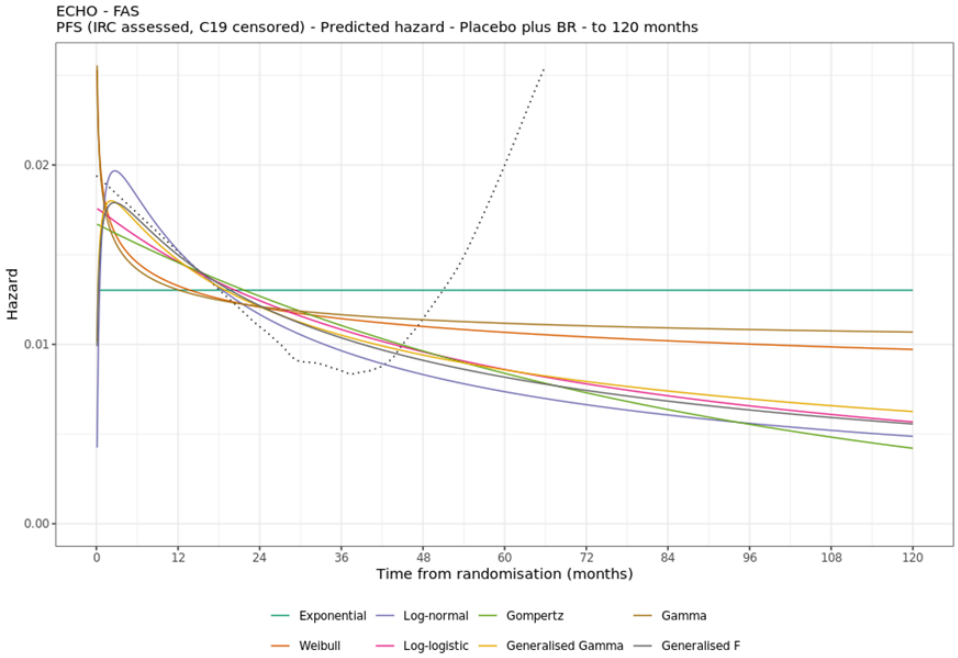
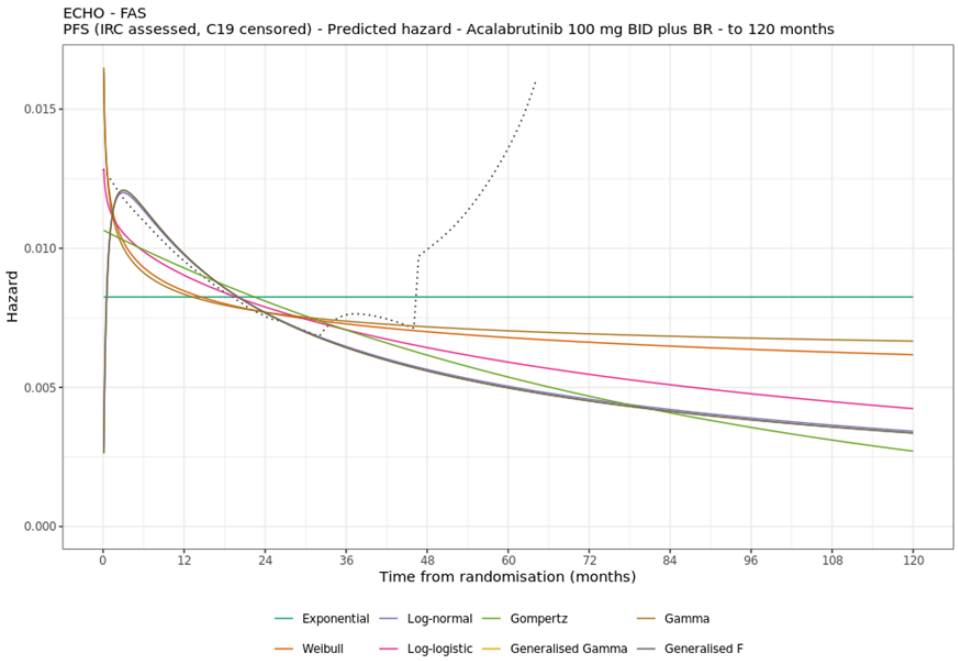


Figure 33 Smoothed empirical hazards and modelled hazards for ABR



D.1.7 Validation and discussion of extrapolated curves

All models have reasonable statistical fits in both arms in terms of AIC and BIC.

The exponential model can be excluded because the estimated PFS does not fit well to the KM data and the estimated hazards fit poorly to the observed hazards. The other models fit well to the KM data. However, of the models with decreasing hazards, Gompertz, Generalized F, log-logistic, generalized gamma and the log-normal seem least

suitable for modelling the stabilization or increase in hazard that happens after some time because they have a steeper decrease in hazards than the other models. A Danish clinical expert stated that the risk of dying from MCL would decrease gradually over time, rather than decreasing quickly, increasing or remaining stable. This could also have some applicability to PFS. Weibull and Gamma fit the initial observed hazards reasonably well while maintaining a slow decrease in hazard over time.

Being shown the results of the OS and general population mortality-adjusted PFS survival models from ECHO, a Danish clinical expert estimated that around 30–35 % of patients in the PBR arm would still be in PFS at 10 years, and 10–15 % at 20 years. However, background mortality adjustment results in estimates lower than this for 20 years. When background-mortality adjusted, the PFS extrapolations generally give estimates in the area 25-35 % at 10 years and 6-10% at 20 years. Log-normal and Gompertz are in the higher end of this range, while Weibull and Gamma are in the lower end, with exponential being even lower.

Overall, Gamma and Weibull were considered to best balance the considerations of fit to observed and predicted hazards and long-term estimates. As a base case, Gamma was chosen.

D.1.8 Adjustment of background mortality

The extrapolation of PFS was adjusted for OS and general population mortality, i.e. the % in PFS in the model can never be higher than OS, and survival according to the general population. Background mortality was estimated using DMC's template "Addendum to the health economic model", with date of last update 14-03-2023. The template only includes mortality up to the age of 99. For the age of 100 to 103, the model uses the same mortality as the age of 99.

Figure 13 in section 8.1.1.1 shows the base case extrapolation for PFS including adjustment for OS and background mortality.

D.1.9 Adjustment for treatment switching/cross-over

NA.

D.1.10 Waning effect

NA.

D.1.11 Cure-point

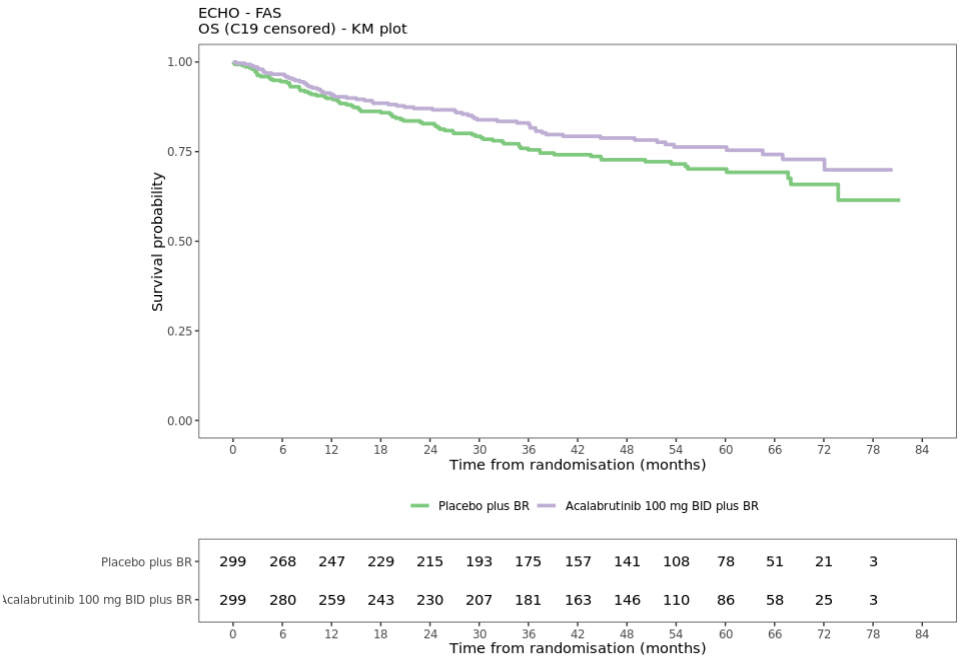
NA.

D.2 Extrapolation of overall survival

D.2.1 Data input

Data from the ECHO trial is used to inform the extrapolation of OS beyond the follow-up in the clinical trial. Figure 34 displays the KM for OS for the covid-19 censored population in ECHO.

Figure 34 KM for OS for the covid-19 censored population in ECHO



D.2.2 Model

Standard parametric models were used to extrapolate OS from ECHO data, the following distributions are options in the model:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma
- Gamma

D.2.3 Proportional hazards

The results of the Schoenfeld residuals test and Log-cumulative hazards plot for the COVID-19 population are presented in Figure 35 and Figure 36 respectively.

The Schoenfeld residual test reports a p-value of 0.834 and suggests that there is no statistically significant evidence (p>0.05) to reject proportional hazards. The plot also shows a reasonably horizontal line aligning with PH assumption.

Visual inspection of the log cumulative hazard plot shows relatively parallel lines, although the lines almost merge at two time points.

The assessment of proportional hazards failed to provide conclusive evidence on whether to reject the proportional hazards assumption for OS. However, as it was more clearly violated for PFS and given some merging of the curves it was decided to fit models separately to each arm of ECHO.

Figure 35 OS Schoenfeld residual plot COVID-19 population

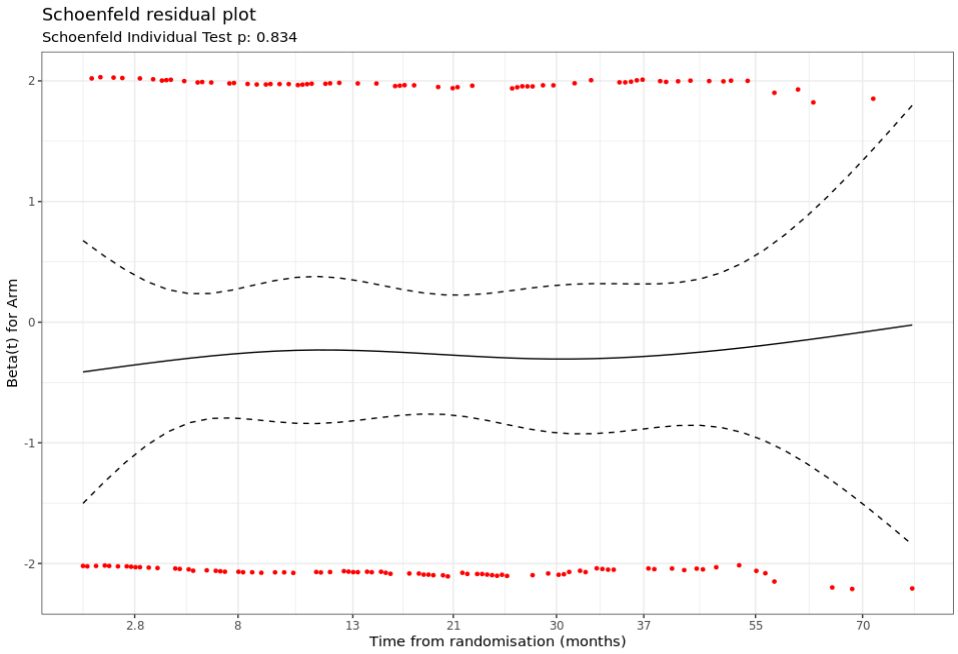
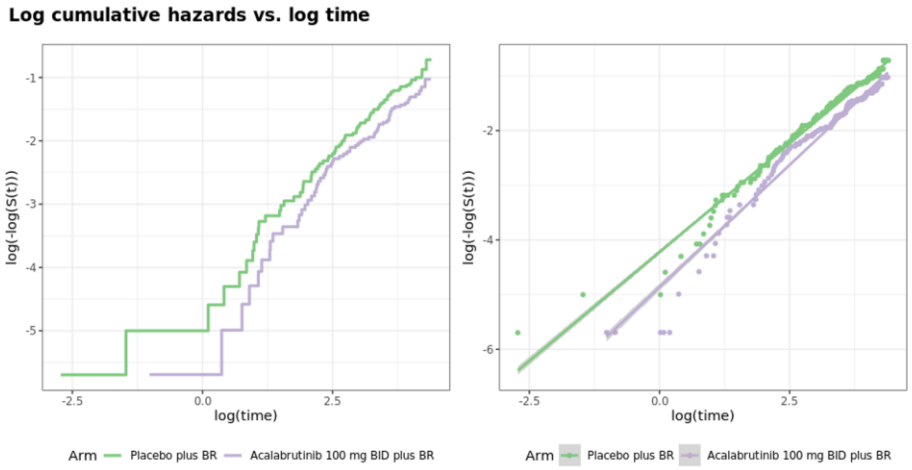


Figure 36 OS log hazard plots COVID-19 population



D.2.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC values for each distribution as fitted to each arm are shown Table 71. In terms of AIC, the lognormal distribution has the best statistical fit to the ABR arm, whereas the Gompertz has the best fit to the PBR arm. All distributions have reasonable statistical fits in both arms (ΔAIC < 5).

Table 71 AIC and BIC for OS

Distribution	AIC (rank)		BIC (rank)	
	ABR	PBR	ABR	PBR
Exponential	808.4 (7)	966.3 (8)	812.1 (1)	970.0 (3)
Weibull	808.1 (5)	962.7 (4)	815.5 (5)	970.1 (5)
Log-normal	805.1 (1)	962.6 (3)	812.5 (2)	970.0 (4)
Log-logistic	807.2 (4)	961.7 (2)	814.6 (4)	969.1 (2)
Gompertz	806.4 (2)	961.4 (1)	813.8 (3)	968.8 (1)
Generalised Gamma	806.9 (3)	963.6 (6)	818.0 (7)	974.7 (7)
Gamma	808.4 (6)	963.2 (5)	815.8 (6)	970.6 (6)
Generalised F	808.9 (8)	965.1 (7)	823.7 (8)	979.9 (8)

D.2.5 Evaluation of visual fit

The extrapolated OS curves were plotted together with the KM data for ABR and PBR from the ECHO trial using standard parametric functions, see figures below. Note that in the model, all time-to-event outcomes are adjusted with general population mortality, making the long-term difference between extrapolation methods smaller than depicted in the figures.

In general, most models fit well to the KM data. The exception is the exponential which is an outlier in terms of overestimating survival at the beginning of follow-up, particularly for the PBR arm.

For long-term OS, exponential predicts lowest OS while Gompertz predicts substantially higher OS than the other models, followed by log-normal, generalized gamma and log logistic.

Figure 37 Standard parametric extrapolations and Kaplan-Meier of OS for PBR for the entire model time horizon

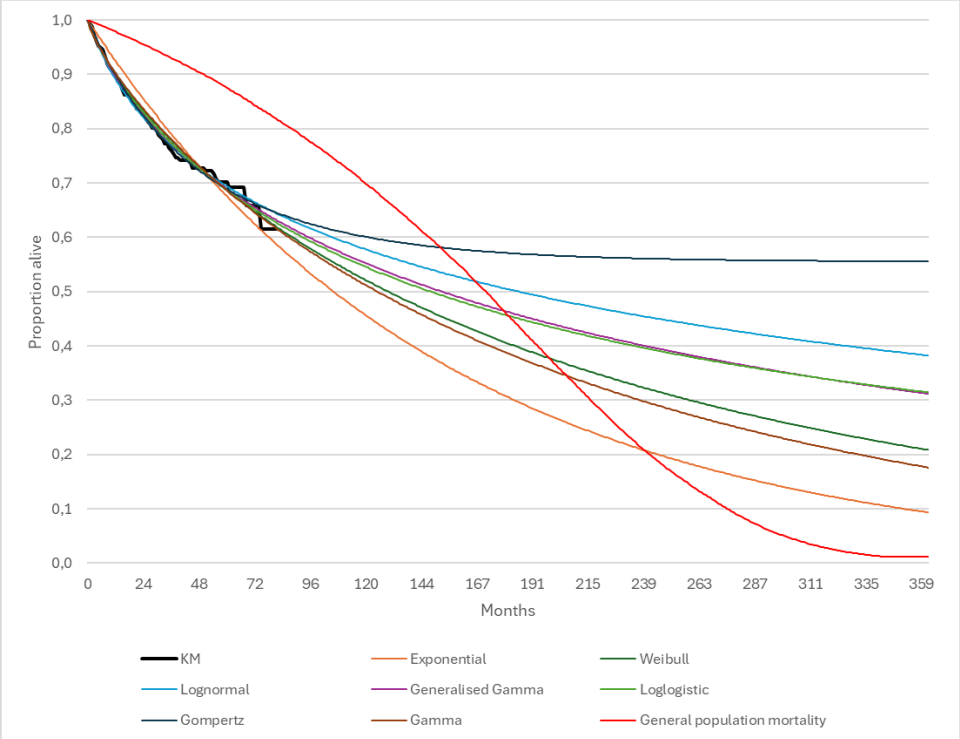


Figure 38 Standard parametric extrapolations and Kaplan-Meier of OS for PBR for 120 months

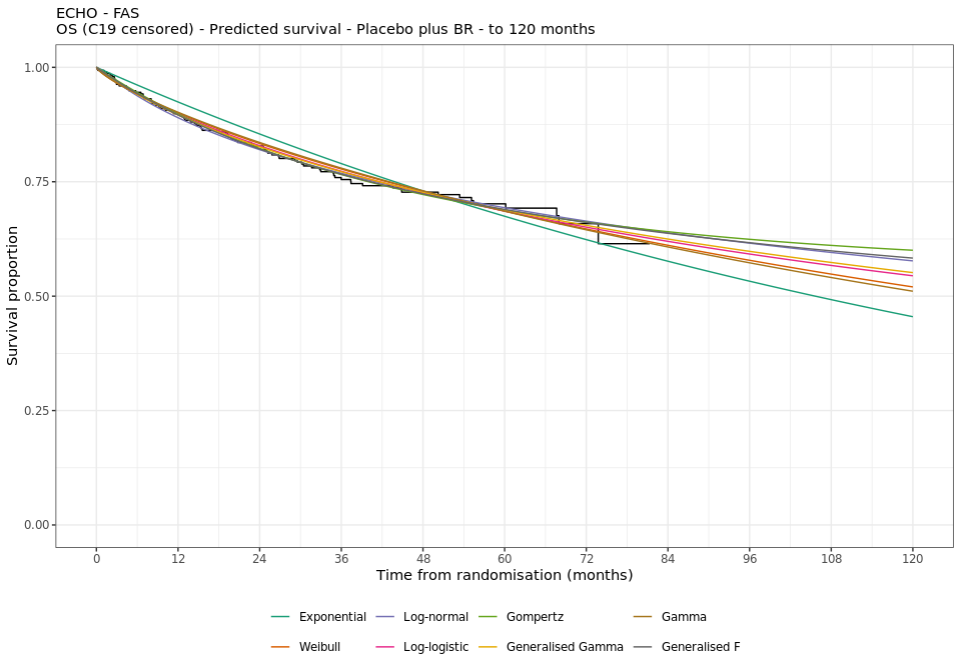


Figure 39 Standard parametric extrapolations and Kaplan-Meier of OS for ABR for the entire model time horizon

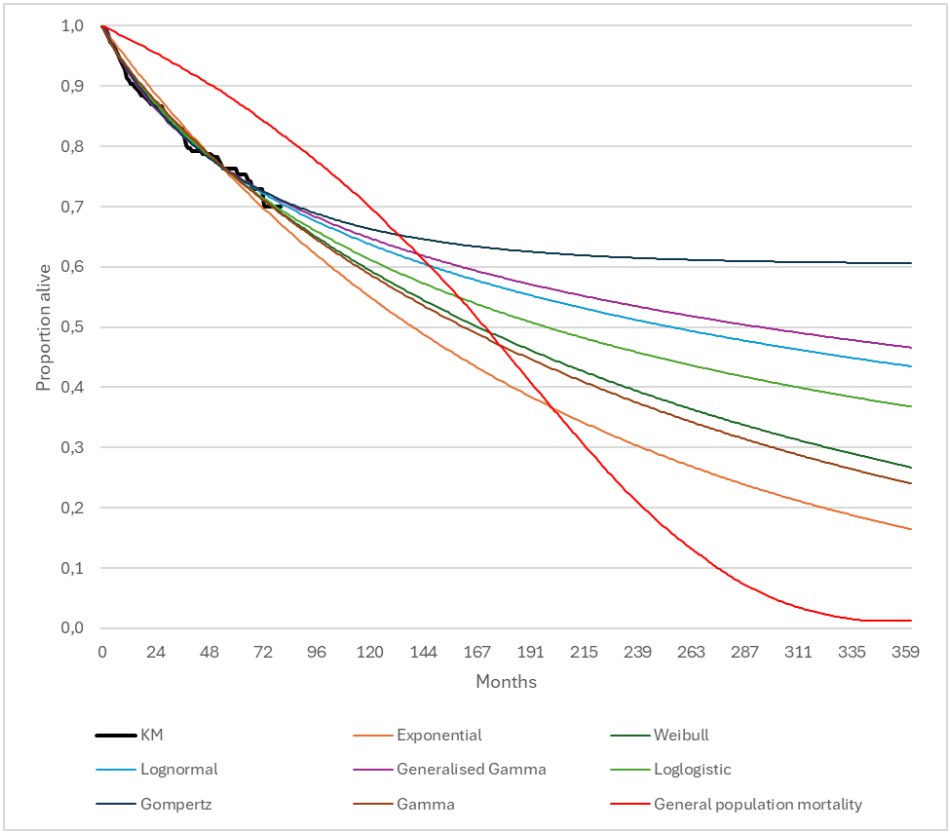
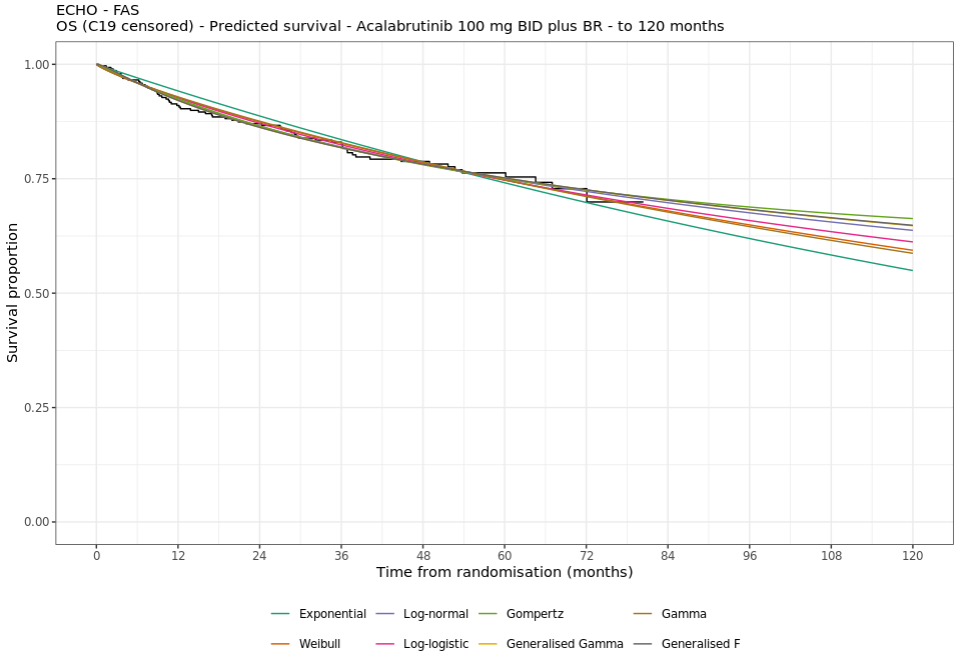


Figure 40 Standard parametric extrapolations and Kaplan-Meier of OS for ABR for 120 months



D.2.6 Evaluation of hazard functions

Figure 41 and Figure 42 show the smoothed empirical hazards and modelled hazard plots for all models for the PBR and ABR arms respectively.

Both the ABR and PBR arm show decreasing hazards throughout the trial, before an increase at about 42 to 48 months. The hazard in the ABR arm increases slowly, but in the PBR arm the increase is steep. When the hazard starts to increase, there are still a few patients at risk (around 150 patients), but it is more unclear whether the further increase at 66 months and beyond is representative due to the low number of patients at risk. Weibull, Gamma, Gompertz, Generalised gamma and log-logistic reflect the initial high and thereafter decreasing empirical hazard. However, the three latter have a more steeply decreasing hazard than Weibull and Gamma.

Figure 41 Smoothed empirical hazards (black dotted line) versus modelled hazards for OS, PBR arm

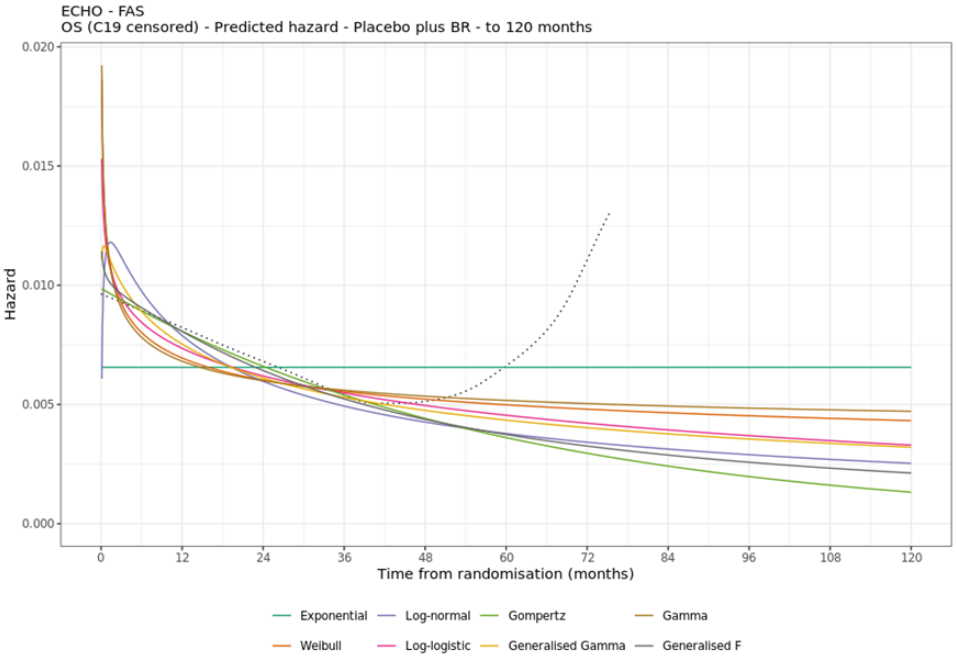
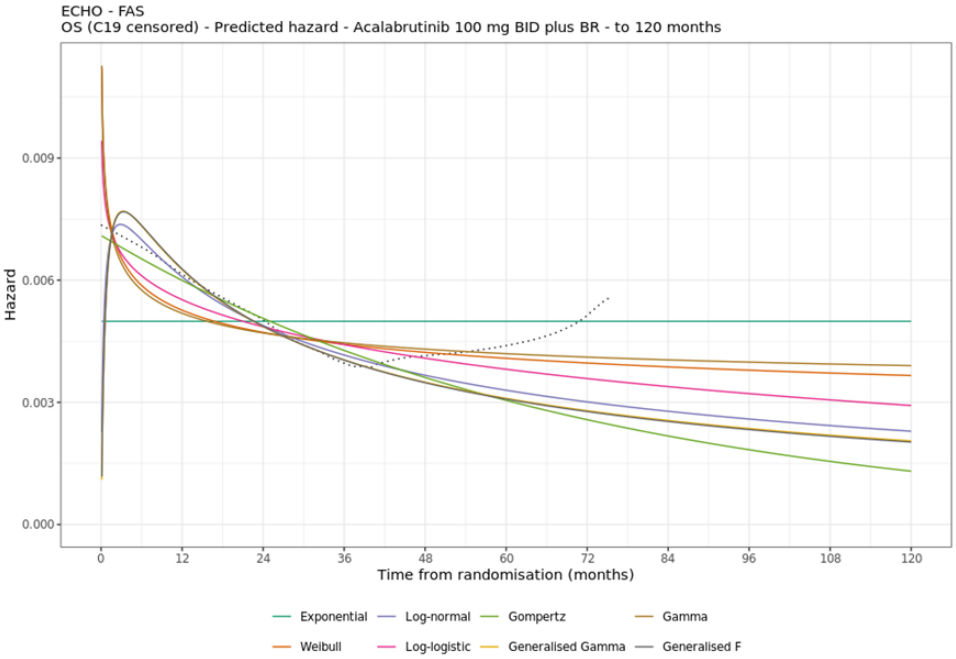


Figure 42 Smoothed empirical hazards (black dotted line) versus modelled hazards for OS, ABR arm



D.2.7 Validation and discussion of extrapolated curves

All models have reasonable statistical fits in both arms in terms of AIC and BIC. The exponential model can be excluded because the estimated OS does not fit well to the KM data and the estimated hazards fit poorly to the observed hazards. While the observed

hazards seem to decrease before stabilizing or increasing, the exponential has a constant hazard over time.

The other models fit well the KM data. However, of the models with initial high then decreasing hazards, Gompertz, log-logistic and the log-normal seem least suitable for modelling the stabilization or increase in hazard that happens after some time because they have a steeper decrease in hazards than the other models. A Danish clinical expert stated that the risk of dying from MCL would decrease gradually over time, rather than decreasing quickly, increasing or remaining stable. Gompertz in particular results in low hazards over time and plateauing of survival. Weibull and Gamma fit the initial observed hazards reasonably well, while maintaining a slow decrease in hazard over time.

Being shown the results of general population mortality-adjusted survival models from ECHO, a Danish clinical expert estimated that around 55 % of patients in the PBR arm would be alive at 10 years, and 16 % at 20 years. When background-mortality adjusted, the survival extrapolations generally give estimates in that area, with the exception of exponential which underestimates the survival.

Overall, Gamma and Weibull were considered to best balance the considerations of fit to observed and predicted hazards and long term estimates. As a base case, Gamma was chosen.

D.2.8 Adjustment of background mortality

The extrapolation of overall survival was adjusted for background mortality, i.e. the % alive in the model can never be higher than the background mortality. Background mortality was estimated using DMC's template "Addendum to the health economic model", with date of last update 14-03-2023. The template only includes mortality up to the age of 99. For the age of 100 to 103, the model uses the same mortality as the age of 99.

D.2.9 Adjustment for treatment switching/cross-over

NA

D.2.10 Waning effect

NA

D.2.11 Cure-point

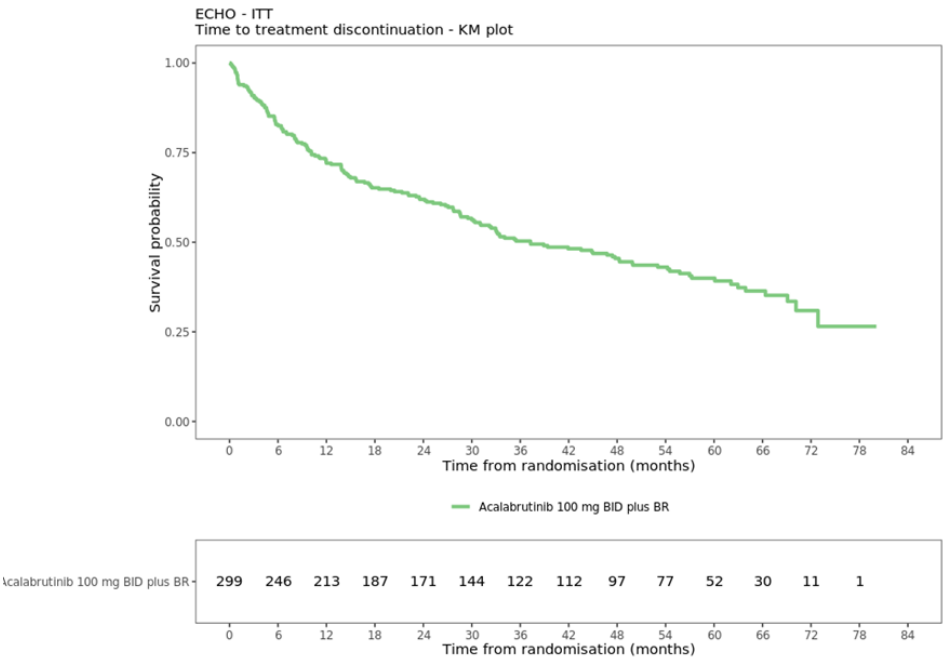
NA

D.3 Extrapolation of time to treatment discontinuation

D.3.1 Data input

Data from the ECHO trial is used to inform the extrapolation of TTD beyond the follow-up in the clinical trial. Figure 43 displays the KM for TTD in ECHO.

Figure 43 KM for TTD in ECHO.



D.3.2 Model

Standard parametric models were used to extrapolate TTD from ECHO data, the following distributions are options in the model:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma
- Gamma
- Generalised F

D.3.3 Proportional hazards

NA. Extrapolation only done for acalabrutinib.

D.3.4 Evaluation of statistical fit (AIC and BIC)

The AIC and BIC values are shown in Table 72. All parametric models fit the data well (ΔAIC < 5) except the exponential which has a larger value than the others, and Gompertz and Generalised F to an extent.

Table 72 Goodness of fit statistic for TTD

Distribution	AIC (rank)	BIC (rank)
Exponential	1723.3 (8)	1727.0 (8)
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 (7)	1718.1 (6)
Generalised Gamma	1706.0 (2)	1717.1 (5)
Gamma	1709.0 (6)	1716.4 (4)
Generalised F	1708.0 (5)	1722.8 (7)

D.3.5 Evaluation of visual fit

The extrapolated TTD for ABR was plotted together with the KM data from the ECHO trial using standard parametric functions. Figure 44 displays the models for the entire model time horizon, while Figure 45 displays the models up to 120 months. Note that in the model, all time-to-event outcomes are adjusted with general population mortality, making the long-term difference between extrapolation methods smaller than depicted in the figures.

Visually, the lognormal, loglogistic, Gompertz and generalised gamma and F seem to overestimate the final 12 months and even more so the final six months of trial data. This may be due to the relatively low numbers at risk towards the end of trial follow-up. And, similar to the ABR PFS, the exponential overestimates the trial up to month 48 and then underestimates the remaining trial follow-up.

Figure 44 Standard parametric extrapolations and Kaplan-Meier of TTD for acalabrutinib – entire follow-up

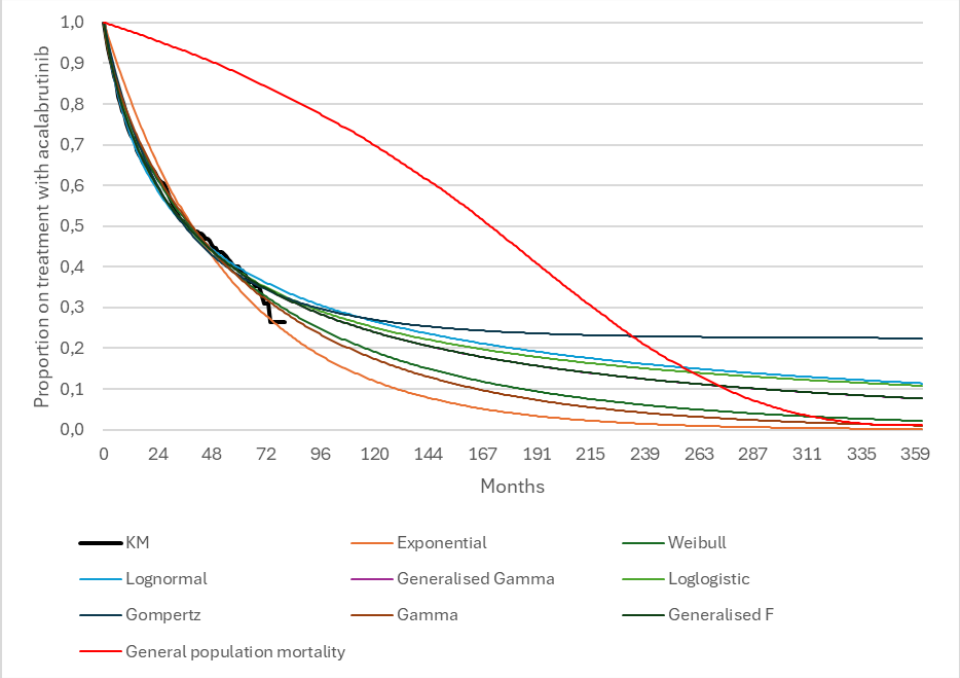
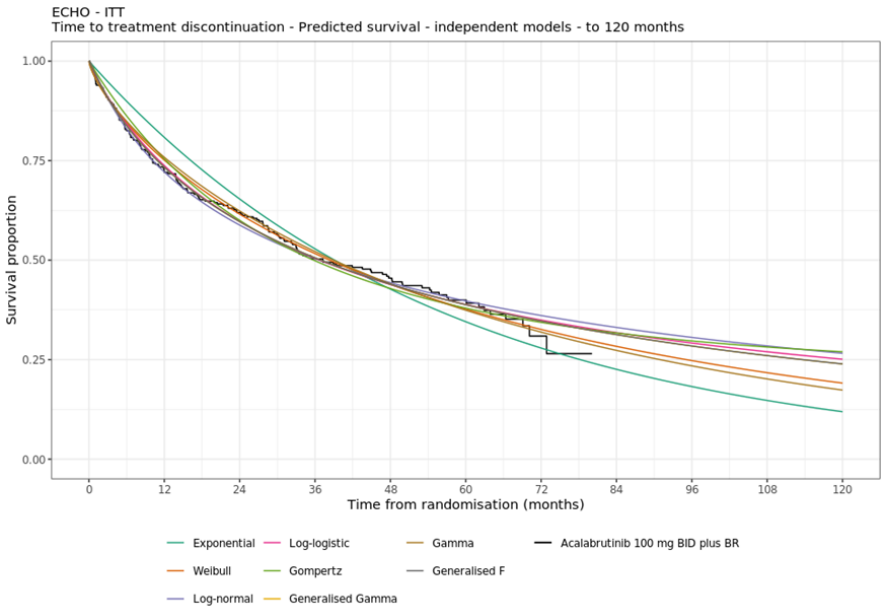


Figure 45 Standard parametric extrapolations and Kaplan-Meier of TTD for acalabrutinib – up to 120 months

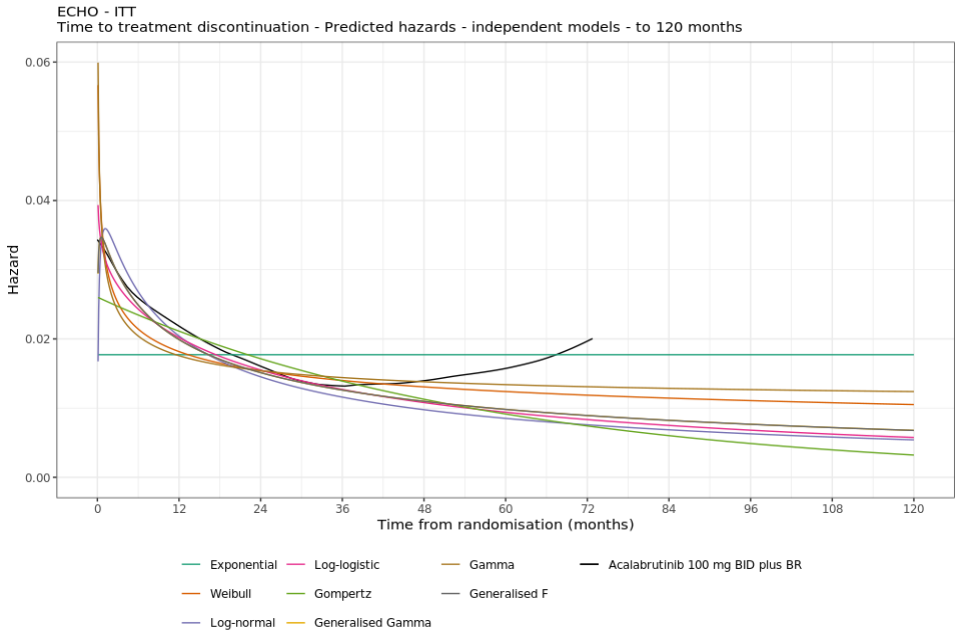


D.3.6 Evaluation of hazard functions

Figure 46 shows the smoothed empirical hazards and modelled hazard plots for TTD for all models.

As for PFS and OS, the hazards decrease throughout the trial, before a slight increase starting at about 48 months. When the hazard starts to increase, there are still a few patients at risk (around 100 patients), but it is more unclear whether the further increase at 66 months and beyond is representative due to the low number of patients at risk.

Figure 46 Smoothed empirical hazards (black line) versus modelled hazards for TTD for acalabrutinib



D.3.7 Validation and discussion of extrapolated curves

All models have reasonable statistical fits in terms of AIC and BIC, with the exception of exponential. The exponential model can further be excluded because the estimated TTD has the worst visual fit to the KM data and the estimated hazards fit poorly to the observed hazards. While the observed hazards seem to decrease before stabilizing or increasing, the exponential has a constant hazard over time.

The other models fit well the KM data. However, of the models with decreasing hazards, Gompertz, log-logistic, Generalized F and the log-normal seem least suitable for modelling the stabilization or increase in hazard that happens after some time because they have a steeper decrease in hazards than the other models. Gompertz in particular results in high estimates of time on treatment over time. Weibull and Gamma fit the initial observed hazards reasonably well while maintaining a slow decrease in hazard over time.

Being shown the results of OS and general population mortality-adjusted TTD models from ECHO, a Danish clinical expert estimated that around 15 to 20% of patients would be on treatment at 10 years, with less than 10% at 20 years. When adjusted for background mortality and OS, the time on treatment extrapolations give estimates in the area of 17 % to 27 % 10 years when excluding exponential. At 20 years the range is 4 % to 8 %. In other words, all models will predict that fewer than 10 % are on treatment at

20 years. However, only Weibull and Gamma predict 15 to 20 % at 10 years, with values of 19 % and 17 % respectively.

Based on the assessment above, Gamma was chosen as the base case model for TTD.

D.3.8 Adjustment of background mortality

The extrapolation of TTD was adjusted for OS and general population mortality, i.e. the % on treatment in the model can never be higher than OS, and survival according to the general population. Background mortality was estimated using DMC's template "Addendum to the health economic model", with date of last update 14-03-2023. The template only includes mortality up to the age of 99. For the age of 100 to 103, the model uses the same mortality as the age of 99.

D.3.9 Adjustment for treatment switching/cross-over

NA

D.3.10 Waning effect

NA

D.3.11 Cure-point

NA

Appendix E. Serious adverse events

All serious adverse events observed in the ECHO study are listed in the table below (by preferred term and grade, SAS). As of the data cut-off on 15 February 2024, the median follow-up was 44.9 months (46.1 months in the ABR arm and 44.4 months in the PBR arm). The median treatment exposure for acalabrutinib in the ABR arm was 28.6 months, compared to 24.6 months for placebo in the PBR arm (*AstraZeneca Data on File: ECHO CSR-tables-and-figures, Table 14.3.4.1.1* (59)).

	Acala + BR (N=297)					Placebo + BR (N=297)				
Preferred Term	**Any Grade**	**Grade 1-2**	**Grade 3-4**	**Grade 5**	**Grade ≥3**	**Any Grade**	**Grade 1-2**	**Grade 3-4**	**Grade 5**	**Grade ≥3**
Subjects with At Least One Serious TEAE	205 (69.0%)	14 (4.7%)	155 (52.2%)	36 (12.1%)	191 (64.3%)	184 (62.0%)	18 (6.1%)	136 (45.8%)	30 (10.1%)	166 (55.9%)
COVID-19 pneumonia	41 (13.8%)	2 (0.7%)	24 (8.1%)	15 (5.1%)	39 (13.1%)	34 (11.4%)	4 (1.3%)	20 (6.7%)	10 (3.4%)	30 (10.1%)
Pneumonia	28 (9.4%)	4 (1.3%)	21 (7.1%)	3 (1.0%)	24 (8.1%)	21 (7.1%)	3 (1.0%)	18 (6.1%)	0	18 (6.1%)
COVID-19	26 (8.8%)	3 (1.0%)	15 (5.1%)	8 (2.7%)	23 (7.7%)	19 (6.4%)	1 (0.3%)	12 (4.0%)	6 (2.0%)	18 (6.1%)
Pyrexia	17 (5.7%)	10 (3.4%)	7 (2.4%)	0	7 (2.4%)	15 (5.1%)	11 (3.7%)	4 (1.3%)	0	4 (1.3%)
Febrile neutropenia	10 (3.4%)	0	10 (3.4%)	0	10 (3.4%)	3 (1.0%)	0	3 (1.0%)	0	3 (1.0%)
Atrial fibrillation	9 (3.0%)	3 (1.0%)	6 (2.0%)	0	6 (2.0%)	6 (2.0%)	2 (0.7%)	4 (1.3%)	0	4 (1.3%)
Sepsis	8 (2.7%)	0	7 (2.4%)	1 (0.3%)	8 (2.7%)	8 (2.7%)	0	6 (2.0%)	2 (0.7%)	8 (2.7%)
Anaemia	7 (2.4%)	0	7 (2.4%)	0	7 (2.4%)	6 (2.0%)	0	6 (2.0%)	0	6 (2.0%)
Acute kidney injury	5 (1.7%)	1 (0.3%)	4 (1.3%)	0	4 (1.3%)	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Cellulitis	5 (1.7%)	0	5 (1.7%)	0	5 (1.7%)	5 (1.7%)	1 (0.3%)	4 (1.3%)	0	4 (1.3%)
Dyspnoea	5 (1.7%)	2 (0.7%)	2 (0.7%)	1 (0.3%)	3 (1.0%)	0	0	0	0	0

Neutropenia	5 (1.7%)	1 (0.3%)	4 (1.3%)	0	4 (1.3%)	6 (2.0%)	0	6 (2.0%)	0	6 (2.0%)
Thrombocytopenia	3 (1.0%)	0	3 (1.0%)	0	3 (1.0%)	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Urosepsis	3 (1.0%)	0	2 (0.7%)	1 (0.3%)	3 (1.0%)	0	0	0	0	0
Alanine aminotransferase increased	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Appendicitis	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	0	0
Atypical pneumonia	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cardiac failure	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	3 (1.0%)	1 (0.3%)	2 (0.7%)	0	2 (0.7%)
Dehydration	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Enteritis	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Escherichia sepsis	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Haematuria	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Hyperkalaemia	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Infusion related reaction	2 (0.7%)	2 (0.7%)	0	0	0	10 (3.4%)	5 (1.7%)	5 (1.7%)	0	5 (1.7%)
Large intestine polyp	2 (0.7%)	2 (0.7%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Lower respiratory tract infection	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Myelodysplastic syndrome	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Myocardial infarction	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Norovirus infection	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Osteoarthritis	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Osteomyelitis	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Pneumonitis	2 (0.7%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pseudomonal bacteraemia	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Pulmonary embolism	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	8 (2.7%)	0	6 (2.0%)	2 (0.7%)	8 (2.7%)

Pulmonary mass	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Rash pruritic	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)	0	0	0	0	0
Squamous cell carcinoma	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Upper respiratory tract infection	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Ventricular extrasystoles	2 (0.7%)	2 (0.7%)	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Vertigo	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Abdominal pain	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Adenocarcinoma gastric	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Anal abscess	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Anaplastic large-cell lymphoma	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Angina pectoris	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Arrhythmia	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Arthralgia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Arthritis bacterial	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Arthritis infective	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Aspartate aminotransferase increased	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Asthenia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0
Bacteraemia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Bacterial sepsis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Basal cell carcinoma	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Blood bilirubin increased	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Bone pain	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Bowen's disease	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0

Bradycardia	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Breast cancer	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Bronchitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Bronchopneumopathy	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Bronchopulmonary aspergillosis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Campylobacter gastroenteritis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cardiac failure chronic	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Cardiac tamponade	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cardiopulmonary failure	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Carotid artery stenosis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Cervical spinal stenosis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cervicobrachial syndrome	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cholecystitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Cholecystitis acute	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Chronic sinusitis	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Chylothorax	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Clostridium difficile colitis	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Clostridium test positive	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cognitive disorder	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Colitis	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Colon cancer	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0

Colorectal adenocarcinoma	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Cystitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Dermatitis bullous	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Dermatitis exfoliative	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Device related thrombosis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Diarrhoea infectious	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Diverticulitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	4 (1.3%)	1 (0.3%)	3 (1.0%)	0	3 (1.0%)
Dizziness	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Dysphagia	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Embolism	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Embolism arterial	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Endophthalmitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Enlarged uvula	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Epilepsy	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Erythema multiforme	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Face oedema	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Fatigue	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Febrile nonhaemolytic transfusion reaction	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Flushing	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Gait disturbance	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Gastrointestinal infection	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Gastrointestinal stromal tumour	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0

General physical health deterioration	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Giardiasis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Groin infection	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Hemiparesis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Hepatic failure	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Hip fracture	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Humerus fracture	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Hypersensitivity	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Inflammation	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Influenza	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Inguinal hernia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Intervertebral discitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Intestinal adenocarcinoma	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Intestinal ischaemia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Jaw cyst	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Lentigo maligna	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Leukopenia	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Limb mass	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Liver injury	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Localised infection	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Lung infiltration	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Lymphadenitis	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Malaise	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0

Malignant melanoma	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Meningitis	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Metastatic malignant melanoma	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Migraine	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Nausea	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Nephrolithiasis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Neuroendocrine carcinoma	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Neutropenic sepsis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Neutrophil count decreased	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Non-cardiac chest pain	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Non-small cell lung cancer	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Obstructive airways disorder	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Ocular melanoma	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Pain in extremity	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Perineal abscess	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Peripheral ischaemia	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Platelet count decreased	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pneumonia cytomegaloviral	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Pneumonia haemophilus	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Post-acute COVID-19 syndrome	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Presyncope	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Prostatitis	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Pruritus	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0

Pulmonary oedema	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Pulmonary tuberculosis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Pyelonephritis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Rash erythematous	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Rectal haemorrhage	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Renal cancer	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Salmonella sepsis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Salmonellosis	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Septic shock	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	3 (1.0%)	0	3 (1.0%)	0	3 (1.0%)
Skin lesion	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Stomatitis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Supraventricular extrasystoles	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Supraventricular tachycardia	1 (0.3%)	1 (0.3%)	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Tooth abscess	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Tooth infection	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Toxic encephalopathy	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Toxic skin eruption	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Toxicity to various agents	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Transient ischaemic attack	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Tumour lysis syndrome	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	5 (1.7%)	0	4 (1.3%)	1 (0.3%)	5 (1.7%)
Urticaria	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Ventricular arrhythmia	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0	0
Vitreous haemorrhage	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)

Volvulus of small bowel	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Vomiting	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
White blood cell count decreased	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Wound dehiscence	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Wound sepsis	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0
Adams-Stokes syndrome	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Adenocarcinoma of colon	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Agranulocytosis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Aortic aneurysm rupture	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Aortic stenosis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Asthma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Babesiosis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Bacterial infection	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Blood creatinine increased	0	0	0	0	0	2 (0.7%)	2 (0.7%)	0	0	0
Blood fibrinogen increased	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Bronchospasm	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Cardiac arrest	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Carotid artery occlusion	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Cerebellar stroke	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Cerebral infarction	0	0	0	0	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Cerebrovascular accident	0	0	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Chills	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Chronic obstructive pulmonary disease	0	0	0	0	0	3 (1.0%)	1 (0.3%)	2 (0.7%)	0	2 (0.7%)

Circulatory collapse	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Constipation	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Corynebacterium bacteraemia	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Cystitis haemorrhagic	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Dementia with Lewy bodies	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Dermatitis exfoliative generalised	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Duodenal perforation	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Duodenal ulcer haemorrhage	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Dyspnoea exertional	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Endometrial cancer	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Erysipelas	0	0	0	0	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Faecaloma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Fall	0	0	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Febrile infection	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Femur fracture	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Gastric polyps	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Gastritis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Gastritis haemorrhagic	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	2 (0.7%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)
Gastrooesophageal reflux disease	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Glioblastoma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Gouty arthritis	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Gun shot wound	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)

H1N1 influenza	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Haemoperitoneum	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Haemophilus test positive	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Haemorrhage	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Haemorrhage intracranial	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Headache	0	0	0	0	0	2 (0.7%)	2 (0.7%)	0	0	0
Hepatitis B	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Hypergammaglobulinaemia benign monoclonal	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Hypertension	0	0	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Hyperthermia	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Hypogammaglobulinaemia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Hypokalaemia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Hypophosphataemia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Incarcerated parastomal hernia	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Interstitial lung disease	0	0	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Ischaemic stroke	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Lacunar infarction	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Large intestinal obstruction	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Lung adenocarcinoma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Lung neoplasm malignant	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Melaena	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Metabolic encephalopathy	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)

Muscular weakness	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Myocardial ischaemia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Neuroendocrine carcinoma of the skin	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Organising pneumonia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Orthostatic hypotension	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pancreatitis chronic	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pasteurella infection	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Physical deconditioning	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Plasma cell myeloma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pneumonia influenzal	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pneumonia streptococcal	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Pneumothorax	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Postoperative wound infection	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Proctalgia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Prostate cancer	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Pulmonary hypertension	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Puncture site haemorrhage	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Pyelonephritis chronic	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Rectal adenocarcinoma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Renal cell carcinoma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Renal colic	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Renal tubular disorder	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Respiratory failure	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)

Retinal artery embolism	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Road traffic accident	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Septic encephalopathy	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Serum sickness	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Sinus bradycardia	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Sinusitis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Small intestinal obstruction	0	0	0	0	0	2 (0.7%)	0	2 (0.7%)	0	2 (0.7%)
Soft tissue infection	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Squamous cell carcinoma of lung	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Staphylococcal bacteraemia	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Staphylococcal sepsis	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Subarachnoid haemorrhage	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Suspected drug-induced liver injury	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Systemic inflammatory response syndrome	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Thyroid cancer	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Tonsil cancer	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Transitional cell carcinoma	0	0	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Traumatic haematoma	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Urethral cancer	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Ventricular tachycardia	0	0	0	0	0	1 (0.3%)	1 (0.3%)	0	0	0
Wound infection	1	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)

(S*ource: AstraZeneca Data on File: ECHO CSR-tables-and-figures, Table 14.3.4.1.1*).

Additional Safety Data

TEAEs of clinical interest

Events of clinical interest, including cardiovascular events, are shown in Table 73. Events of clinical interest were generally similar between treatment arms, except for any grade major haemorrhage, which was experienced by a numerically lower percentage of patients in the ABR arm than the PBR arm (2.4% vs 5.4%), and any grade haemorrhage, which was experienced by a numerically higher percentage of patients in the ABR arm compared to the PBR arm (28.3% vs 17.2%). The percentage of patients reporting cardiac events was low for each treatment arm, with most events classed as grade 1 or 2. Cardiac events of any grade were reported in 23.9% of patients in the ABR arm and 18.5% of patients in the PBR arm. Grade ≥ 3 cardiac events occurred in 7.7% of patients in the ABR arm and 6.1% of patients in the PBR arm (5).

Table 73 Summary of TEAE of clinical interest (SAS)

	ABR (*n* = 297)		PBR (*n* = 297)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Cardiac events, *n* (%)	71 (23.9)	23 (7.7)	55 (18.5)	18 (6.1)
Atrial fibrillation	20 (6.7)	12 (4.0)	13 (4.4)	5 (1.7)
Ventricular tachyarrhythmias	7 (2.4)	0	7 (2.4)	0
Cytopenias, *n* (%)				
Anaemia	72 (24.2)	28 (9.4)	62 (20.9)	30 (10.1)
Leukopenia	175 (58.9)	158 (53.2)	182 (61.3)	162 (54.5)
Neutropenia	163 (54.9)	149 (50.2)	166 (55.9)	138 (46.5)
Other leukopenia	74 (24.9)	62 (20.9)	75 (25.3)	60 (20.2)
Thrombocytopenia	68 (22.9)	29 (9.8)	61 (20.5)	24 (8.1)
Haemorrhage, *n* (%)	84 (28.3)	6 (2.0)	51 (17.2)	10 (3.4)
Major haemorrhage	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Hepatotoxicity, *n* (%)	42 (14.1)	20 (6.7)	38 (12.8)	6 (2.0)
Hypertension, *n* (%)	37 (12.5)	17 (5.7)	48 (16.2)	25 (8.4)
Infections, *n* (%)	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Interstitial lung disease/pneumonitis, *n* (%)	10 (3.4)	2 (0.7)	10 (3.4)	4 (1.3)
Second primary malignancies, *n* (%)	53 (17.8)	22 (7.4)	43 (14.5)	22 (7.4)
Second primary malignancies, excluding non-melanoma skin	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)
Tumour lysis syndrome, *n* (%)	4 (1.3)	4 (1.3)	6 (2.0)	6 (2.0)

A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity grading. ABR, acalabrutinib plus bendamustine and rituximab; CSR, clinical study report; ECI, events of clinical interest; PBR, placebo plus bendamustine and rituximab; SAS, safety analysis set; TEAE, treatment-emergent adverse event Source: ECHO CSR, Table 47 (5).

Exposure-adjusted TEAE

The median duration of exposure to acalabrutinib was 4 months longer in the ABR arm than the duration of exposure to placebo in the PBR arm (28.6 vs 24.6 months, respectively). To understand the differences in the safety profile between the ABR and PBR arms while accounting for differences in duration of exposure, exposure-adjusted incidence was calculated (Table 74).

Adjusting for exposure attenuated the observed differences for grade 3 or higher SAEs in the ABR arm compared with the PBR arm when considering exposure-adjusted incidence (32.6 vs 29.3 patients per 100 patient-years of exposure). Similarly, the exposure-adjusted incidence per 100 patient-years of exposure attenuated the differences for TEAEs, resulting in a 42.8% discontinuation rate of acalabrutinib/placebo in the ABR arm compared with a 31.0% discontinuation rate in the PBR arm. However, the differences between the ABR and placebo arms in the rates of TEAEs leading to withholding of acalabrutinib/placebo persisted after adjusting for exposure (73.7% vs 60.3%). The exposure-adjusted incidence of TEAEs for the ABR arm compared with the PBR arm was 58.3 vs 44.7 patients per 100 patient-years of exposure (5).

Table 74 Exposure-adjusted incidence of overall TEAEs (SAS)

	Patients per 100 patient-years of exposure	
	ABR (*n* = 297)	PBR (*n* = 297)
TEAE		
Any grade	1367.2	1424.6
Grade ≥ 3	83.3	106.8
Treatment-emergent SAE		
Any grade	40.0	36.3
Grade ≥ 3	32.6	29.3
TEAE leading to dose withholding		
Any study drug	78.29	64.9

Acalabrutinib/placebo	58.3	44.7
Bendamustine	16.1	13.8
Rituximab	25.8	23.0
TEAE leading to study drug discontinued		
Any study drug	20.2	14.9
Acalabrutinib/placebo	15.5	12.4
Bendamustine	5.9	4.8
Rituximab	7.2	8.1

A patient with multiple severity grades for a given TEAE was counted only once under the maximum severity. Incidence is defined as (total number of patients with TEAEs for each category) × 100 / (Total exposure time for all patients at risk in years in the main study period). ABR, acalabrutinib plus bendamustine and rituximab; CSR, clinical study report; PBR, placebo plus bendamustine and rituximab SAE, serious adverse event; SAS, safety analysis set; TEAE, treatment-emergent adverse event. Source: ECHO CSR, Table 38 (5).

Impact of COVID-19

During the main study period, 40.7% of patients in the ABR arm and 29.6% of patients in the PBR arm experienced at least one COVID-19 AE of any grade (Table 75). The incidence of grade 3 to 4 COVID-19 AEs was similar between the ABR arm and the PBR arm (10.8% vs 10.1%). Grade 5 COVID-19 AEs that occurred during the main study period (excluding crossover) were reported in 9.4% of patients in the ABR arm and 6.7% of patients in the PBR arm (5).

Table 75 Confirmed or suspected COVID-19 AEs by preferred term and grade (SAS)

	***N* (%) of patients**							
	ABR (*n* = 297)				**PBR (*n* = 297)**			
	Any grade	**Grade 3–4**	**Grade 5**	**Grade ≥ 3**	**Any grade**	**Grade 3–4**	**Grade 5**	**Grade ≥ 3**

Patients with at least one COVID-19 AE	121 (40.7)	32 (10.8)	28 (9.4)	60 (20.2)	88 (29.6)	30 (10.1)	20 (6.7)	50 (16.8)
COVID-19	96 (32.3)	18 (6.1)	10 (3.4)	28 (9.4)	67 (22.6)	17 (5.7)	7 (2.4)	24 (8.1)
COVID-19 pneumonia	49 (16.5)	25 (8.4)	17 (5.7)	42 (14.1)	40 (13.5)	22 (7.4)	13 (4.4)	35 (11.8)
SARS-CoV-2 test positive	7 (2.4)	0	0	0	8 (2.7)	0	0	0
Post-acute COVID-19 syndrome	5 (1.7)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)	0	0	0
Suspected COVID-19	5 (1.7)	0	0	0	0	0	0	0

Confirmed/suspected COVID-19 infection was defined as an AE occurring during the pandemic time frame after March 2020. The preferred terms in the AE search criteria were developed by the latest MedDRA MSSO guidance for COVID-19, which all indicate suspected or confirmed COVID-19 AEs. A patient with multiple severity grades for a given AE was counted only once under the maximum severity. Preferred terms are listed in descending order of frequency (any grade) for the ABR arm.
ABR, acalabrutinib plus bendamustine and rituximab; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MSSO, Maintenance and Support Services Organization; PBR, placebo plus bendamustine and rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAS, safety analysis set. Soruce: ECHO CSR, Table 45 (5) .

Death

At the time of the DCO, in the entire FAS population, 32.4% patients had died in the ABR arm, and 35.5% patients had died in the PBR arm during the study, including the crossover period (Table 76). Disease progression was the cause of death in 10.0% of

patients in the ABR arm and 14.4% of patients in the PBR arm, and AEs were the cause of death in 15.4% of patients in the ABR arm and 13.7% of patients in the PBR arm (5).

Table 76 Summary of deaths (FAS, including crossover period)

	N (%) of patients	
	ABR (n = 299)	PBR (n = 299)
Deaths	97 (32.4)	106 (35.5)
Primary cause of death		
Adverse event	46 (15.4)	41 (13.7)
Disease progression[a]	30 (10.0)	43 (14.4)
Other	14 (4.7)	16 (5.4)
Unknown	7 (2.3)	6 (2.0)
Within 30 days of last dose of study drug		
Deaths	37 (12.4)	49 (16.4)
Primary cause of death		
Adverse event	27 (9.0)	27 (9.0)
Disease progression	9 (3.0)	18 (6.0)
Other	0	3 (1.0)
Unknown	1 (0.3)	1 (0.3)
More than 30 days after last dose of study drug		
Deaths	60 (20.1)	57 (19.1)
Primary cause of death		
Adverse event	19 (6.4)	14 (4.7)
Disease progression	21 (7.0)	25 (8.4)
Other	14 (4.7)	13 (4.3)
Unknown	6 (2.0)	5 (1.7)

[a]*Includes one patient in the PBR arm who did not receive any study drug and died of disease progression. All deaths included both treatment-emergent and non-treatment-emergent deaths. Source: ECHO CSR, Table 54 (5).*

Appendix F. Health-related quality of life

[If specific domains from the assessment instrument need to be highlighted, data should be presented here. Argue for the relevance of the domain-specific data.]

This chapter details the analysis of Danish utility values derived from the EQ-5D-5L profiles in ECHO using the 5L Danish value set by Jensen et al (57). The analysis was based on ITT data from DCO 1. This chapter summarises the background, methods and results of the descriptive summary and regression analysis of EQ-5D-5L health state utility data in the ECHO study.

F.1 Methods

A descriptive summary of the EQ-5D health state utilities by arm and study visit, and by arm and progression by ICR status is provided in the results section. The summary analysis includes estimates of mean, standard deviations, median, and interquartile range (IQR) of utility scores in the ITT analysis set of ECHO, consisting of all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method (60) was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression by ICR status (pre-progression by ICR, post-progression by ICR)
- Treatment + Progression by ICR status
- Treatment + Progression by ICR status + Treatment * Progression by ICR status (Both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. This chapter presents the results from the models using the first covariance structure in the sequence that successfully converged for all models (i.e., for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results are presented

for that model, and the remaining model results are based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, parameter estimates, and marginal ('least square') means are presented including 95% confidence intervals.

The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Progression by ICR status) that is averaged over observations and with adjustment for repeated measures. The estimated marginal mean and its associated standard error or confidence interval can be used as utility inputs to the global cost-effectiveness model.

All regression output is saved as a spreadsheet file including covariance matrices for the parameters. Confidence intervals are based on robust standard error estimates.

Analysis was performed in R 4.1.0 using the mmrm package 0.3.14 for model fitting.

F.2 Results - Descriptive analysis

In total, 5225 EQ-5D-5L observations were available from 585 patients. Of these, 4868 observations were recorded pre progression, 74 were recorded post progression and 283 were recorded after censoring for progression by icr.

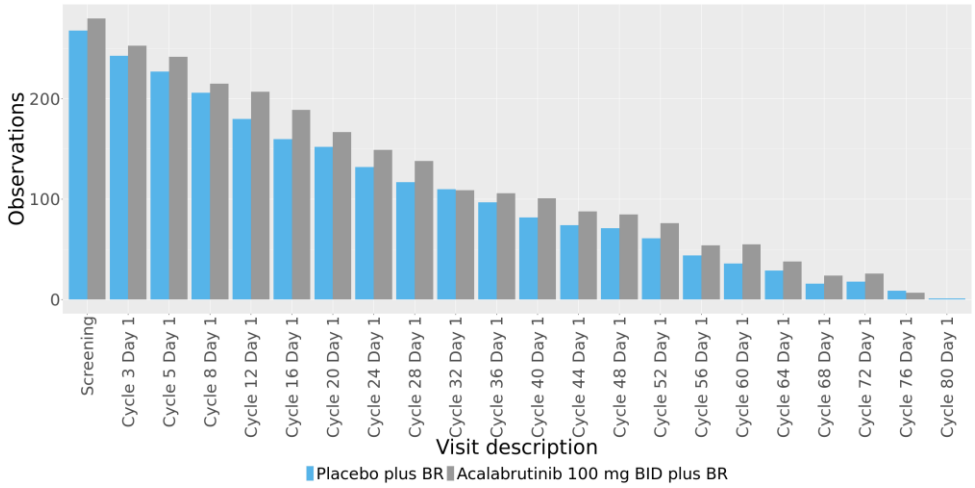
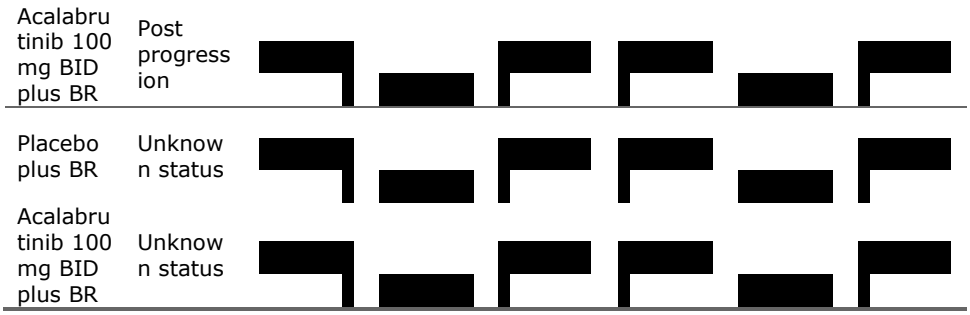


Figure 47 Observations EQ-5D-5L per visit per treatment arm

Table 77 Utility summary statistics

Treatment	Scenario	Subjects	Observations	Mean (SD)	Median (IQR)	Min	Max
Placebo plus BR	At baseline visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	At baseline visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus BR	All visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	All visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled treatments	Pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled treatments	Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus BR	Pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo plus BR	Post progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	Pre progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



F.3 Results - Regression analysis

The results presented in this section were generated from MMRMs with the following covariance structure: Autoregressive - order 1 with Heterogeneity.

Table 78 Goodness of fit

Description	Converges	AIC	BIC
Treatment	TRUE	[redacted]	[redacted]
Progression by ICR status	TRUE	[redacted]	[redacted]
Treatment + Progression by ICR status	TRUE	[redacted]	[redacted]
Treatment * Progression by ICR status	TRUE	[redacted]	[redacted]

The best fitting model in terms of AIC was the model including a term for Progression by ICR status.

F.4 Results - Summary of Statistical fits

The following tables contain summaries of the point estimates and marginal means produced from each model. Complete tables for each model with degrees of freedom and standard errors are in the appendix.

F.4.1 Point Estimates

Summary of point estimates

Table 79 Summary of point estimates

Parameter	Treatment	Progression by ICR status	Treatment + Progression by ICR status	Treatment * Progression by ICR status
(Intercept)	[redacted]	0.892 [SE = 0.005] (p = <0.001)	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	[redacted]		[redacted]	[redacted]

Post progression		0.003 [SE = 0.017] (p = 0.871)		
Acalabrutinib 100 mg BID plus BR: Post progression				
AIC score				

F.4.2 Marginal Means

Parameter	Treatment	Progression by ICR status	Treatment + Progression by ICR status	Treatment * Progression by ICR status
Placebo plus BR				
Acalabrutinib 100 mg BID plus BR				
Pre progression				
Post progression				
Placebo plus BR: Pre progression				
Acalabrutinib 100 mg BID plus BR: Pre progression				
Placebo plus BR: Post progression				
Acalabrutinib 100 mg BID plus BR: Post progression				
AIC score				

Table 80 Summary of marginal means

F.4.3 Appendix

Observations per visit

Table 81 Observations per visit

Visit description	Placebo plus BR	Acalabrutinib 100 mg BID plus BR
Screening		
Cycle 3 Day 1		
Cycle 5 Day 1		
Cycle 8 Day 1		
Cycle 12 Day 1		
Cycle 16 Day 1		
Cycle 20 Day 1		
Cycle 24 Day 1		

Cycle 28 Day 1	[redacted]	[redacted]
Cycle 32 Day 1	[redacted]	[redacted]
Cycle 36 Day 1	[redacted]	[redacted]
Cycle 40 Day 1	[redacted]	[redacted]
Cycle 44 Day 1	[redacted]	[redacted]
Cycle 48 Day 1	[redacted]	[redacted]
Cycle 52 Day 1	[redacted]	[redacted]
Cycle 56 Day 1	[redacted]	[redacted]
Cycle 60 Day 1	[redacted]	[redacted]
Cycle 64 Day 1	[redacted]	[redacted]
Cycle 68 Day 1	[redacted]	[redacted]
Cycle 72 Day 1	[redacted]	[redacted]
Cycle 76 Day 1	[redacted]	[redacted]
Cycle 80 Day 1	[redacted]	[redacted]

F.4.4 Model fits

F.4.4.1 Model terms: Treatment

Table 82 Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Marginal means

Table 83 Marginal means

TRT01P	Estimate	SE	DF	95% LCL	95% UCL
Placebo plus BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acalabrutinib 100 mg BID plus BR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

F.4.4.2 Model terms: Progression by ICR status

Table 84 Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL

(Intercept)	0.892	0.005	4940.0	179.595	<0.001	0.883	0.902
Post progression	0.003	0.017	4940.0	0.163	0.871	-0.031	0.037

Table 85 Marginal means

PROGFLIRC	Estimate	SE	DF	95% LCL	95% UCL
Pre progression	0.892	0.005	4940.0	0.883	0.902
Post progression	0.895	0.018	4940.0	0.860	0.930

F.4.4.3 Model terms: Treatment + Progression by ICR status

Table 86 Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL
(Intercept)	[redacted]						
Acalabrutinib 100 mg BID plus BR	[redacted]						
Post progression	[redacted]						

Table 87 Marginal means

TRT01P	PROGFLIRC	Estimate	SE	DF	95% LCL	95% UCL
Placebo plus BR	Pre progression	[redacted]				
Acalabrutinib 100 mg BID plus BR	Pre progression	[redacted]				
Placebo plus BR	Post progression	[redacted]				
Acalabrutinib 100 mg BID plus BR	Post progression	[redacted]				

F.4.4.4 Model terms: Treatment * Progression by ICR status

Table 88 Parameter Estimates

Parameter	Estimate	SE	DF	t.value	p_value	95% LCL	95% UCL

(Intercept)	0.891	[redacted]					
Acalabrutinib 100 mg BID plus BR	0.002	[redacted]					
Post progression	-0.002	[redacted]					
Acalabrutinib 100 mg BID plus BR: Post progression	0.021	[redacted]					

Table 89 Marginal means

TRT01P	PROGFLIRC	Estimate	SE	DF	95% LCL	95% UCL
Placebo plus BR	Pre progression	[redacted]				
Acalabrutinib 100 mg BID plus BR	Pre progression	[redacted]				
Placebo plus BR	Post progression	[redacted]				
Acalabrutinib 100 mg BID plus BR	Post progression	[redacted]				

Appendix G. Probabilistic sensitivity analyses

Table 90. Overview of parameters in the PSA

Parameter	Point estimate	α	β	Distribution
Patient population parameters				
Population starting age	71,60	71,60	0,19	Normal
Proportion of male	0,71	423,00	175,00	Beta
Height	168,38	168,38	0,39	Normal
Weight	77,04	77,04	0,69	Normal
Survival extrapolation parameters OS/PFS				
BR PFS - Parameter 1	0,85	0,00	0,00	Multivariate normal using Cholesky decomposition of variance-covariance matrices
BR PFS - Parameter 2	0,01	0,00	0,00	
BR PFS - Parameter 3	0,00	0,00	0,00	
BR PFS - Parameter 4	0,00	0,00	0,00	
BR PFS - Parameter 5	0,00	0,00	0,00	
BR OS - Parameter 1	0,77	0,00	0,00	
BR OS - Parameter 2	0,00	0,00	0,00	
BR OS - Parameter 3	0,00	0,00	0,00	
BR OS - Parameter 4	0,00	0,00	0,00	
BR OS - Parameter 5	0,00	0,00	0,00	
Acalabrutinib + BR PFS - Parameter 1	0,85	0,00	0,00	

Acalabrutinib + BR PFS - Parameter 2	0,01	0,00	0,00	
Acalabrutinib + BR PFS - Parameter 3	0,00	0,00	0,00	
Acalabrutinib + BR PFS - Parameter 4	0,00	0,00	0,00	
Acalabrutinib + BR PFS - Parameter 5	0,00	0,00	0,00	
Acalabrutinib + BR OS - Parameter 1	0,83	0,00	0,00	
Acalabrutinib + BR OS - Parameter 2	0,00	0,00	0,00	
Acalabrutinib + BR OS - Parameter 3	0,00	0,00	0,00	
Acalabrutinib + BR OS - Parameter 4	0,00	0,00	0,00	
Acalabrutinib + BR OS - Parameter 5	0,00	0,00	0,00	
Time on treatment				
Acalabrutinib + BR TTD - Parameter 1	0,71	0,00	0,00	
Acalabrutinib + BR TTD - Parameter 2	0,01	0,00	0,00	
Acalabrutinib + BR TTD - Parameter 3	0,00	0,00	0,00	
Acalabrutinib + BR TTD - Parameter 4	0,00	0,00	0,00	
Acalabrutinib + BR TTD - Parameter 5	0,00	0,00	0,00	
Acalabrutinib + BR KM Rituximab	-	0,00	0,00	See KM Sheet
BR KM Rituximab	-	0,00	0,00	See KM Sheet
Bendamustine Time on treatment- Acalabrutinib + BR	5,40	5,40	0,07	Normal
Bendamustine Time on treatment- BR	5,40	5,40	0,07	Normal
Dosing				
RDI of Acalabrutinib In Acalabrutinib + BR	0,89	9129,51	0,00	Gamma
RDI of Bendamustine In Acalabrutinib + BR	0,86	4446,64	0,00	Gamma
RDI of Rituximab In Acalabrutinib + BR	0,93	7513,79	0,00	Gamma

RDI of Bendamustine In BR	0,87	4583,31	0,00	Gamma
RDI of Rituximab In BR	0,91	4754,92	0,00	Gamma
RDI of Rituximab In R-maintenance	0,77	47500,00	0,00	Gamma
Adverse events				
Acalabrutinib + BR: Anaemia	0,05	16,07	281,59	Beta
Acalabrutinib + BR: Cardiac events	0,02	5,88	288,20	Beta
Acalabrutinib + BR: Diarrhoea	0,02	5,10	294,77	Beta
Acalabrutinib + BR: Fatigue	0,02	7,26	295,06	Beta
Acalabrutinib + BR: Febrile neutropenia	0,03	8,04	289,65	Beta
Acalabrutinib + BR: Infections	0,01	2,16	306,53	Beta
Acalabrutinib + BR: Leukopenia	0,05	16,07	281,59	Beta
Acalabrutinib + BR: Lymphopenia	0,03	8,04	289,65	Beta
Acalabrutinib + BR: Neutropenia	0,34	100,97	196,00	Beta
Acalabrutinib + BR: Peripheral sensory Neuropathy	0,00	0,00	0,00	Beta
Acalabrutinib + BR: Pneumonia	0,05	15,29	284,48	Beta
Acalabrutinib + BR: Thrombocytopenia	0,05	16,07	281,59	Beta
BR: Anaemia	0,06	16,86	278,97	Beta
BR: Cardiac events	0,01	2,94	291,11	Beta
BR: Diarrhoea	0,02	5,88	288,20	Beta
BR: Fatigue	0,03	8,82	285,29	Beta
BR: Febrile neutropenia	0,01	2,94	291,11	Beta
BR: Infections	0,00	0,00	0,00	Beta
BR: Leukopenia	0,05	16,07	281,59	Beta

BR: Lymphopenia	0,05	16,07	281,59	Beta
BR: Neutropenia	0,35	105,20	191,98	Beta
BR: Peripheral sensory Neuropathy	0,00	0,00	0,00	Beta
BR: Pneumonia	0,04	11,77	282,38	Beta
BR: Thrombocytopenia	0,05	15,29	284,48	Beta
Disutility: Anaemia	-0,01	99,29	14085,42	Beta
Disutility: Cardiac events	-0,22	77,78	275,77	Beta
Disutility: Diarrhoea	-0,10	89,70	789,69	Beta
Disutility: Fatigue	-0,04	96,16	2434,42	Beta
Disutility: Febrile neutropenia	-0,01	98,59	6943,27	Beta
Disutility: Infections	-0,22	77,78	275,77	Beta
Disutility: Leukopenia	-0,04	95,76	2184,19	Beta
Disutility: Lymphopenia	-0,07	93,44	1344,03	Beta
Disutility: Neutropenia	-0,03	96,77	2927,23	Beta
Disutility: Peripheral sensory Neuropathy	-0,09	91,21	957,21	Beta
Disutility: Pneumonia	-0,06	94,14	1529,00	Beta
Disutility: Thrombocytopenia	-0,04	96,16	2434,42	Beta
Duration: Anaemia	9,73	9,73	0,97	Normal
Duration: Cardiac events	14,00	14,00	1,40	Normal
Duration: Diarrhoea	6,23	6,23	0,62	Normal
Duration: Fatigue	23,03	23,03	2,30	Normal
Duration: Febrile neutropenia	8,33	8,33	0,83	Normal
Duration: Infections	14,00	14,00	1,40	Normal

Duration: Leukopenia	9,45	9,45	0,95	Normal
Duration: Lymphopenia	16,73	16,73	1,67	Normal
Duration: Neutropenia	9,10	9,10	0,91	Normal
Duration: Peripheral sensory Neuropathy	148,68	148,68	14,87	Normal
Duration: Pneumonia	16,03	16,03	1,60	Normal
Duration: Thrombocytopenia	10,08	10,08	1,01	Normal
Utility				
Utility Progression free	0,89	246,97	29,90	Beta
Utility Progressed disease	0,82	15,04	3,28	Beta
HCRU frequencies				
PFS frequency: Full blood count	0,33	100,00	0,00	Gamma
PFS frequency: X-ray	0,00	0,00	0,00	Gamma
PFS frequency: Blood glucose	0,00	0,00	0,00	Gamma
PFS frequency: Lactate dehydrogenase	0,33	100,00	0,00	Gamma
PFS frequency: Lymphocyte count	0,00	0,00	0,00	Gamma
PFS frequency: Bone marrow exam	0,00	0,00	0,00	Gamma
PFS frequency: Haematologist visit	0,33	100,00	0,00	Gamma
PFS frequency: Inpatient visit (medical)	0,00	0,00	0,00	Gamma
PFS frequency: Biopsy	0,00	0,00	0,00	Gamma
PFS frequency: Blood transfusion	0,00	0,00	0,00	Gamma
PFS frequency: Platelet transfusion	0,00	0,00	0,00	Gamma
PD frequency: Full blood count	0,67	100,00	0,01	Gamma
PD frequency: X-ray	0,17	100,00	0,00	Gamma

PD frequency: Blood glucose	0,00	0,00	0,00	Gamma
PD frequency: Lactate dehydrogenase	0,67	100,00	0,01	Gamma
PD frequency: Lymphocyte count	0,00	0,00	0,00	Gamma
PD frequency: Bone marrow exam	0,00	0,00	0,00	Gamma
PD frequency: Haematologist visit	0,50	100,00	0,01	Gamma
PD frequency: Inpatient visit (medical)	0,17	100,00	0,00	Gamma
PD frequency: Biopsy	0,00	0,00	0,00	Gamma
PD frequency: Blood transfusion	0,83	100,00	0,01	Gamma
PD frequency: Platelet transfusion	0,00	0,00	0,00	Gamma
Parameters for subsequent treatments				
Acalabrutinib + BR- Proportion of non fatal PFS	0,69	57,00	26,00	Beta
BR- Proportion of non fatal PFS	0,85	99,00	18,00	Beta
Ibrutinib Duration of Subsequent treatment	22,00	22,00	3,60	Normal
R-CHOP Duration of Subsequent treatment	5,52	5,52	0,55	Normal
R-Lenalidomide Duration of Subsequent treatment	11,10	11,10	4,23	Normal
Rituximab Duration of Subsequent treatment	1,00	1,00	0,10	Normal
Lenalidomide Duration of Subsequent treatment	11,10	11,10	4,23	Normal
Venetoclax Duration of Subsequent treatment	3,20	3,20	2,58	Normal
Total use of 1L subsequent treatment from Acalabrutinib + BR group	0,53	30,00	27,00	Beta
Total use of 1L subsequent treatment from BR group	0,89	88,00	11,00	Beta
Acalabrutinib + BR: Subsequent 1L Ibrutinib	0,00	0,00	0,00	Dirichlet
Acalabrutinib + BR: Subsequent 1L R-CHOP	0,00	0,00	0,57	Dirichlet
Acalabrutinib + BR: Subsequent 1L Lenalidomide + Rituximab	0,20	0,00	3,34	Dirichlet

Acalabrutinib + BR: Subsequent 1L Rituximab	0,20	0,00	5,11	Dirichlet
Acalabrutinib + BR: Subsequent 1L Venetoclax	0,60	0,00	17,21	Dirichlet
Acalabrutinib + BR: Subsequent 1L Lenalidomide	0,00	0,00	0,00	Dirichlet
BR: Subsequent 1L Ibrutinib	0,80	0,00	66,24	Dirichlet
BR: Subsequent 1L R-CHOP	0,00	0,00	0,00	Dirichlet
BR: Subsequent 1L Lenalidomide + Rituximab	0,10	0,00	9,05	Dirichlet
BR: Subsequent 1L Rituximab	0,05	0,00	11,63	Dirichlet
BR: Subsequent 1L Venetoclax	0,05	0,00	3,46	Dirichlet
BR: Subsequent 1L Lenalidomide	0,00	0,00	0,00	Dirichlet
Total use of 2L subsequent treatment from Acalabrutinib + BR group	0,18	10,00	47,00	Beta
Total use of 2L subsequent treatment from BR group	0,32	32,00	67,00	Beta
Acalabrutinib + BR: Subsequent 2L Ibrutinib	0,20	0,00	2,24	Dirichlet
Acalabrutinib + BR: Subsequent 2L R-CHOP	0,00	0,00	0,00	Dirichlet
Acalabrutinib + BR: Subsequent 2L Lenalidomide + Rituximab	0,20	0,00	1,69	Dirichlet
Acalabrutinib + BR: Subsequent 2L Rituximab	0,05	0,00	0,07	Dirichlet
Acalabrutinib + BR: Subsequent 2L Venetoclax	0,45	0,00	1,77	Dirichlet
Acalabrutinib + BR: Subsequent 2L Lenalidomide	0,10	0,00	1,46	Dirichlet
BR: Subsequent 2L Ibrutinib	0,21	0,00	10,66	Dirichlet
BR: Subsequent 2L R-CHOP	0,00	0,00	0,00	Dirichlet
BR: Subsequent 2L Lenalidomide + Rituximab	0,11	0,00	3,93	Dirichlet
BR: Subsequent 2L Rituximab	0,05	0,00	3,11	Dirichlet
BR: Subsequent 2L Venetoclax	0,53	0,00	15,94	Dirichlet
BR: Subsequent 2L Lenalidomide	0,11	0,00	4,82	Dirichlet

Total use of 3L subsequent treatment from Acalabrutinib + BR group	0,05	3,00	54,00	Beta
Total use of 3L subsequent treatment from BR group	0,13	13,00	86,00	Beta
Acalabrutinib + BR: Subsequent 3L Ibrutinib	0,00	0,00	0,00	Dirichlet
Acalabrutinib + BR: Subsequent 3L R-CHOP	0,00	0,00	0,00	Dirichlet
Acalabrutinib + BR: Subsequent 3L Lenalidomide + Rituximab	0,06	0,00	0,02	Dirichlet
Acalabrutinib + BR: Subsequent 3L Rituximab	0,06	0,00	1,56	Dirichlet
Acalabrutinib + BR: Subsequent 3L Venetoclax	0,82	0,00	5,44	Dirichlet
Acalabrutinib + BR: Subsequent 3L Lenalidomide	0,06	0,00	0,11	Dirichlet
BR: Subsequent 3L Ibrutinib	0,00	0,00	0,13	Dirichlet
BR: Subsequent 3L R-CHOP	0,00	0,00	0,01	Dirichlet
BR: Subsequent 3L Lenalidomide + Rituximab	0,06	0,00	3,11	Dirichlet
BR: Subsequent 3L Rituximab	0,06	0,00	0,29	Dirichlet
BR: Subsequent 3L Venetoclax	0,82	0,00	6,65	Dirichlet
BR: Subsequent 3L Lenalidomide	0,06	0,00	0,72	Dirichlet

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

[Follow section 3 of the methods guide. Describe how the literature search was performed. Explain the selection of the search criteria and terms used, search filters, and the inclusion and exclusion criteria. Sufficient details should be provided so that the results may be reproduced.
Literature searches that are more than one year old are generally not accepted. If this is the case, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

If an existing/global systematic literature review (SLR) is (re)used the appendix must be filled out with data/information from such SLR and it must be clear how the SLR has been adapted to the current application. The inclusion and exclusion criteria, PRISMA flowchart, and list of excluded full text references should reflect the purpose of the application. Thus, unedited technical reports or SLRs will not be accepted in/as the appendix. Please find an editable PRISMA flowchart at the end of this document. This diagram is to be used when existing SLRs are (re)used, so it is clear how it has been locally adapted, i.e. how many references are included and excluded from the original SLR. As mentioned above, if the literature search is more than a year old, a new search (e.g. in PubMed) should be carried out for more recent literature on the intervention and chosen comparator(s).

Objective of the literature search: What questions is the literature search expected to answer?

Databases/other sources: Fill in the databases and other sources, e.g. conference material used in the literature search.]

Table 91 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy

Database	Platform/source	Relevant period for the search	Date of search completion
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 92 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 93 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

[Describe the development of the search strategy and search string. Specify the inclusion and exclusion criteria for the search and justify (e.g. patient population, intervention, comparator, outcomes, study design, language, time limits, etc.).]

[The search must be documented with exact search strings line by line as run, incl. results, for each database.]

Table 94 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517

No.	Query	Results
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

[Describe the selection process, incl. number of reviewers and how conflicts were resolved. Provide a table with criteria for inclusion or exclusion. If the table relates to an existing SLR broader in scope, please indicate which criteria are relevant for the current application.]

Table 95 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

[Insert the PRISMA flow diagram(s) here (see example here) or use the editable diagram at the end of this document. If an existing SLR is used, the editable diagram is to be used, so it is clear how many references have been included and excluded from the original SLR.]

Table 96 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

[Please provide in a list or table the references that were excluded during fulltext screening along with a short reason. If using an existing, locally adapted SLR, please fill in the references originally included in the SLR but excluded in the current application.]

H.1.4 Quality assessment

[Describe strengths and weaknesses of the literature search performed.]

H.1.5 Unpublished data

[The quality of any unpublished data must be specifically addressed and a publication plan for unpublished data must be submitted].

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A

Table 97 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase			dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Table 98 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 99 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

N/A

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A.

J.1.1 Example: Systematic search for […]

N/A

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

Appendix K. High-risk subgroup analysis presented at EHA

Abstract available here: https://library.ehaweb.org/eha/2025/eha2025-congress/4159310/martin.dreyling.efficacy.of.rituximab-bendamustine.with.or.without.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D2%2Asearch%3Dacalabrutinib

Efficacy of Rituximab-Bendamustine With or Without Acalabrutinib in Patients With Untreated, High-risk Mantle Cell Lymphoma: An Analysis of the Phase 3 ECHO Trial

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[1]Medizinische Klinik III, Klinikum der Universitaet Munchen, Muenchen, Germany; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli" and Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy; [3]Fundaleu, Clinical Research Center Buenos Aires, Buenos Aires, Argentina; [4]Service d'Hématologie Clinique et de Thérapie Cellulaire, CHU Bordeaux, Bordeaux, France; [5]Department of Hematology Hospital General Universitario Gregorio Marañón, Madrid, Spain; [6]AstraZeneca, Cambridge, United Kingdom; [7]AstraZeneca, Gaithersburg, MD, USA; [8]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ, USA

Presented at the European Hematology Association (EHA) Annual Meeting; June 12–15, 2025; Milan, Italy

Introduction

- Triple-combination therapy with ABR significantly improved PFS over PBR (HR 0.73; 95% CI 0.57, 0.94; *P* = .0160) in older patients with previously untreated MCL in the randomized, double-blind, placebo-controlled, phase 3 ECHO trial (NCT02972840)[1]
- Patients with high-risk features, namely Ki-67 index ≥30%, high-risk MIPI, blastoid/pleomorphic histology, or *TP53* mutation, tend to respond poorly to conventional treatment[2]
- Our objective was to examine efficacy outcomes in patients with high-risk MCL in the ECHO trial

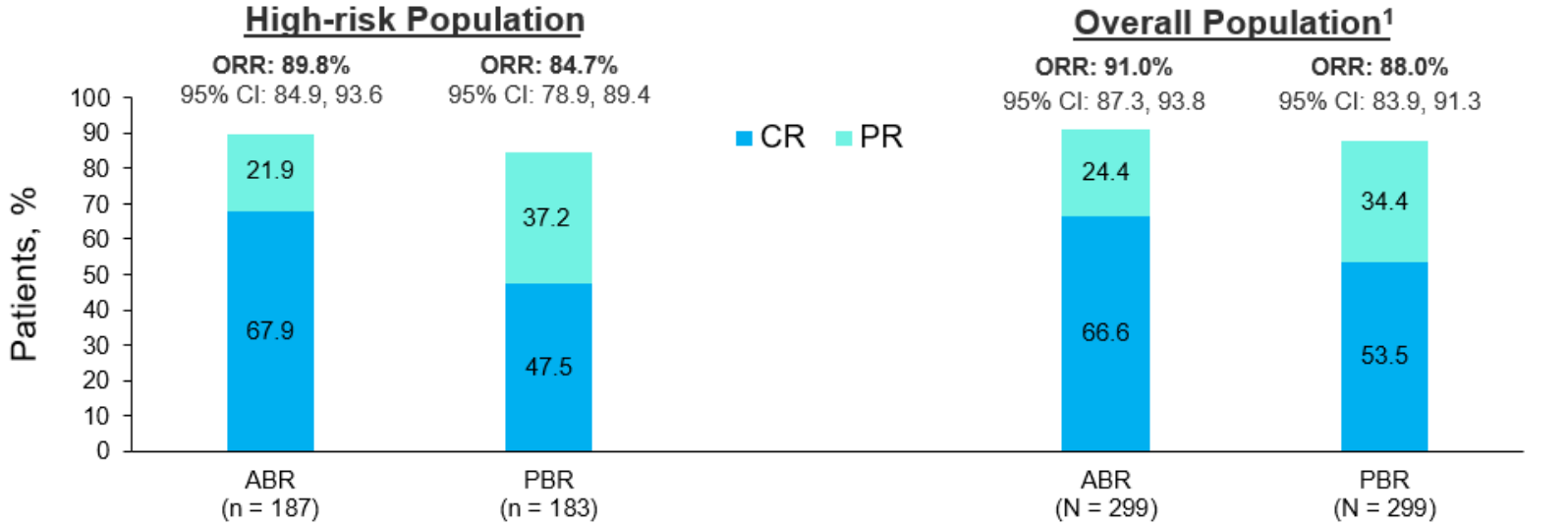
Patients

Characteristic, % [n]	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)	Total (N = 598)
High-risk MIPI (6–11)	24.1 [72]	24.4 [73]	24.2 [145]
Ki-67 ≥30%	46.5 [139]	49.2 [147]	47.8 [286]
Ki-67 ≥50%	20.7 [62]	24.7 [74]	22.7 [136]
Blastoid/pleomorphic histology	13.7 [41]	12.7 [38]	13.2 [79]
TP53 mutation	7.4 [22]	9.7 [29]	8.5 [51]
TP53 status missing	60.2 [180]	62.5 [187]	61.4 [367]
Total high-risk	**62.5 [187]**	**61.2 [183]**	**61.9 [370]**

Demographics and Baseline Characteristics of High-risk and Overall Study Populations

	High-risk population			Overall population[1]		
Characteristic[a]	Acalabrutinib + BR (n = 187)	Placebo + BR (n = 183)	Total (N = 370)	Acalabrutinib + BR (n = 299)	Placebo + BR (n = 299)	Total (N = 598)
Age, median (range), years	72.0 (65–85)	72.0 (65–86)	72.0 (65–86)	71.0 (65–85)	71.0 (65–86)	71.0 (65–86)
Age ≥75 years	31.0 [58]	27.9 [51]	29.5 [109]	28.1 [84]	25.8 [77]	26.9 [161]
Male	75.4 [141]	69.4 [127]	72.4 [268]	71.6 [214]	69.9 [209]	70.7 [423]
ECOG PS						
0	50.3 [94]	45.4 [83]	47.8 [177]	52.2 [156]	46.8 [140]	49.5 [296]
1	43.9 [82]	43.7 [80]	43.8 [162]	43.1 [129]	44.1 [132]	43.6 [261]
2	4.8 [9]	9.8 [18]	7.3 [27]	4.0 [12]	7.7 [23]	5.9 [35]
Tumor bulk ≥5 cm	38.5 [72]	43.7 [80]	41.1 [152]	37.5 [112]	37.8 [113]	37.6 [225]
LDH > ULN	24.1 [45]	26.2 [48]	25.1 [93]	17.4 [52]	18.1 [54]	17.7 [106]
Ann Arbor stage						
I	0	0.5 [1]	0.3 [1]	0.7 [2]	0.3 [1]	0.5 [3]
II	7.5 [14]	4.9 [9]	6.2 [23]	5.0 [15]	3.7 [11]	4.3 [26]
III	8.6 [16]	7.7 [14]	8.1 [30]	10.4 [31]	8.0 [24]	9.2 [55]
IV	84.0 [157]	86.9 [159]	85.4 [316]	83.9 [251]	88.0 [263]	86.0 [514]
High-risk MIPI (6–11)	38.5 [72]	39.9 [73]	39.2 [145]	24.1 [72]	24.4 [73]	24.2 [145]

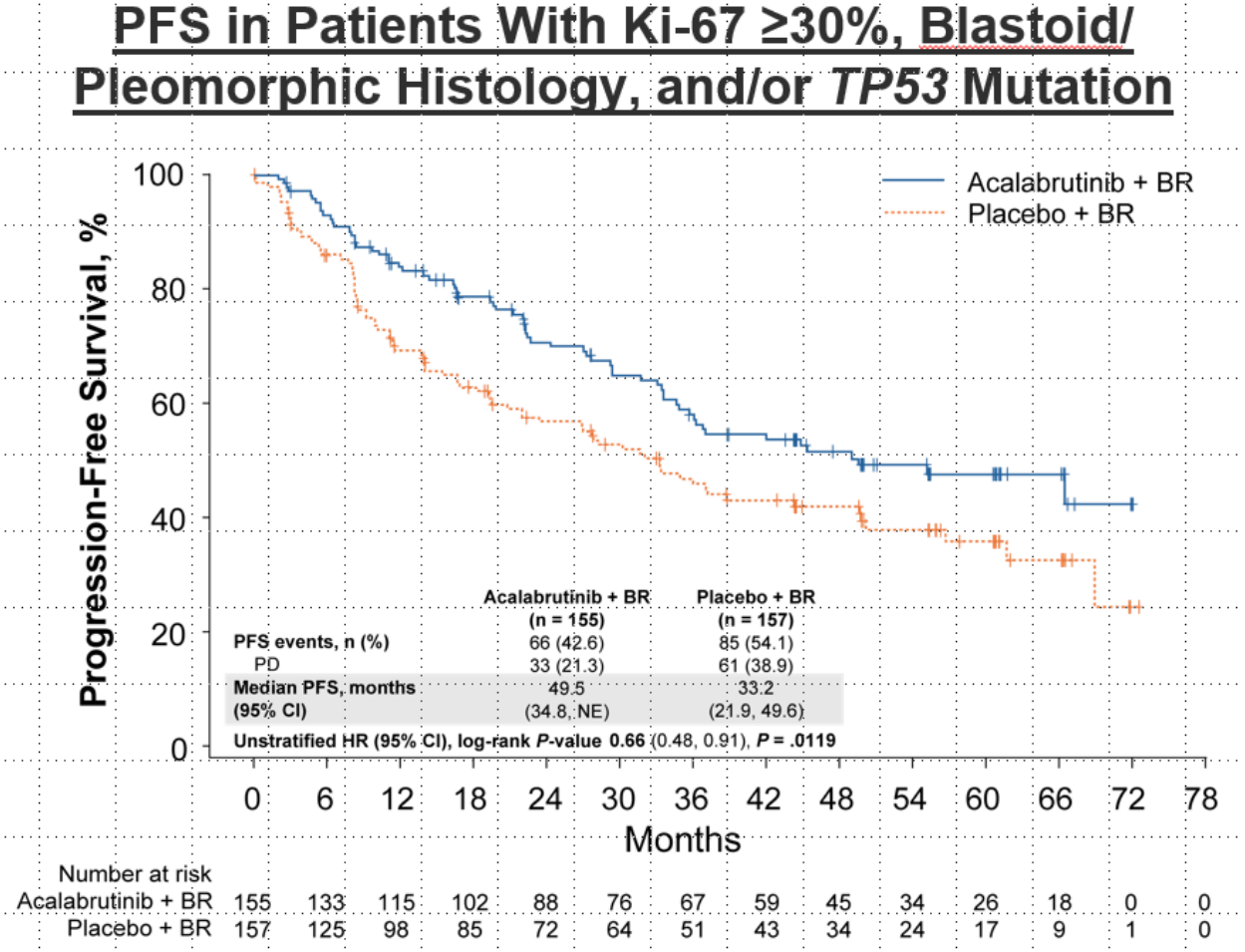
Best Response of CR Significantly Higher With ABR in Patients With High-risk MCL



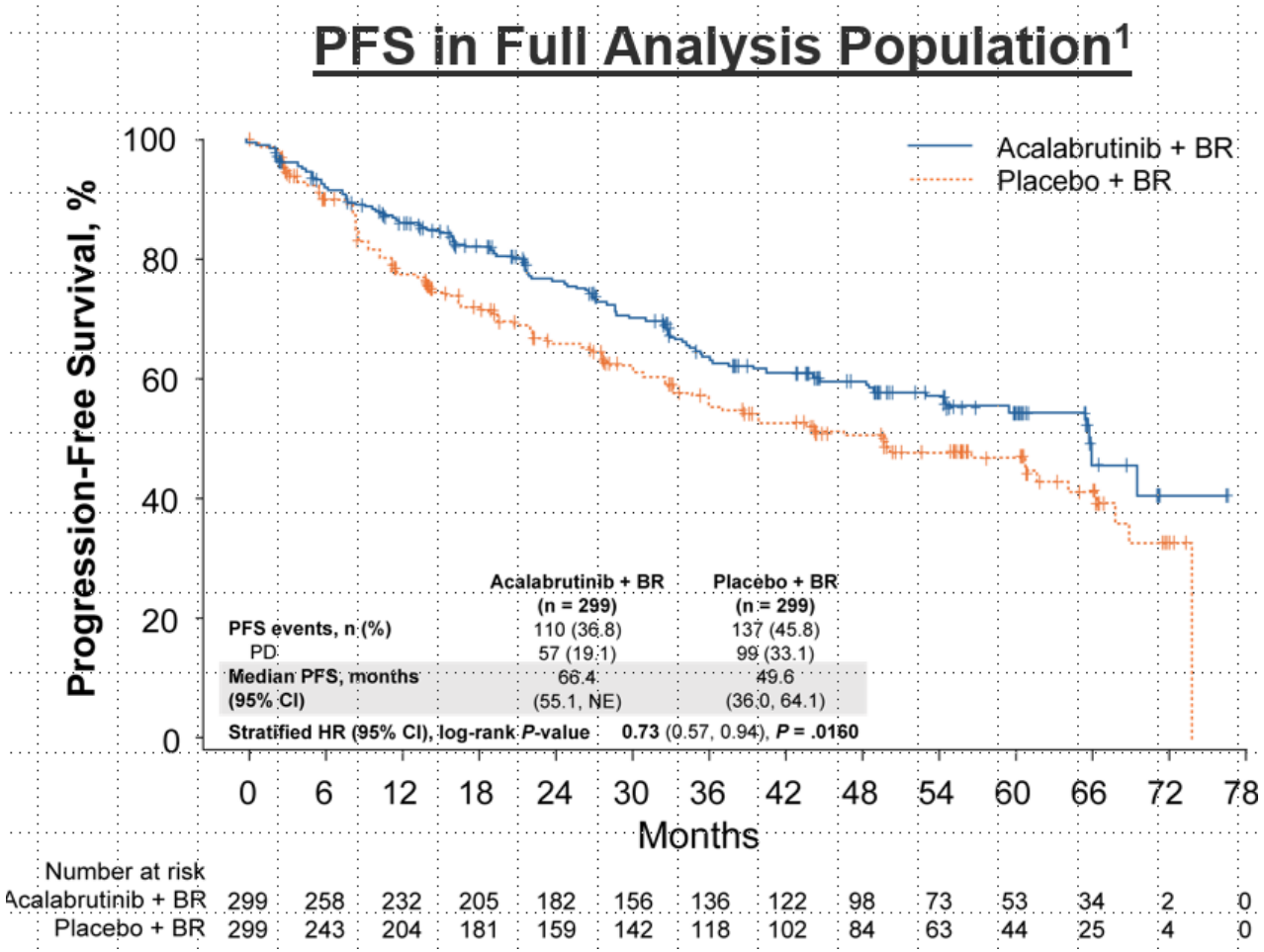
	ORR	CR
Difference (ABR vs PBR)	5.1%	20.4%
95% CI	-1.7, 12.1	10.4, 30.0
P-value	.1382	**<.0001**

	ORR
Difference (ABR vs PBR)	3.0%
95% CI	-2.0, 8.1
P-value	.2196

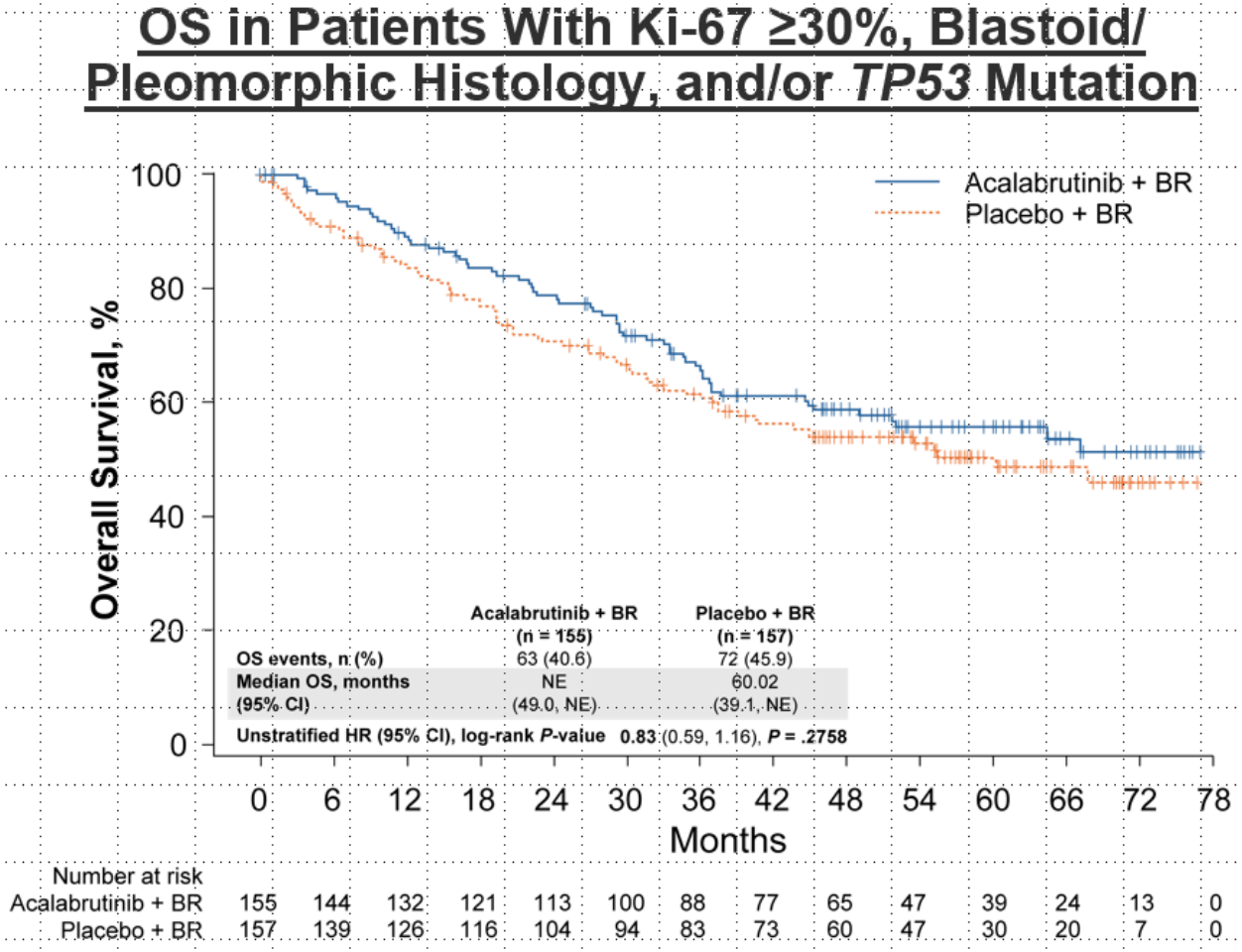
PFS in Patients With Ki-67 ≥30%, Blastoid/ Pleomorphic Histology, and/or *TP53* Mutation



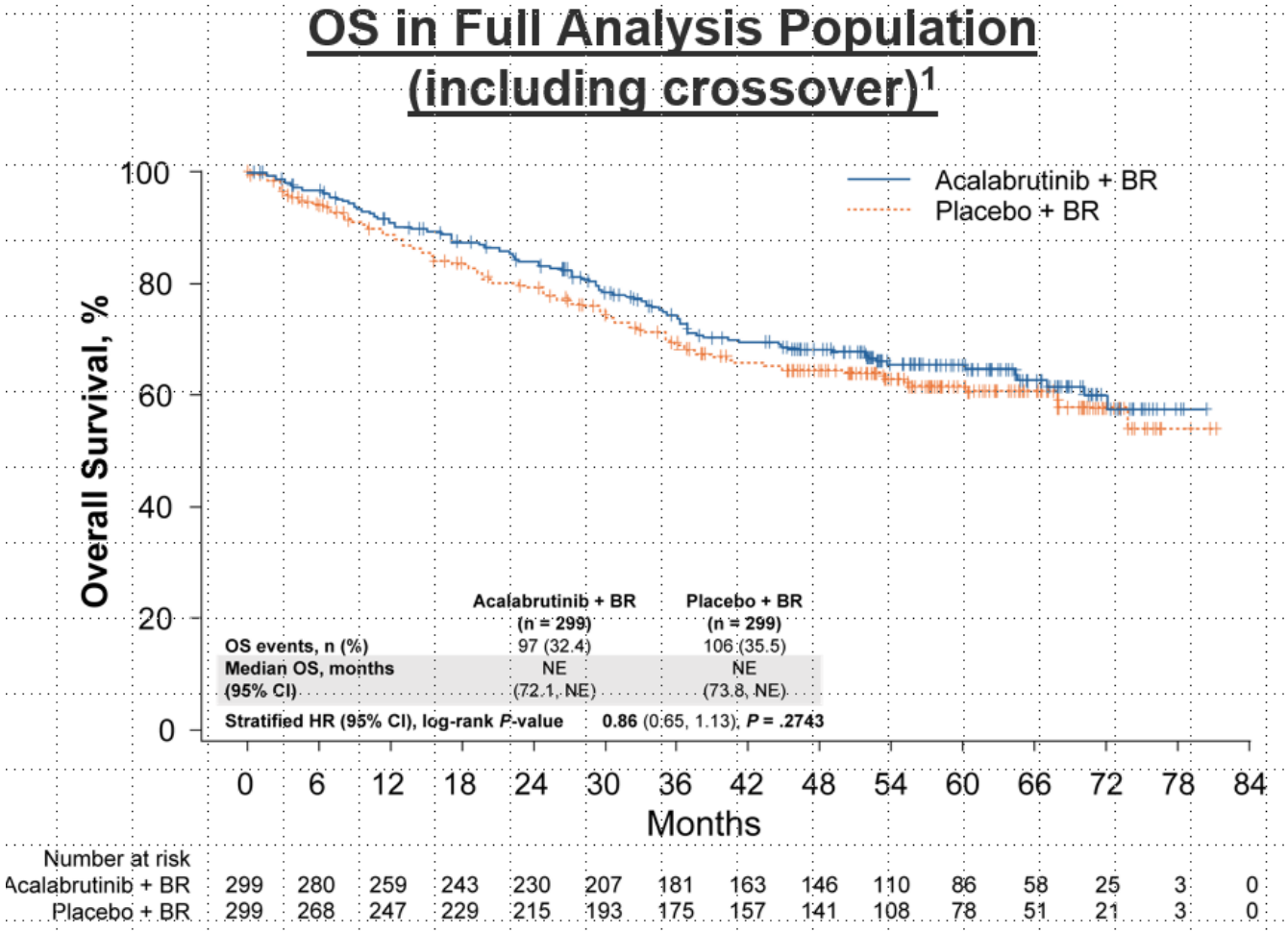
PFS in Full Analysis Population[1]



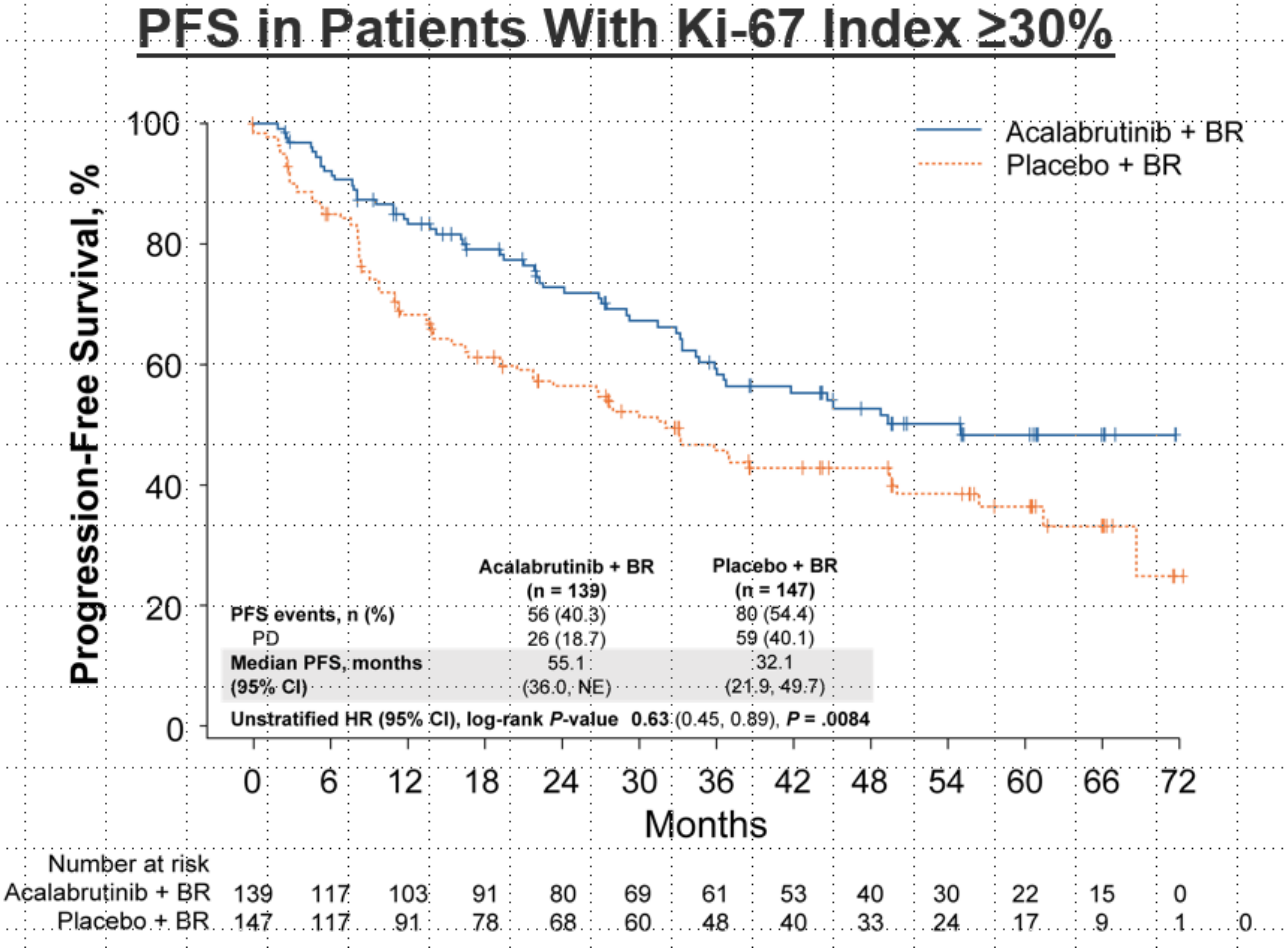
OS in Patients With Ki-67 ≥30%, Blastoid/ Pleomorphic Histology, and/or *TP53* Mutation



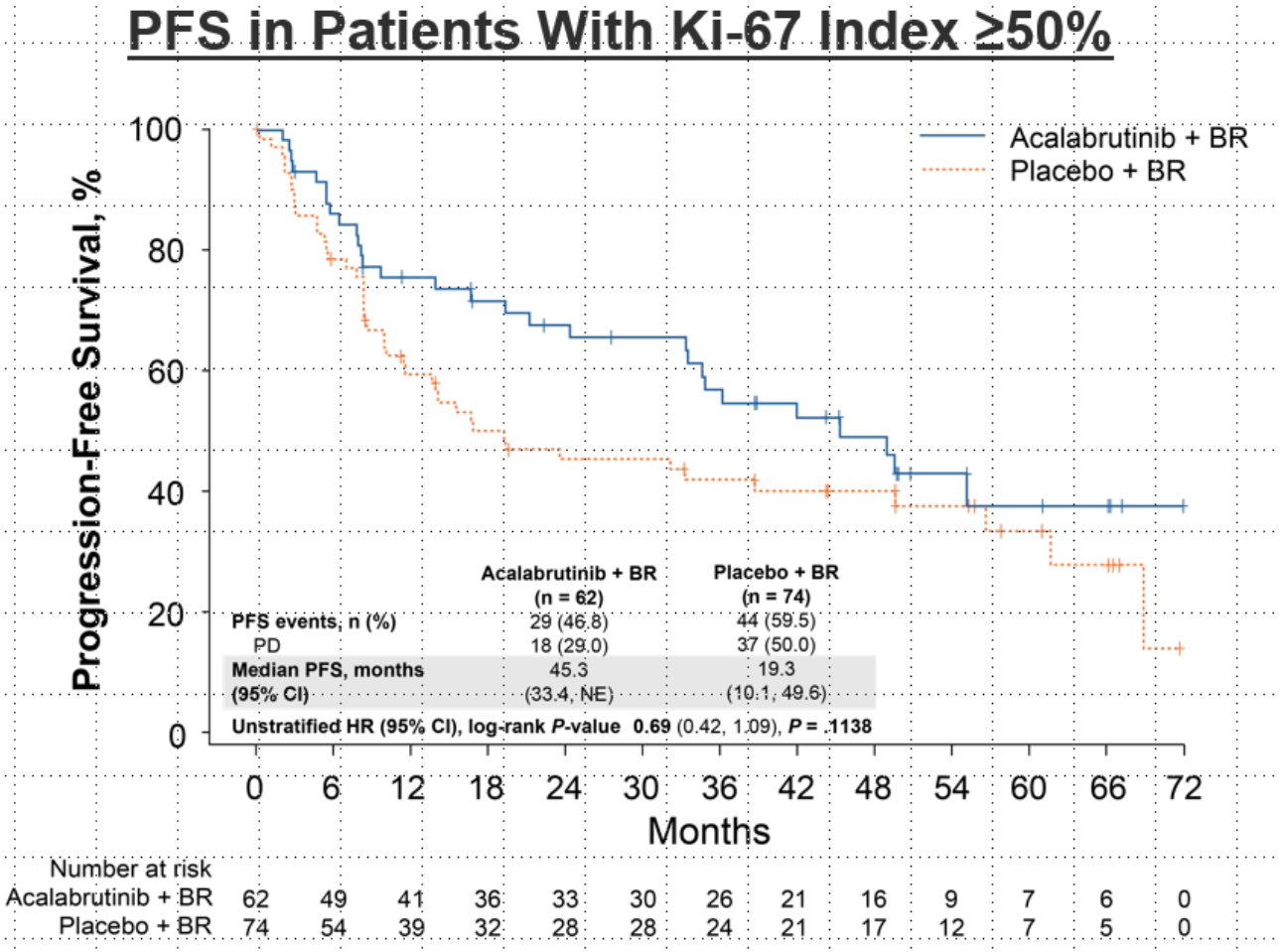
OS in Full Analysis Population (including crossover)[1]



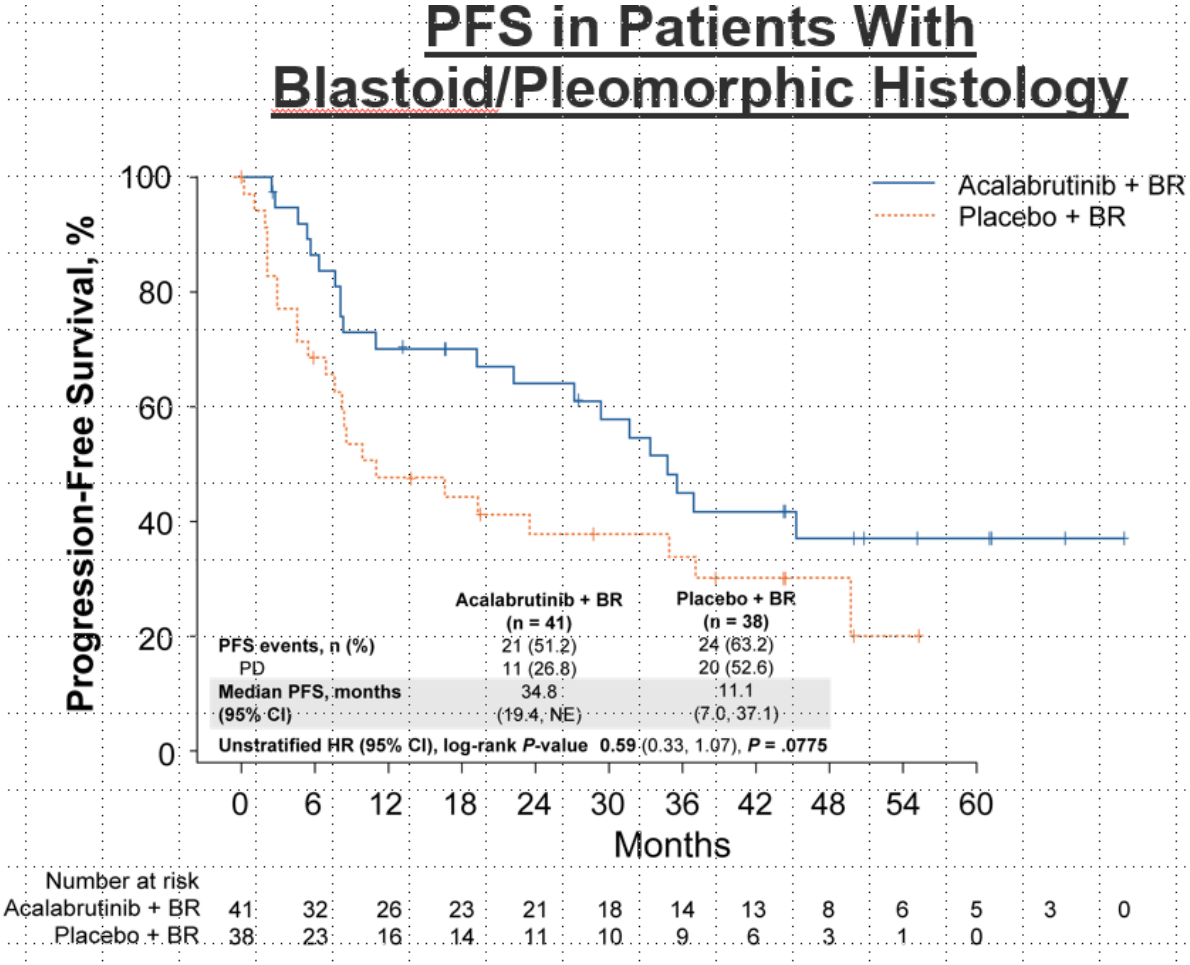
PFS in Patients With Ki-67 Index ≥30%



PFS in Patients With Ki-67 Index ≥50%



PFS in Patients With Blastoid/Pleomorphic Histology



Conclusions

- ABR significantly improved PFS in patients with high-risk MCL compared with PBR
- A significantly higher proportion of patients in the ABR arm had CR compared with the PBR arm among patients with high-risk MCL
- The hazard ratio for OS comparing ABR with PBR was 0.87 (95% CI: 0.64, 1.19)
- Patients with biological high-risk features had a numerically more pronounced benefit in PFS (blastoid/pleomorphic: HR 0.59; Ki-67 ≥30%: HR 0.63) compared with the total study population (HR 0.73)
  - Data on *TP53* alterations were incomplete and did not allow for meaningful analysis
- Efficacy outcomes in the subgroup of patients with high-risk MCL aligned with those in the overall ECHO study population

ABR, acalabrutinib-bendamustine-rituximab; CI, confidence interval; CR, complete response; HR, hazard ratio; MCL, mantle cell lymphoma; NE, not estimable; OS, overall survival; PBR, placebo-bendamustine-rituximab; PFS, progression-free survival.

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