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

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Technology appraisal committee C [3 February 2026]

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Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on mantle cell lymphoma

Causes and Epidemiology

- MCL rare subtype of NHL, approx. 3–10% of NHL in Western countries
- 1.6% of diagnosed haematological malignancies in the UK, approx. 590 new cases diagnosed each year
- More likely to occur at older ages with median age of at diagnosis 72 years

Diagnosis and classification

- Typically a high grade (fast growing) lymphoma
- Most patients diagnosed at advanced stages and 87.9% diagnosed with Stage IV disease

Symptoms and prognosis

- The most common symptom is painless swelling in the lymph nodes, with various other symptoms depending on the lymphatic sites affected
- Generally incurable - relapsing disease course
- Poor survival with overall 5-year survival rate from diagnosis 47.4% (2022) across all patients with MCL
- Management of advanced MCL is based on suitability for ASCT. Those for whom ASCT is not suitable are our focus for this appraisal.

Abbreviations: ASCT, autologous stem cell transplant; MCL, mantle cell lymphoma; NHL, Non-Hodgkin lymphoma

Patient perspectives

Increasing amount of progression-free time between relapses is an important outcome for patients

Submissions from Lymphoma Action and a patient expert

- The psychological impact of a diagnosis of lymphoma is enormous. Patients have described insomnia, anxiety and a constant fear of dying.
- MCL usually responds well to treatment, but is likely to relapse. Multiple relapses mean patients may need many different treatment options.
- In most cases treatment would be chemotherapy in combination with immunotherapy. Treatments can be very difficult to endure and patients struggle with side effects.
- Some current treatment options can only be given intravenously which require repeated hospital appointments. This can be incredibly disruptive, so oral treatment options are preferred.
- Patients would welcome a new treatment which prolongs time between relapses, but also has tolerable side effects

"…anxious about anything which would impact on my ability to have contact with grandchildren etc. but if it were to give a longer 1st remission, any additional risks would be tolerable"

"Chemotherapy appeared to be the best plan for me personally. I did get into serious trouble with immune system failure during my rituximab maintenance and had recurrent pneumonias"

Abbreviations: MCL, mantle cell lymphoma

Clinical perspectives

Improving 1st line treatment options could lead to better patient outcomes

Submissions from the Royal College of Pathologist and clinical experts from University Hospitals Plymouth NHS Trust and Gloucestershire Hospitals NHS Foundation Trust

- MCL is an incurable blood cancer with an inevitable pattern of relapse.
- Patients experience their best response to treatment in the first line setting, so optimising this is key to improving outcomes.
- Overall survival is the most clinically significant outcome, progression-free survival is a well-accepted clinical endpoint in clinical trials.
- Current SoC is induction chemotherapy and maintenance rituximab with ibrutinib monotherapy at relapse. Ibrutinib's toxicities include cardiac side-effects that are much rarer with acalabrutinib.
- Acalabrutinib is commonly used in CLL, so clinicians are familiar with management and additional training is not likely to be required.
- In frail patients, acalabrutinib is likely to be poorly tolerated.

"There is currently no way for patients to access BTK inhibitors in the 1st line setting in the UK. The triplet combination of bendamustine, acalabrutinib and rituximab could become a standard of care 1st line treatment option for this group of patients"

"Acalabrutinib has a more favourable toxicity profile compared to ibrutinib which is the only currently available BTKi in the UK for MCL (as 2nd line)"

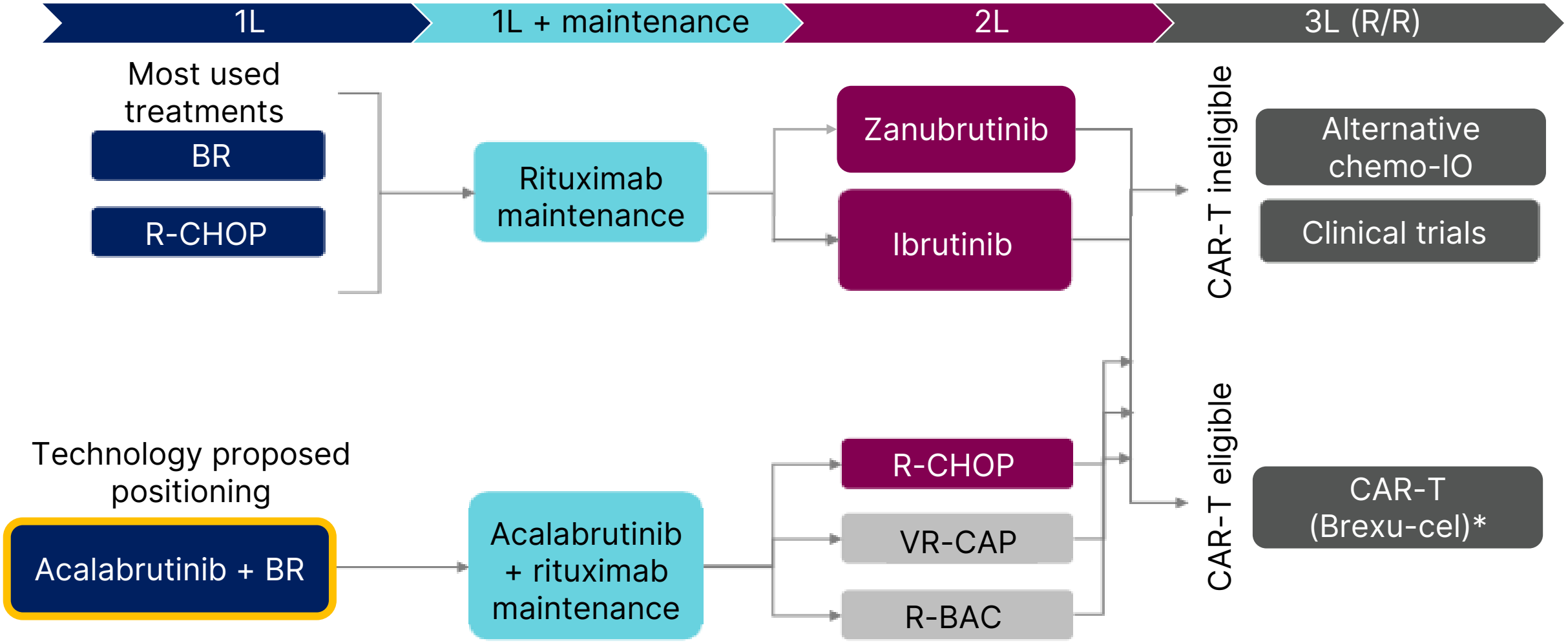
NICE Abbreviations: BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; SoC, standard of care

Equality considerations

- No equality issues were identified during scoping, in the company submission or in the EAG report
- Related appraisal ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502) noted that ibrutinib would offer an alternative to less effective but better tolerated chemotherapy agents for older or frailer people

Are there any equalities issues which can be addressed in this appraisal?

Treatment pathway – people with MCL not eligible for ASCT



Pathway adapted from Figure 2 in CS (Jan 2025)

Is the treatment pathway accurate?

*Brexu-cel is in the CDF and a negative FDG was issued Dec 2025 (ID6325). Previous topics have excluded CDF treatments as subsequent treatments, e.g. TA874.

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Abbreviations: 1L, first line; 2L, second line; 3L, third line; ASCT, autologous stem cell transplant; BR, bendamustine + rituximab; CAR-T, chimeric antigen receptor T-cell; CDF, Cancer Drugs Fund; CS, company submission; R-BAC, Rituximab, bendamustine, cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R/R, relapsed/refractory; VR-CAP, Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone

Acalabrutinib (Calquence, AstraZeneca)

Marketing authorisation	• Acalabrutinib in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are not eligible for autologous stem cell transplant (ASCT) • UK marketing authorisation was granted November 2025
Mechanism of action	• Acalabrutinib is a selective inhibitor of Bruton's tyrosine kinase (BTK) • In B-cells, BTK signalling results in B-cell survival and proliferation, and is required for cellular adhesion, trafficking, and chemotaxis • Acalabrutinib and its active metabolite, ACP-5862, bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK
Administration	• Acalabrutinib is taken orally with water at approximately the same time each day • Recommended dose is 100 mg twice daily (total daily dose 200 mg), with a dose interval of approximately 12 hours • Bendamustine and rituximab are administered via intravenous infusion
Price	• List price £5,059 per pack of 60 tablets • List price for 12 months of treatment £61,593* • A confidential patient access scheme is applicable

*Assuming an average of 30.4375 days in a month

Key issues

No.	Issue	ICER impact
1	Economic model structure	Unknown
2a	Censoring of COVID-19 deaths	Moderate
2b	Extrapolation of PFS and OS data	
3	Progressed disease utility value	Large
4a	Inclusion of 3L treatment costs	Large
4b	Subsequent treatment durations and distributions	Large

Abbreviations: 2L, second line; 3L, third line; PD, progressed disease; PFS, progression-free survival

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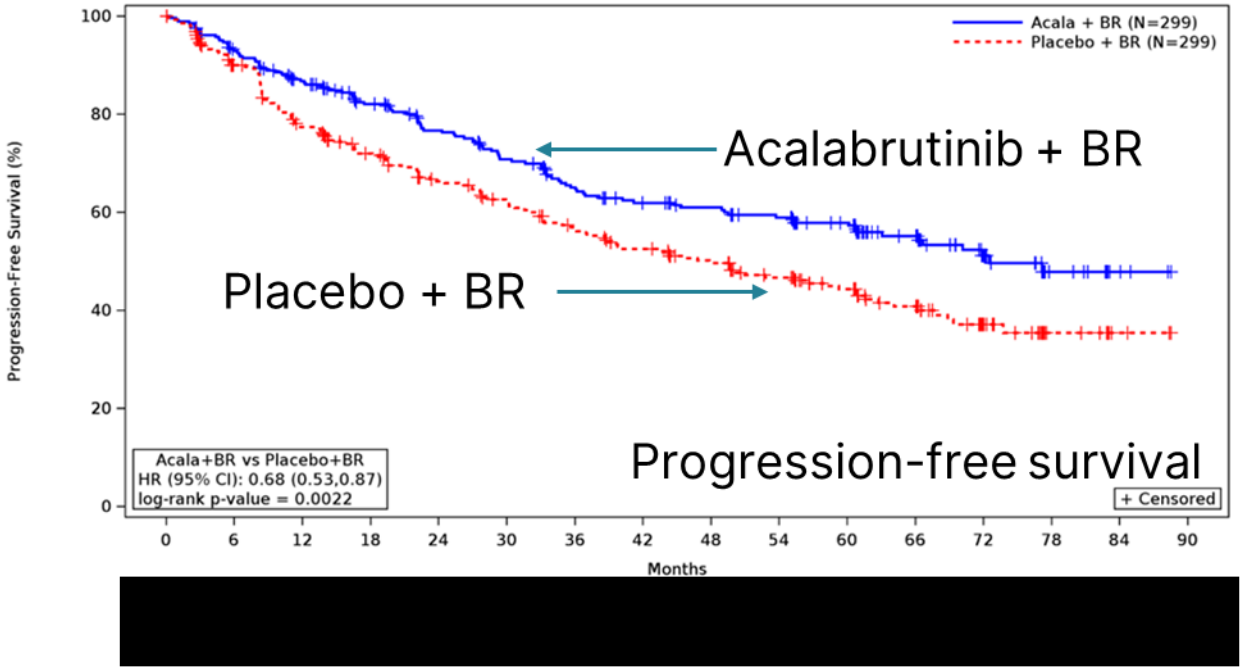
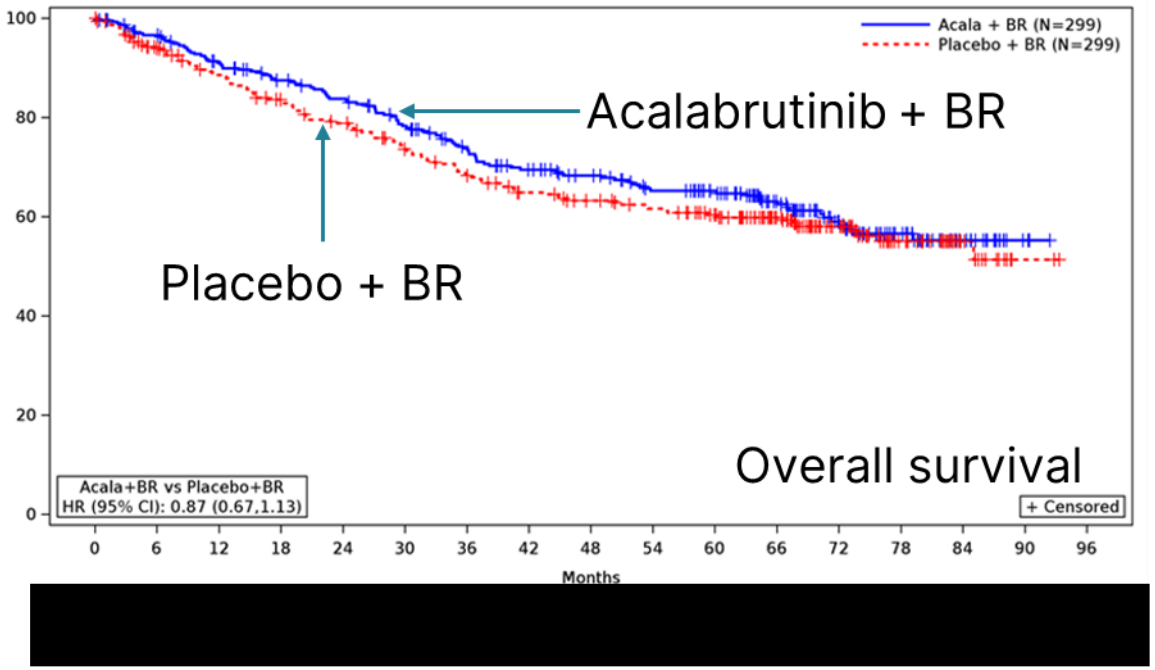
Key clinical trial results – ECHO: PFS and OS

Acalabrutinib + BR (n=299) statistically improves PFS and numerically improves OS compared to placebo + BR (n=299) – DCO2: 15th February 2025 (FAS)





	Progression-free survival		Overall survival	
Outcome	**Acalabrutinib + BR**	**Placebo + BR**	**Acalabrutinib + BR**	**Placebo + BR**
Median (months)	72.5 (60.7, NE)	47.8 (36.1, 60.8)	NE (73.3, NE)	NE (73.8, NE)
HR (95% CI); log-rank p-value	0.68 (0.53, 0.87); p=0.0022		0.87 (0.67, 1.13); p=NR	

analysis set; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression free survival

See appendix – Summary of ECHO trial

Additional data sources

Background

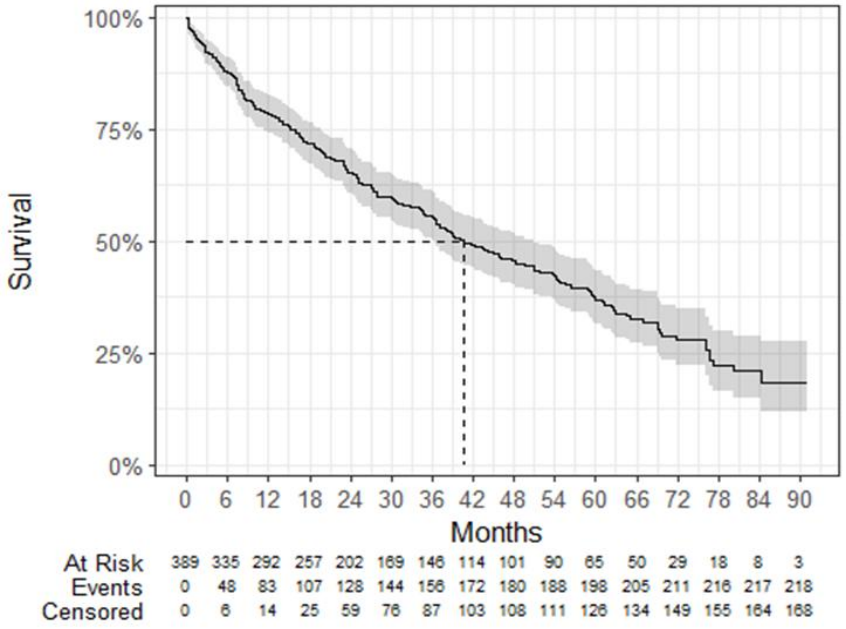
- Company conducted ITC in a Bayesian framework to compare ABR versus R-CHOP
- BRIGHT and StiLNHL1 trials included in ITC, along with company's ECHO trial
- SACT data provided by NICE for those receiving 1L BR or R-CHOP for MCL diagnosed from 2017–2022
  - SACT data was used for external validation of ECHO trial KM plots only

	BRIGHT	StiLNHL1	SACT
Treatment arms	BR + R (n=37) R-CHOP/R-CVP + R (n=37)	BR (n=46) R-CHOP (n=38)	BR (n=389) R-CHOP (n=508)
Outcomes	PFS and OS	PFS and OS	OS
Used in ITC?	Yes	Yes	No
ITC results HR (95% CrI)	**ABR vs BR** PFS: [redacted] OS: [redacted] **ABR vs R-CHOP** PFS: [redacted] OS: [redacted]		N/A
Used in model?	Yes	Yes	No (validation only)

Abbreviations: ABR, acalabrutinib, bendamustine, rituximab; BR, bendamustine + rituximab; BVR, bendamustine, bortezomib, rituximab; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan–Meier; MCL, mantle cell lymphoma; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisolone; +R, rituximab maintenance; VR-CAP, rituximab, cyclophosphamide, doxorubicin, bortezomib, prednisolone

KM plots for OS of people receiving 1L BR – SACT vs ECHO

SACT OS for those receiving 1L BR



ECHO OS for those receiving 1L BR

[redacted]

ECHO data DCO2: 15th February 2025

Outcome	SACT	ECHO (ITT)	ECHO (COVID-censored)
Median survival	40.51 months	NE (73.8, NE)	[redacted]
Median follow-up	25.1 months	51.9 months	NR (expected to be 51.9 months)

EAG comments

- Substantial differences between ECHO and SACT data in OS data for BR arm
- Raises uncertainty about generalisability of OS from ECHO trial (BR arm) to UK clinical practice
- No PFS data from SACT, if real-world PFS for BR also lower in UK clinical practice than in ECHO trial, applying both OS and PFS HRs from the trial to the UK population might be expected to lower incremental QALYs and increase ICER

Abbreviations: 1L, first line; ABR, acalabrutinib + bendamustine and rituximab; BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; KM, Kaplan–Meier; NE, not estimable; NR, not reported; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

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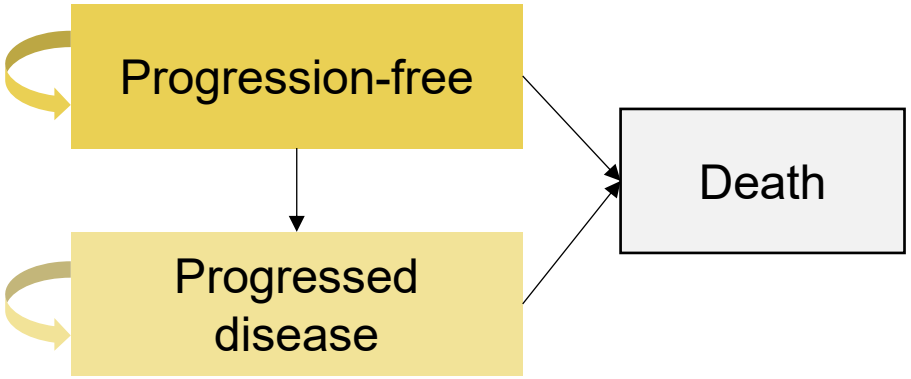
Company's model overview

Model structure



Company

- The chosen model structure was a partitioned survival model with three mutually exclusive health states

Technology affects **costs** by:

- Increasing the treatment acquisition costs of first line treatment
- Reducing the treatment acquisition and administration costs of 2nd and 3rd line treatments.

Technology affects **QALYs** by:

- Increasing progression free survival and reducing the proportion of the cohort in the progressed disease at any given point in time.

Assumptions with greatest ICER effect:

- The decision to use a partitioned survival model instead of a Markov state transition model.
- Decisions about the most appropriate progressed disease health state utility value.
- Assumptions underpinning the calculation of 2nd and 3rd line subsequent treatment costs.

Abbreviations: BR, bendamustine + rituximab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

Key Issue 1: Economic model structure

Background

- The company chose a partitioned survival model (PSM) structure with three mutually exclusive health states: progression free, progressed disease, and death

Company

- No clear consensus on the preferred modelling approach based on precedents in MCL
- PSMs are widely accepted and commonly used in oncology
- PSM allows for both PFS and OS, key endpoints collected in ECHO trial, to be utilised directly in the model
- Clinical and health economic experts from an advisory board indicated that a PSM was acceptable
  - Additional health states within a state transition model, and requirement to independently model post-progression survival, may increase discrepancies in long-term OS projections

EAG comments

- Not satisfied that company have sufficiently justified the decision to use PSM for 1L treatment of MCL
- Concerned that the PSM structure creates a bias in favour of ABR
- Model substantially under-estimates the QALY benefits of subsequent treatment lines by ignoring PFS benefits and under-estimating OS benefits for these treatments
- PSM identified in company literature review was for 3L CAR-T for MCL (TA677)
  - Modelling requirements for 3L not transferrable to earlier in the pathway
- Would've preferred Markov model structure that explicitly captures PFS benefits of subsequent treatments

Is a partitioned survival model acceptable for decision making?

Abbreviations: 1L, first line; ABR, acalabrutinib + bendamustine + rituximab; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Key issue 2a: Censoring of COVID-19 deaths

Background

- Company censored COVID-19 deaths for its base case analysis, EAG preferred to use ITT population
- COVID-19 deaths (DCO2): ABR, [redacted]; PBR, [redacted]; (COVID-censored KM curves shown on next slide)

Company

- Confirmed or suspected COVID-19 deaths included in IRC-assessed and investigator-assessed analyses
- Analysis conducted excluding patients with COVID-related death and without PD prior to death
  - Median PFS improved in both arms
  - Treatment effect of ABR on OS became more pronounced
- COVID deaths had relevant impact on PFS and OS but clinical benefit of ABR over PBR not compromised

EAG comments

- Pandemic would have impacted OS but not appropriate to censor COVID-related deaths in model population
- EAG's clinical expert suggests BTK inhibitors could have an impact on other respiratory infections
- COVID-19 and other respiratory illnesses remain in widespread circulation and remain relevant considerations for treatment selection
- Prefers to use ITT analysis as it maintains the benefits randomisation from ECHO trial and is less biased

Note: Alternative approaches to adjust for COVID-19 deaths also available (suggested for ID6338)

Is it appropriate to adjust for COVID-19 deaths? If so, how should they be adjusted?

Abbreviations: ABR, acalabrutinib + bendamustine + rituximab; BTK, Bruton's tyrosine kinase; IRC, Independent Review Committee; ITT, intent-to-treat; PBR, placebo + bendamustine + rituximab; PD, progressed disease; OS, overall survival; PFS, progression-free survival

Key clinical trial results – ECHO: PFS and OS, COVID censored

Acalabrutinib + BR (n=299) statistically improves PFS and numerically improves OS compared to placebo + BR (n=299) – DCO2: 15th February 2025 (COVID deaths censored)

	Progression-free survival				Overall survival			
	FAS		COVID censored		FAS		COVID censored	
Outcome	ABR	PBR	ABR	PBR	ABR	PBR	ABR	PBR
Median (months)	72.5 (60.7, NE)	47.8 (36.1, 60.8)	[redacted]	[redacted]	NE (73.3, NE)	NE (73.8, NE)	[redacted]	[redacted]
HR (95% CI)	0.68 (0.53, 0.87)		[redacted]		0.87 (0.67, 1.13)		[redacted]	

Abbreviations: ABR, acalabrutinib + bendamustine and rituximab; BR, bendamustine + rituximab; CI, confidence interval; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo, bendamustine, rituximab; PFS, progression free survival

Key issue 2b: Extrapolation of PFS and OS data

Background

- Company and EAG disagree on most appropriate method for extrapolation of PFS and OS data
- Disagree on whether PH holds between ABR and PBR in ECHO trial and preferred extrapolation curves

Company

- Assessment of PH between two arms done using Schoenfeld residuals and log-cumulative hazards plots
- Schoenfeld residual test reported p value >0.05 – can't reject the null hypothesis of PH
- However, Schoenfeld residuals plot shows deviations at the tails and a non-zero gradient for residuals is observed over the follow-up period indicating that proportionality may not be reasonable to assume
- Visually, log-cumulative hazard curves do not appear to be parallel over time with crossing of hazards seen
- So independent parametric models were fitted to the patient-level PFS and OS data from the ECHO trial

EAG comments

- Application of independently fitted curves in the economic model is inconsistent with the decision to use Cox proportional hazards modelling for the clinical effectiveness analyses
- In all cases PH assumption test is non-significant, and log-cumulative hazard functions are mostly parallel
- Prefer to assume PH assumption holds and a HR from joint models should be applied to a PH compliant parametric survival curve for BR. Allows for consistency of approach when modelling R-CHOP.
- Prefer to use Gompertz for extrapolation of PFS and OS data, as opposed to company's preferred Gamma

Is it appropriate to assume that the proportional hazards assumption holds?

See appendix – Schoenfeld residual plots and log-cumulative hazard

Abbreviations: BR, bendamustine + rituximab; HR, hazard ratio; PFS, progression-free survival; PH, proportional hazards; ; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone

Company and EAG preferred extrapolations for ABR and BR

[redacted]

[redacted]

Company vs EAG curve assumptions:

	Company	EAG
PH assumption	Doesn't hold	Holds
Model type	Independently fitted curves	Joint – HR applied to BR curve
Dataset	COVID-censored	ITT
Preferred distribution	Gamma	Gompertz

How should PFS and OS be extrapolated?

See appendix – Preferred extrapolations by dataset

Abbreviations: ABR, acalabrutinib + bendamustine and rituximab; BR, bendamustine + rituximab; HR, hazard ratio; KM, Kaplan–Meier; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; PH, proportional hazards

Key issue 3: Progressed disease utility value (1/3)

Background

- Progression-free HSUV from ECHO is capped by general population utility, and modelled as equal to general population utility
- EAG and company agree value for progressed disease from ECHO does not have face validity
- Company and EAG calculate progressed disease utility values by different methods
  - Company apply a multiplier using data from TA502: ibrutinib for treating relapsed or refractory MCL
  - EAG use progressed disease utility from TA370: bortezomib for previously untreated MCL

Company

- ECHO-derived progressed-disease HSUV estimate is inappropriate for the appraisal
  - Estimate is [redacted]
  - Estimate is [redacted] than age-gender matched general population utility (0.787)
- TA502 considered most appropriate TA to inform PD HSUVs because it is the most recent appraisal in MCL
  - TA502 committee accepted utility values: PF = 0.78; PD = 0.68
- PD HSUV calculated by multiplying the general population utility value by a PD HSUV multiplier ([redacted])
- Company's PD HSUV multiplier calculated by removing absolute decrement of HSUVs in TA502 from the ECHO trial derived estimate for the PF state, divided by the ECHO trial derived estimate

See appendix – Calculating progressed disease utility value

Abbreviations: 1L, first line; 2L, second line; HSUV, health state utility value; MCL, mantle cell lymphoma; PD, progressed disease; PF, progression-free; QoL, quality of life; TA, technology appraisal

Key issue 3: Progressed disease utility value (2/3)

EAG comments

- Agrees that ECHO HSUV inappropriate for PD – due to [redacted] and time HSUV measured
- Prefers TA370 to inform HSUVs for base case but notes that using values from TA370 over TA502 has limited impact on ICER when used with multiplier
- TA370 committee accepted utility values: PF = 0.68, PD from 1L treatment = 0.693; PF from 2L treatment = 0.764; PD from 2L treatment = 0.45
- Concerned with use of multiplier:
  - Overestimates PD utility in the long term as PD state captures all future treatment lines
  - Progression-free HSUV is equal to general population utility so it reduces with age
  - Difference in between the PF and PD decreases over time ([redacted] in cycle 1 and [redacted] by age 100)
- Prefer to reduce PD HSUV over time (2.06 years) using an exponential function from PFS HSUV in cycle 0 to HSUV for people progressed from 2L treatment state in TA370 (0.45)
- Note this reduces ICER and likely biases in favour of acalabrutinib as those in acalabrutinib arm spend more time in PF state overall

Is the company's or EAG's method for calculating progressed disease HSUV more appropriate? What is the impact of progression and the introduction of new treatments on HRQoL?

Abbreviations: 2L, second line; HRQoL, health-related quality of life; HSUV, health state utility value; PD, progressed disease; PF, progression-free

Key issue 3: Progressed disease utility value (3/3)

Company and EAG utility values over time

EAG's exponential decrease of PD HSUV over ~2 years

Difference between company PF and PD HSUV reduces slowly over time

EAG's PD HSUV capped at 0.45 (TA370 PD from 2L treatment)

Outcome	Company approach	EAG approach
Calculation method	Multiplier applied to age-sex matched general population HSUV throughout model	Exponential decrease from PF HSUV in cycle 0 over ~2 years but capped at 0.45
PD utility value start point	[redacted]	0.787
PD utility value after 36 months	[redacted]	0.45
PD utility value after lifetime	[redacted]	0.45

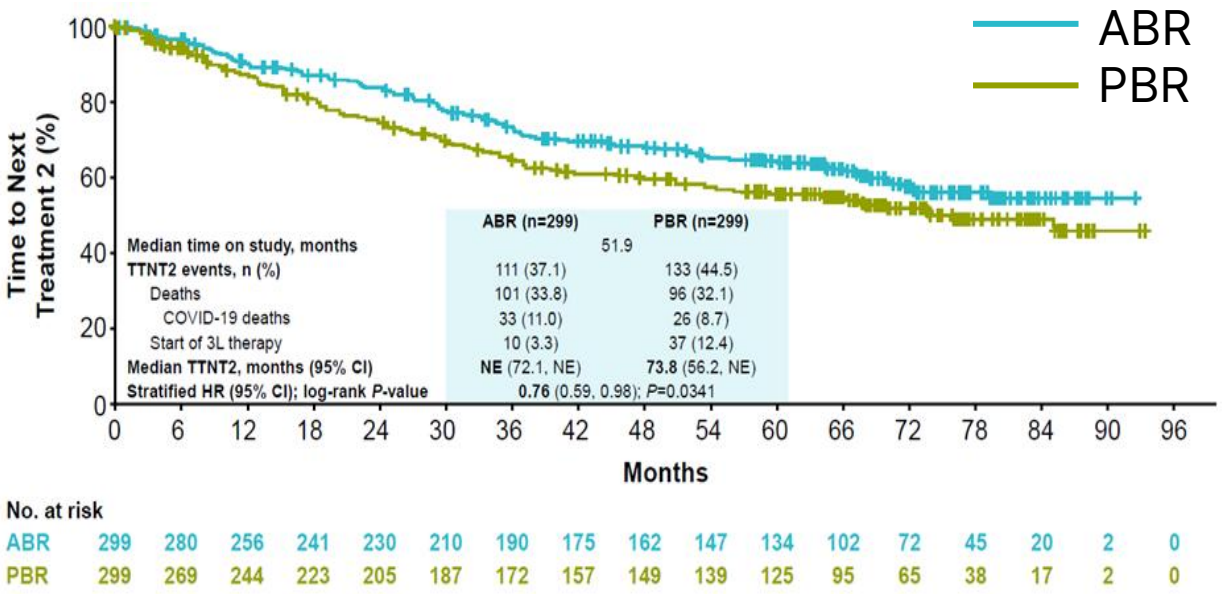
Abbreviations: 2L, second line; HSUV, health state utility value; PD, progressed disease; PF, progression-free

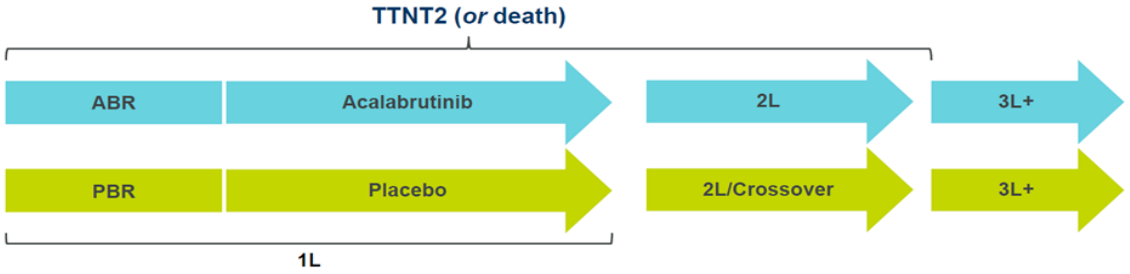
Time to next treatment 2 – post-hoc analysis

Company TTNT2 analysis reports 1L ABR reduces risk of needing 3L treatment compared to 1L PBR

Background

- Company submitted a post-hoc TTNT2 analysis to understand impact of treatment sequencing





Outcome	ABR vs. PBR
Full analysis set	
Risk of needing 3L therapy	24% reduction with ABR
HR (95% CI)	0.76 (0.59, 0.98)
COVID-19-censored data	
Risk of needing 3L therapy	33% reduction with ABR
HR (95% CI)	0.67 (0.50, 0.89)

Company

- TTNT2 defined as time from randomisation to 3L therapy after discontinuing randomised treatment or death
- TTNT2 may be considered a surrogate for PFS2 (time from initial treatment to second disease progression)
- Despite crossover, TTNT2 was prolonged in the ABR arm, emphasising clinical value of ABR in 1L

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Abbreviations: 1L, first line; 2L, second line; 3L, third line; ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; PBR, placebo + bendamustine + rituximab; TTNT, time to next treatment

Key issue 4a: Inclusion of 3L subsequent treatment costs

Background

- Company and EAG disagree on the inclusion of 3L subsequent treatments in their analyses

Company

- TTNT2 showed that despite crossover, there was a 33% reduction (HR: 0.67; 95% CI: 0.50, 0.89) in risk of needing 3L therapy with ABR versus PBR (data censored for COVID-19 deaths) in the ECHO trial
- For ABR, subsequent therapy was needed less often and later, reflecting more durable disease control
- Evidence significantly reduces the uncertainty in the model inputs associated with subsequent treatments and supports the inclusion of 3L therapies (including CAR-T treatments) in the base case results

EAG comments

- Note the observed reduction in the proportion of patients requiring a 3L treatment over the observed time period in company's TTNT2 analysis
- Unclear whether differences between treatment arms in ECHO trial would translate to UK clinical practice
- Unclear whether reduction in proportion of patients requiring 3L treatment in TTNT2 analysis represents delay in treatment need driven by longer PFS, or absolute effect that would continue indefinitely over modelled time horizon
- Differences in 3L treatment proportions are highly uncertain and not suitable for decision making
- 3L treatment costs removed in EAG base case; to avoid capturing costs of these without OS benefit

Should 3L subsequent treatments be included in the cost-effectiveness analysis? If yes, should CAR-T be included as a subsequent treatment?

Abbreviations: 3L, third line; ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; PBR, placebo + bendamustine + rituximab; TTNT, time to next treatment

Key issue 4b: Subsequent treatment durations and distributions

Background

- Company and EAG use different durations for subsequent treatments in the economic model

Company

- Subsequent treatment costs applied as one-off cost to the incident progressed disease patients per cycle
- Reported that cost calculated from number of PFS events at each cycle, multiplied by the proportion of PFS events that were non-fatal, and the proportion of progressed patients that had subsequent treatment
- One-off costs applied based on the distribution of subsequent treatment options and time on treatment

EAG comments

- Company has assumed a variety of approaches for calculating subsequent treatment durations
- Concerned that using PFS data may over-estimate subsequent treatment duration as a proportion of progression free patients will discontinue treatment prior to progression
- Prefer more consistent approach that relies (where possible) on mean estimates of treatment duration
- Prefer to assume that R-Chemo (R-CHOP, RBAC & VR-CAP) regimens are given for a maximum of 6 treatment cycles which is consistent with R-CHOP in 1L
- Agree with company distribution of 2L treatments in base case, but presents scenario based on ECHO data
- Provide scenario with zanubrutinib as 2L treatment instead of ibrutinib

Which treatments should be included at 2L? Is the company's or EAG's method more appropriate for calculating subsequent treatment durations?

NICE See appendix – Summary of company and EAG treatment durations and 2L treatment distributions

Abbreviations: 3L, third line; ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; PBR, placebo + bendamustine + rituximab; TTNT, time to next treatment

Summary of company and EAG base case assumptions

Key assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Preferred analysis set	COVID-19 mortality censored dataset	ITT dataset
Extrapolation approach	Independently fitted curves to ECHO trial data Preferred extrapolation – Gamma	Extrapolations from joint (dependent) models Preferred extrapolation – Gompertz
Progressed disease utility value	Utility value informed by TA502 Constant multiplier applied to PD HSUV	Utility value informed by TA370 Reduce PD HSUV over time (2.06 years) using an exponential function from PFS HSUV
3L subsequent treatments	3L subsequent treatments **included** in analysis (includes CAR-T)	3L subsequent treatments **excluded** in analysis
Subsequent treatment durations	One-off cost	Use mean estimates of treatment duration (where possible) Max. 6 treatment cycles for R-Chemo

See appendix – Other company and EAG base case assumptions

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Abbreviations: 1L, first line; 2L, second line; 3L, third line; HSUV, health state utility value; ITT, intent-to-treat; PD, progressed disease; PF, progression free

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

- There are confidential discounts in place for acalabrutinib and for other medicines used in the model
- The company's base case ICER above the range NICE normally considers cost-effective
- The EAG's base case ICER is above the range NICE normally considers cost-effective

Acalabrutinib with bendamustine and rituximab for untreated mantle cell lymphoma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**

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Committee decision making

What are the committee's preferred assumptions?

Key issue	Question for committee
Economic model structure	• Is a partitioned survival model acceptable for decision making?
Censoring of COVID-19 deaths	• Is it appropriate to adjust for COVID-19 deaths? If so, how should they be adjusted?
Extrapolation of PFS and OS data	• Is it appropriate to assume that the proportional hazards assumption holds? • How should PFS and OS be extrapolated?
Progressed disease utility value	• Is the company's or EAG's method for calculating progressed disease HSUV more appropriate? • What is the impact of progression and the introduction of new treatments on HRQoL?
Inclusion of 3L treatment costs	• Should 3L subsequent treatments be included in the cost-effectiveness analysis? • If yes, should CAR-T be included as a subsequent treatment?
Subsequent treatment durations and distributions	• Which treatments should be included at 2L? • Is the company's or EAG's method more appropriate for calculating subsequent treatment durations?
Equality	• Are there any equalities issues which can be addressed in this appraisal?

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Abbreviations: 3L, third line; HRQoL; health-related quality of life, HSUV, health state utility value; ITT, intent-to-treat; PD, progressed disease; PFS, progression-free survival

Key issues

No.	Key issue	ICER impact	Slide
1	Economic model structure	Unknown	16
2a	Censoring of COVID-19 deaths	Moderate	17
2b	Extrapolation of PFS data		19
3	Calculating progressed disease HSUV	Large	21
4a	Inclusion of 3L subsequent treatment costs	Large	25
4b	Subsequent treatment durations	Large	26

Abbreviations: 2L, second line; 3L, third line; HSUV; health state utility value; PD, progressed disease; PFS, progression-free survival

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

Supplementary appendix

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Back to – Key clinical trial results – ECHO: PFS and OS

Summary of ECHO trial

	ECHO trial (N=598)
Design	Global, Phase 3, randomised, double-blind, multicentre trial
Population	Patients with previously untreated MCL
Intervention	Acalabrutinib + BR
Comparator	Placebo + BR
Duration	March 2017 – ongoing (latest DCO: February 2025)
Primary outcome	PFS
Key secondary outcomes	OS, investigator-assessed PFS, investigator-assessed ORR, IRC-assessed ORR, IRC-assessed and investigator-assessed DOR, IRC-assessed and investigator-assessed TTR
Locations	189 sites across 26 countries
Used in model?	Yes
Age, mean (SD)	71.6 (4.66)
Sex, n (%)	Male: 423 (70.7); Female: 175 (29.3)
ECOG performance status, n (%)	0 = 296 (49.5); 1 = 261 (43.6); 2 = 35 (5.9); 3 = 2 (0.3); Missing = 4 (0.7)

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Abbreviations: BR, bendamustine + rituximab; DCO, data cut-off; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; MCL, mantle cell lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS, progression-free survival; PR, partial response; SD, standard seviation; TTR, time to response

Schoenfeld residual plots and log-cumulative hazard plots for PFS data (1/2)

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

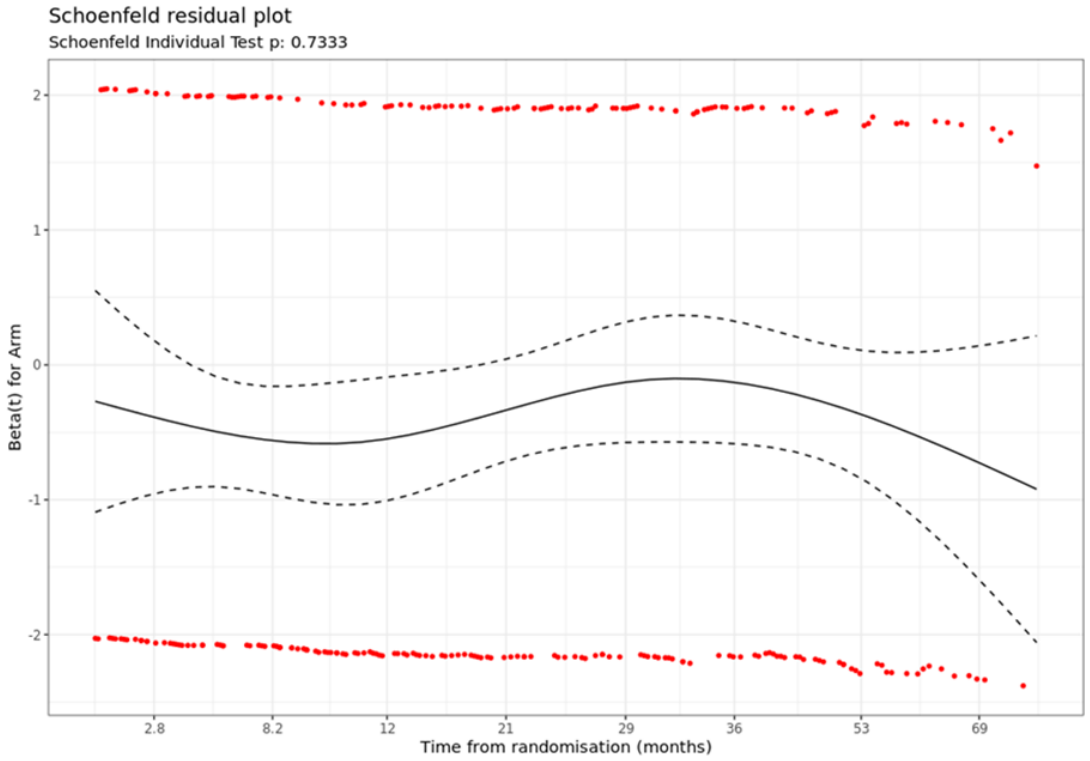
Log-cumulative hazard plots for PFS data: censored COVID-19 deaths analysis, DCO2

Back to – Extrapolation of PFS and OS data

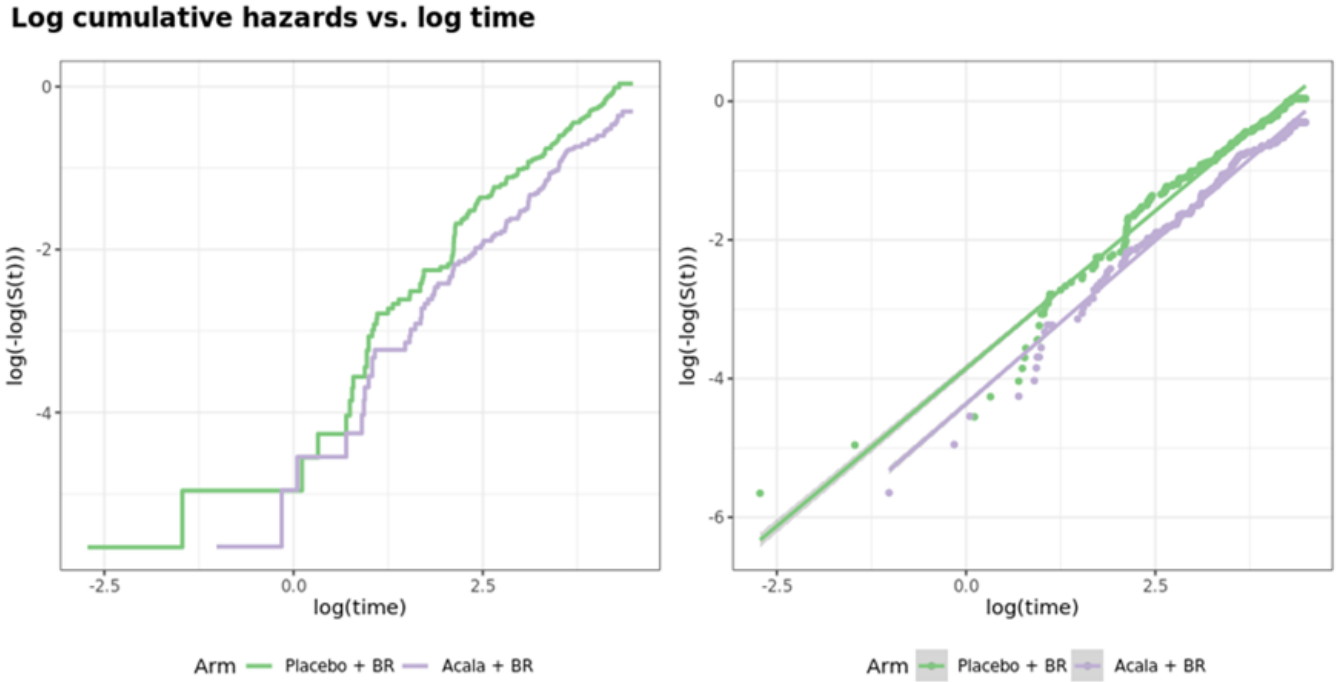
Abbreviations: DCO, data cut-off; PFS, progression-free survival

Schoenfeld residual plots and log-cumulative hazard plots for PFS data (2/2)

Schoenfeld residual plots for PFS data:
ITT analysis, DCO2



Log-cumulative hazard plots for PFS data:
ITT analysis, DCO2



Back to – Extrapolation of PFS and OS data

Abbreviations: DCO, data cut-off; PFS, progression-free survival

Schoenfeld residual plots and log-cumulative hazard plots for OS data (1/2)

Schoenfeld residual plots for OS data: censored COVID-19 deaths analysis, DCO2

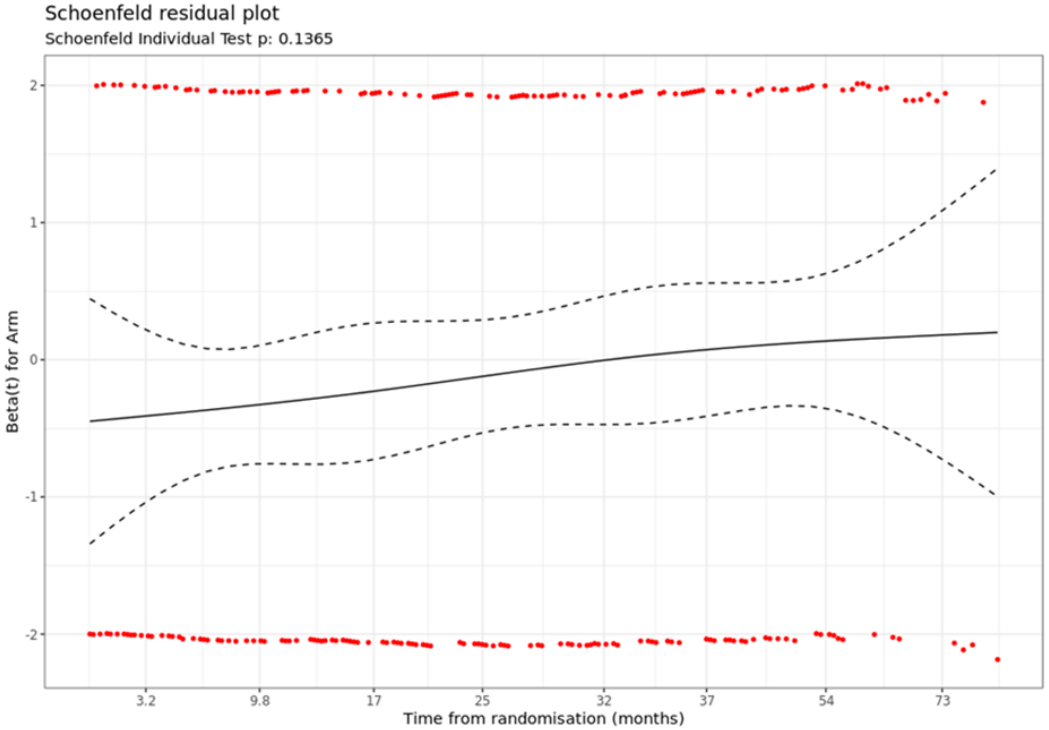
Log-cumulative hazard plots for OS data: censored COVID-19 deaths analysis, DCO2

Back to – Extrapolation of PFS and OS data

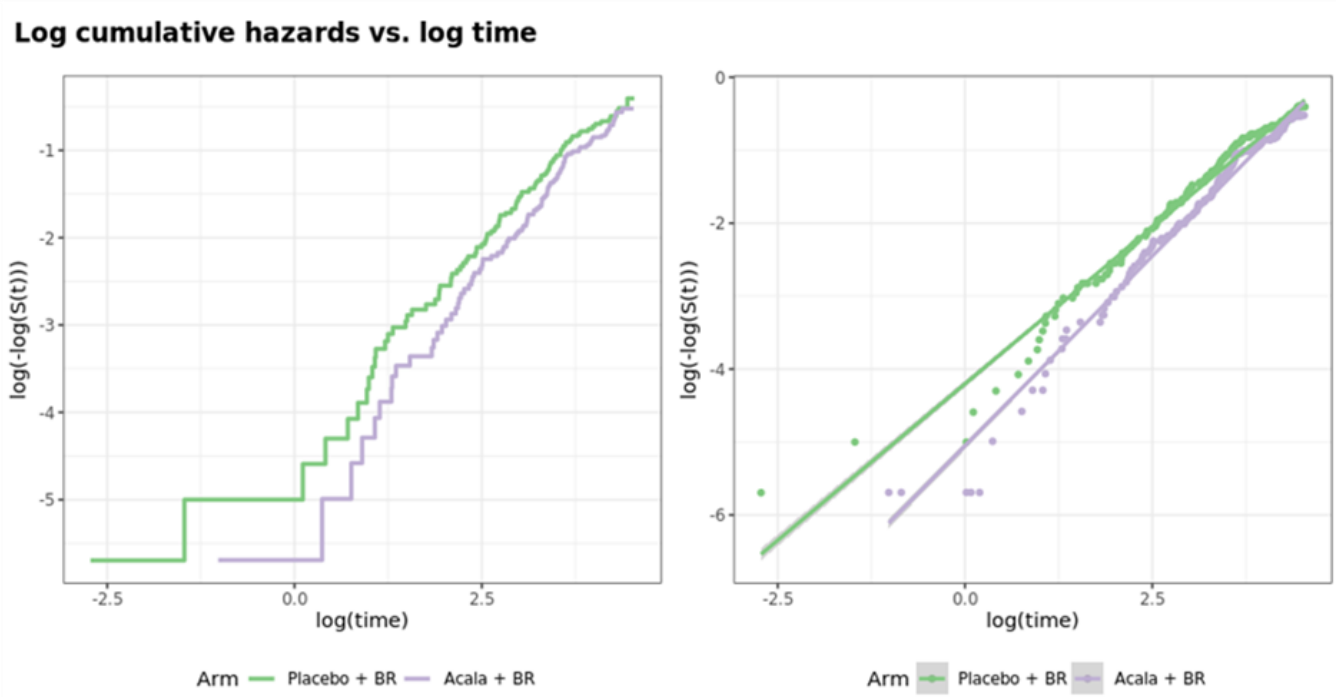
Abbreviations: DCO, data cut-off; OS, overall survival

Schoenfeld residual plots and log-cumulative hazard plots for OS data (2/2)

Schoenfeld residual plots for OS data:
ITT analysis, DCO2



Log-cumulative hazard plots for OS data:
ITT analysis, DCO2



Back to – Extrapolation of PFS and OS data

Abbreviations: DCO, data cut-off; OS, overall survival

KM, company and EAG preferred extrapolations by dataset

Abbreviations: ABR, acalabrutinib + bendamustine and rituximab; BR, bendamustine + rituximab; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival

Calculating progressed disease utility value

$$\text{Company PD HSUV multiplier} = \frac{\left(\text{ECHO derived PF HSUV} - (\text{absolute decrement of HSUVs in TA502})\right)}{\text{ECHO derived PF HSUV}}$$

$$\text{Company PD HSUV multiplier} = \frac{\left([redacted] - (0.780 - 0.680)\right)}{[redacted]} = [redacted]$$

$$\text{Company cycle 1 PD HSUV} = \text{PD HSUV multiplier} \times \text{age and sex matched general population utility}$$

$$\text{Company cycle 1 PD HSUV} = [redacted] \times 0.787 = [redacted]$$

Back to – Progressed disease utility value

Abbreviations: HSUV, health state utility value; PD, progressed disease; PF, progression-free

2L treatment distributions

2L treatment distributions obtained from ECHO trial compared to company sought clinical expert opinion

Subsequent treatment	ECHO trial distribution		Company sought clinical expert distribution	
	ABR	PBR	ABR	PBR
Ibrutinib	[redacted]	[redacted]	0.00%	100.00%
R-CHOP	[redacted]	[redacted]	74.44%	0.00%
Lenalidomide + rituximab	[redacted]	[redacted]	0.00%	0.00%
Rituximab	[redacted]	[redacted]	0.00%	0.00%
RBAC	[redacted]	[redacted]	11.11%	0.00%
VR-CAP	[redacted]	[redacted]	14.44%	0.00%

No change since DCO1: 15th February 2024

Back to – Subsequent treatment durations and distributions

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Abbreviations: ABR, acalabrutinib, bendamustine + rituximab; BR, bendamustine + rituximab; R-BAC, rituximab, bendamustine and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone

Summary of company and EAG subsequent treatment durations

Company and EAG preferred subsequent treatment durations

Subsequent treatment	Company preferred		EAG preferred	
	Time on treatment (months)	Source	Time on treatment (months)	Source
Ibrutinib	22.00	RMST cross over (Acalabrutinib), ECHO	12.72*	Based on median duration of treatment (11.70 months) of MCL presented in the SmPC for Ibrutinib
R-CHOP	5.52	Maximum treatment duration, LYM3002	4.14	Consistent with 1L R-CHOP. 6 21-day treatment cycles
CAR-T	One-off	Assumption	One-off	Assumption
R-BAC	10.10	Median PFS, R-BAC in R/R MCL	5.52	Assumption. 6 28-day treatment cycles
VR-CAP	30.50	Median PFS, VR-CAP in 1L MCL	5.52	Assumption. 6 x 28-day treatment cycles

*Estimation of the mean assuming an exponential distribution based on median duration of 11.70 months and dividing by ln(2)

Back to – Subsequent treatment durations and distributions

Abbreviations: CAR-T, Chimeric antigen receptor T-cell; MCL, mantle cell lymphoma; R-BAC; Rituximab, bendamustine, cytarabine; R-CHOP, Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RMST, restricted mean survival time; R/R, relapsed or refractory; VR-CAP, Bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone

Other company and EAG base case assumptions

Assumption	Company base case	EAG base case
Vial sharing	No vial sharing **across** patients	No vial sharing **across or between** patients
Adverse events disutilities	Duration and disutility of COVID-19 pneumonia based on average of other unspecified events equal to 23.78 days and -0.032 Duration and disutility of COVID-19 pneumonia, COVID-19 and rash maculo-papular equal to 23.78 days and -0.032	Disutility and duration associated with COVID-19 pneumonia is equal to pneumonia (16.03 days and -0.058) Duration and disutility of COVID-19, COVID-19 pneumonia and rash maculo-papular equal to average of all other included events (11.80 days and -0.051)
RDI for subsequent treatments	Assume RDIs for R-Chemo regimens are equal to 100%	RDIs for subsequent treatments are equal to those assumed in 1L If data unavailable, assume RDI equal to TA370

The differences above had minimal impact on the ICER so were not discussed as key issues

Abbreviations: 1L, first line; RDI, relative dose intensity

Back to – Summary of company and EAG base case assumptions