Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments [ID6325, review of TA677]

For projector – all confidential information is redacted

Technology appraisal committee A: 2nd Committee Meeting [2nd September 2025]

Chair: Radha Todd

Lead team: Richard Ballerand, Patrick De Barr, James Fotheringham (presenter)

External assessment group: Birmingham Centre for Evidence and Implementation Science

Technical team: Luke Cowie, Alan Moore, Emily Crowe

Company: Gilead Sciences

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments

- ✓ **Background and ACM1 conclusions**
- ❑ Summary of DG responses
- ❑ ACM1 outstanding issues
- ❑ Other considerations
- ❑ Summary

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Brexucabtagene autoleucel (Tecartus, Gilead Sciences)

Marketing authorisation (EMA, Dec 2020)	Adult patients with relapsed or refractory mantle cell lymphoma who have previously received two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor
Mechanism of action	• Single-chain anti CD19 antibody fragment • Patients undergo leukapheresis to harvest T-cells which are then engineered to express CD19 antigen-specific CAR, and given back to the patient enabling them to kill CD19-expressing tumour
Administration	• Single-infusion containing anti-CD19 CAR T-cells in approximately 68 mL for a target dose of 2 x 106 CAR T-cells/kg body weight • Prior to infusion, patients treated with a conditioning chemotherapy regimen of intravenous fludarabine and cyclophosphamide for 3 days
Price	• List price: £316,118 • A patient access scheme is applicable subject to a commercial agreement

Recap of ACM1 conclusions (1)

Issue at ACM1	Committee conclusion
Generalisability of ZUMA-2	ZUMA-2 generalisable to patients in the NHS. But prefer mean age of 66 from SACT as starting age in economic model
Data sources for OS and PFS	RWE from SACT (OS) and O'Reilly (PFS) pooled with ZUMA-2
Proportion having subsequent alloSCT after R-BAC	15%, but welcome more data/clinical input to inform this estimate
Population for analysis	Costs and outcomes for whole ITT population, including people who had leukapheresis but not infusion
Cure assumption	Would like additional data to support assumption of a functional cure and at which timepoint, and data about the most appropriate SMR to use. Company should explore possibility of no functional cure point (standard parametric modelling) and mixture cure modelling
CAR-T tariff and ICU costs	All costs in model to be for same financial year, ICU costs to be incorporated separately

OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; RWE, real-world evidence; alloSCT, allogeneic stem-cell transplant; ITT, intention-to-treat; ICU, intensive care unit; SMR, standardised mortality ratio

Recap of ACM1 conclusions (2)

Issue at ACM1	Committee conclusion
Utility values	Pre progression utility should not exceed general-population utility at the baseline age, 0.68 from TA502 for post progression
Proportion having IVIg after brexu-cel	38% of people having IVIg for 1 year after brexu-cel is appropriate (Wang et al. 2023), if RWE not available
Severity modifier	Will be considered at ACM2

RWE, real-world evidence; IVIg, intravenous immunoglobulin; ACM, appraisal committee meeting

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Response to draft guidance: Gilead Sciences (1)

Company accepts the following committee preferred assumptions:

- **mean age of 66** from SACT as starting age in the economic model
- **pooled data using ZUMA-2 and RWE data** (SACT and O'Reilly 2024) to inform survival (however, company use restricted SACT overall survival data to only follow-ups from August 2022 onward)
- **15% use of alloSCT** after R-BAC

Company maintains original ACM1 preferences in the following areas:

- **mITT population**
    - Analysis from point of leukapheresis not part of updated base case. Provides exploratory analysis using drop-out rate from ZUMA-2. ZUMA-2 used to estimate outcomes for those who do not reach infusion (SACT does not report this, DESCAR-T study felt not appropriate)
- **48-month LTS (cure) assumption**. Company did not provide standard parametric analysis or mixture cure modelling, as not considered appropriate approaches
- Maurer et al. (2014) as source of mortality weighting in LTS **(SMR of 1.09)**
- NHSE **CAR-T tariff of £41,101** (disagrees with calculation of NHSE uplifts for 2024/2025 and 2025/2026 financial years)

SACT, Systemic Anti-Cancer Therapy; RWE, real-world evidence; alloSCT, allogeneic stem-cell transplant; mITT, modified intention-to-treat; LTS, long-term survivorship; SMR, standardised mortality ratio; NHSE, NHS England

Response to draft guidance: Gilead Sciences (2)

- Maintains use of **ZUMA-2 utility value data for preprogression** (without capping to general population mortality). Agrees with use of TA502 utilities to estimate the relative difference between these 2 health states (post progression utility 13% lower than pre progression utility)
- Agrees with clinical experts at ACM1 that rate of **IVIg use after brexu-cel is 10-20%,** and duration of 1 year is appropriate (uses mid-point of 15% in its updated base case). Disagrees that 38% IVIg use from Wang et al. (2023) reflects UK clinical practice
- States there should be flexibility in committee's choice of decision modifier (1.2 or 1.7) and considers that **1.7 should be accepted** to account for uncaptured benefits of brexu-cel

- Company's updated analyses:
    - For brexu-cel, pooled dataset created using ZUMA-2 plus SACT for OS and ZUMA-2 plus O'Reilly (2024) for PFS;
    - For R-BAC, outcomes estimated separately for people not having subsequent alloSCT (estimated from McCulloch 2020) and people having subsequent alloSCT (data from Liebers 2025)
- Company provide technical addendum alongside response

OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy; alloSCT, allogeneic stem-cell transplant; ITT, intention-to-treat; IVIg, intravenous immunoglobulin; ACM, appraisal committee meeting

Response to draft guidance: UK clinical experts

Joint response from 6 UK clinical experts

- Express concern at possibility of brexu-cel not being available for people with relapsed or refractory MCL in England and Wales, unlike many other countries in Europe
- CAR-T cell therapy represents a national and internationally recognised standard of care approach for suitable patients in third line and beyond
- Durable response rates observed with CAR-T cell therapy remain unprecedented
- Without this treatment, 3rd line options are very limited: people will either have relatively ineffective and toxic chemoimmunotherapy, or would be considered for alloSCT, which has documented risks and health care utilisation costs
- People from ethnic minorities have fewer donor options and are less likely to have alloSCT

MCL, mantle cell lymphoma; alloSCT, allogeneic stem-cell transplant

Response to draft guidance: Patient groups

Joint response from Lymphoma Action, Anthony Nolan, Blood Cancer UK

- Do not feel that draft recommendation gives due consideration to patient perspectives, which offer invaluable perspectives that quantitative data cannot fully capture
- Brexu-cel can be a transformative treatment for many people
- People report *"gradually returning to a near-normal life",* that they feel *"more or less cured",* and one testimony stated
    - *"I was very fortunate to undergo CAR-T cell replacement and can see no disadvantages to the treatment"*
- Concerned draft recommendation does not sufficiently take account of psychological burden arising from fear of relapse and that no other suitable treatments are available
- Brexu-cel is only CAR-T option currently available and an important option for patients who have relapsed after autoSCT, who may not be able to find a match on stem cell transplant register
- Without a CAR-T option, only option left for these people is likely palliative care

autoSCT, autologous stem-cell transplant

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Key Issues

Issue	ICER impact
Modelling of pre-infusion period (population, drop-out rate and outcomes)	Large
Cure assumption (long-term survivorship and mortality weighting)	Large
CAR-T Tariff and ICU costs	Large
Severity modifier	Large
Utility values	Moderate
Use of alloSCT after R-BAC	Small
IVIg use	Small

alloSCT, allogeneic stem-cell transplant; ICU, intensive care unit; IVIg, intravenous immunoglobulin

Large impact

Key issues Modelling pre-infusion period: population

ACM1 conclusion

- To include both costs and outcomes for whole ITT population, including people who had leukapheresis but not infusion

Company

- Maintains mITT population for base case (but includes costs of leukapheresis for people who go through this stage of CAR-T process but do not have an infusion)
- Very few ([redacted]%) will not reach infusion
- Many similar recent NICE evaluations have accepted mITT populations
- Comparator data does not capture broader real-world population, where a significant % of patients may not be eligible/may discontinue R-BAC due to toxicity (expert estimates 20-30%)

EAG comments

- Maintains preference to base cost and efficacy estimates on ITT population for brexu-cel, starting at point of leukapheresis
- Company has not provided any supporting evidence in terms of time from previous therapy or disease progression to either R-BAC or CAR-T leukapheresis or infusion
- So EAG does not consider it appropriate to apply an adjustment to the R-BAC extrapolations

Which population should be considered (at which point should the analysis start?)

ITT, intention-to-treat; mITT, modified intention-to-treat

Large impact

Key issues Modelling pre-infusion period: drop-out (1)

ACM1 conclusion

- Use SACT data to inform proportion who receive leukapheresis but do not proceed to infusion (estimated by NHSE at ACM1 to be approximately 25%)

Company

- Did exploratory scenario analysis on drop-out rates using ZUMA-2 data
- Distinguish between drop-out prior to leukapheresis and drop-out after leukapheresis (but before infusion), presents data from its ordering system (Kite-Konnect, January 2024 to June 2025)
- SACT data not reliable: drop outs after initial request approved but before having leukapheresis
- In O'Reilly et al. (2024) 14 approved patients did not progress to leukapheresis

EAG comments

- Unable to verify Kite-Konnect data, uncertain whether for MCL indication only
- Kite-Konnect combined dropout is below SACT and O'Reilly et al ([redacted]% drop put prior to leukapheresis, [redacted]% drop out post leukapheresis and pre infusion).
- SACT only reports combined drop-out from approval to leukapheresis (30%)
- This is consistent with O'Reilly (2024), which does provide breakdown (20% drop-out between leukapheresis and infusion), and is maintained as EAG's preferred source

Comparison of drop-out rates between key CAR-T process steps

NICE

SACT, Systemic Anti-Cancer Therapy; NHSE, NHS England; ACM, appraisal committee meeting; MCL, mantle cell lymphoma

Large impact

Key issues Modelling pre-infusion period: drop-out (2)

SACT proportion not infused with brexu-cel after leukapheresis

- Data from NHS England prior approval system (Blueteq, 4th August 2025) to identify patients with an approved Blueteq Form A (leukapheresis) but no Form B (infusion)
- 65 patients identified with an A form but no B form. Of these 65, CAR-T centres confirmed that 5 have been infused
- Of the 60 not infused, 20 did not proceed to leukapheresis
- 40 patients confirmed as being leukapheresed but not infused

Reason for not proceeding to leukapheresis

Reason for not proceeding to leukapheresis	Total
Progressive disease	15
High white cell count	2
Deterioration in performance status	2
Alternative therapy pursued	1
	20

Reason for not proceeding to infusion

Reason for not proceeding to infusion	Total
Progressive disease	26
Patient fitness/deterioration in performance status	7
Manufacturing failure	6
Second malignancy diagnosed	1
	40

- Which drop out rate should be assumed in the analysis?

SACT, Systemic Anti-Cancer Therapy; NHSE, NHS England; ACM, appraisal committee meeting; MCL, mantle cell lymphoma

Key issues Modelling pre-infusion population: outcomes

ACM1 conclusion

- Clinical outcomes for people who had leukapheresis but not an infusion to be taken from SACT data. But if this is not available, from the DESCAR-T study

Company

- SACT does not report outcomes for those who do not reach infusion
- Committee noted at ACM1 that DESCAR-T is not generalisable to UK population (e.g.15% had ECOG score of 2 or more - would not be eligible for CAR-T in NHS)
- So, prefer ZUMA-2 to estimate outcomes for those who had leukapheresis but not infusion
- If brexu-cel arm is adjusted, reasonable to also adjust R-BAC arm: McCulloch cohort only reports outcomes for patients who had R-BAC (equivalent to brexu-cel mITT population)

EAG comments

- Notes that outcomes for non-infused people from ZUMA-2 are [redacted] than those from DESCAR-T study
- Inclusion of outcomes for people considered for but not treated with R-BAC remains unjustified
- Agree to use company's preference for ZUMA-2 data in EAG base case

- What source should be used to model outcomes for those not infused?

NICE

SACT, Systemic Anti-Cancer Therapy; mITT, modified intention-to-treat; ACM, appraisal committee meeting; ECOG, Eastern Cooperative Oncology Group

Large impact

Key issues Cure assumption: long-term survivorship (1)

ACM1 conclusion

- Would like to see additional data to support assumption of functional cure and at which timepoint

Company

- Maintains 48-month LTS (cure) assumption, because few events after this timepoint (none after month 65, from 88-month follow up)
- PFS and OS curves from ZUMA-2 do not cross, suggesting sustained benefit over time
- [redacted]% remain progression-free at 60 months, compared with 0-5% extrapolated for R-BAC arm
- Standard parametric modelling gives implausible MRAF when calculated from tails of ZUMA-2 survival curves
- Mixture cure modelling not re-explored: LTS-based model preferred by committee in TA677

NICE technical team comment:

- Preference for LTS approach did not form part of committee's preferred assumptions from TA677
- Key reason for CDF entry for this indication was to potentially help to resolve uncertainties around whether this treatment was curative

LTS, long-term survivorship; PFS, progression-free survival; OS, overall survival; MRAF, mortality rate adjustment factor; CDF, Cancer Drugs Fund

Large impact

Key issues Cure assumption: long-term survivorship (2)

EAG comments

- Accepts it is plausible that a proportion of people could be cured, but unclear whether that proportion is reliably estimated from the implemented methods due to the limited follow-up, and ultimately long-term outcomes (10+ years) remain unknown
- Does not accept that company's breakdown of OS events from ZUMA-2 supports 48-month LTS (cure) assumption
- Maintains preference for 60-month LTS (cure) assumption
- EAG explores models without a cure assumption, to support the committee's decision-making

- Should a cure be assumed?
- If so, at which timepoint?

Large impact

Key issues Cure assumption: mortality weighting (1)

ACM1 conclusion

- Would like to see additional data about the most appropriate SMR to use, if LTS appropriate

Company

- Maintains its preferred source for SMR of 1.09 in LTS (Maurer 2014, untreated DLBCL)
- Maurer 2014 mean age = 63 (same as ZUMA-2), general population mortality over 5 years after 63 averages 1.18% per year. SMR of 1.09 implies excess mortality of 0.11% per year
- EAG preferred source (TA893*) has mean age of 46. General population mortality over 5 years after 46 averages 0.30% per year. SMR of 3 implies excess mortality of 0.59% per year
  - But when SMR of 3 applied in EAG model at 72.5 years, excess mortality = 5.91% per year, ~10 times excess mortality than observed in TA893
- This is not plausible, unreasonable extrapolation of 0.59% annual excess mortality from TA893
- Committee for TA893 noted risk of dying (SMR of 3) was linked to high proportion of prior alloSCT in the ALL cohort (38%), which is not an expected treatment for patients with MCL
- Eskelund (2016) offers another example for MCL: mean age of 56, SMR of 2.36 and excess mortality of 0.87% per year

*TA893: Brexu-cel for relapsed or refractory B-cell acute lymphoblastic leukaemia

SMR, standardised mortality ratio; LTS, long-term survivorship; alloSCT, allogeneic stem-cell transplant; MCL, mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukaemia

Key issues Cure assumption: mortality weighting (2)

Sources of excess mortality in LTS

	Maurer 2014	TA893	Eskelund 2016	Company model	EAG model
Condition	DLBCL	ALL	MCL	DLBCL	ALL
Age at which SMR applied	63	46	56	67	72.5
SMR	1.09	3	2.36	1.09	3
General population mortality, deaths per year	1.18%	0.30%	0.64%	1.70%	2.95%
Annual mortality in LTS, deaths per year	1.29%	0.89%	1.50%	1.85%	8.86%
Excess mortality in LTS, deaths per year	0.11%	0.59%	0.87%	0.15%	5.91%

EAG comments

- Company has not described how sources identified, raising questions about whether these are truly representative of relevant modelling assumptions
- Maurer questionable generalisability: newly diagnosed DLBCL treated with immunochemotherapy
- Only source below company's preferred SMR is that from which they source their data (Maurer)
- Value of 2.36 from Eskelund (2016) appears to be a hazard ratio, reported alongside another hazard ratio of 4.37 (EAG expect true value will lie between 2.36 and 4.37, as in TA893)
- No clear evidence to suggest EAG's preferred SMR of 3 is inaccurate

- What is the most appropriate SMR to use if a cure assumption is accepted?

LTS, long-term survivorship; SMR, standardised mortality ratio; DLBCL, diffuse large B-cell lymphoma, MCL, Mantel cell lymphoma; ALL, acute lymphoblastic leukemia

Large impact

Key issues CAR-T tariff and ICU costs (1)

ACM1 conclusion

- All costs in model to be for same financial year. ICU costs to be incorporated separately

Company

- Maintains outdated CAR-T tariff of £41,101 for its base case (originally used in TA872, 2023)
- Bottom-up costing estimate done by EAG is close to the tariff figure of £41,101
- £41,101 reflects a negotiated consensus between company, NICE, and NHSE, grounded in real-world delivery costs and consistent with prior CAR-T appraisals
- Does not consider that NHSE has been transparent in its calculation of the 2024/25 tariff (£58,964) or 2025/26 tariff (£60,462), despite repeated requests to NHSE for this information
  - So not possible to scrutinise or validate the uplifted cost inputs

NICE technical team comment:

- The NICE technical team believe that the 2025/26 NHS tariff should be used. This is the most recent price outlined by NHSE. This will also ensure consistency with other topics that will use this tariff in this financial year

ICU, intensive care unit; NHSE, NHS England

Key issues CAR-T tariff and ICU costs (2)

EAG comments

- Company criticises NHSE's updated tariff values for being non-transparent and methodologically weak, but it continues to apply a lower historic tariff without providing robust evidence that this figure remains valid or accurately reflects current NHS delivery costs
- Acknowledges company's concern that details of NHSE's methodology have not been published and agrees that greater transparency in tariff construction would be beneficial
- But this does not justify continued reliance on an outdated and likely underestimated figure
- The most recent NHSE tariff reflects the best available evidence, and should be considered the most appropriate value for base case analysis

- What costs should be assumed for delivery of CAR-T treatment?

ICU, intensive care unit; NHSE, NHS England

Key issues Severity modifier (1)

ACM1 conclusion

- Severity modifier will be reconsidered at ACM2

Company

- Request flexibility for severity modifier of 1.7, accounts for uncaptured benefits of brexu-cel:
  - Overestimation of R-BAC efficacy in McCulloch (2020) because of fitter patient population
  - Impact of Covid-19 with less favourable patient outcomes during this period (ZUMA-2)
  - New BSH guidelines aim to improve earlier identification and referral of high-risk MCL
  - O'Reilly (2024) shows increase in infusion rates from 59.8% (2022) to 69.7% (2024), attributed to earlier referral, better disease control, and reduced manufacturing failure rates
  - Boyle et al. (2023) shows clear learning curve in UK CAR-T delivery (2019 vs 2020 to 2022): improvements in infusion rates (from 73% to 83%), 1-year PFS (from 32% to 50%), 1-year OS (from 40% to 60%), and ICU admission rates (from 32% to 20%)
- NICE has previously shown flexibility to allow continued access to a highly effective treatment option after period of managed access within CDF (e.g. TA509)

NICE technical team comment:

- Some of the company's comments relate to intervention outcomes, rather than standard care (which is the relevant outcomes for the severity modifier)

ACM, appraisal committee meeting; BSH, British Society of Haematology; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; ICU, intensive care unit; CDF, Cancer Drugs Fund

Key issues Severity modifier (2)

EAG comments

- Maintains severity weight of 1.2 is appropriate
- Based on preferred assumptions, both company's and EAG's base-cases support a 1.2 weight

Severity calculations

Factor	EAG's preferred assumptions	Company's preferred assumptions
Sex distribution (proportion of female)	23.00%	16.00%
Starting age	66 years	66 years
Expected years of life	[redacted]	[redacted]
Quality of life by age	[redacted]	[redacted]
Discount rate	3.5%	3.5%
Expected total QALYs general population (QALYs)	10.52	10.49
absolute shortfall	[redacted]	[redacted]
proportional shortfall	[redacted]%	[redacted]%
QALY weight	x 1.2	x 1.2

- What severity weighting should be applied?

QALY, quality-adjusted life-year

Key issues Utility values

ACM1 conclusion

- Preprogression utility should not exceed general-population utility at the baseline age, and value of 0.68 from TA502 used for postprogression health state

Company

- Maintains preprogression utility values from ZUMA-2 in base case, [redacted] (not capped at general population utility). NICE reference case states preference for patient-generated utilities
- Considers post-progression utility should be estimated using relative difference in utility values from TA502 (0.78 pre-progression, 0.68 post-progression), so post-progression utility is 13% lower than pre-progression utility

EAG comments

- Recognises importance of patient-reported outcomes but, based on clinical expert advice, not reasonable for preprogression utility values to exceed general population at the same age (highly treated population)
- Company's approach to postprogression utilities (relative difference using TA502 values) lacks robustness because it extrapolates relative changes without direct trial data
- So considers that directly applying the TA502 postprogression value of 0.68 is more appropriate

- What utility values should be used for each health state? (pre and post progression)

Key issues Use of alloSCT after R-BAC

ACM1 conclusion

- Committee preferred to assume 15% of people would have subsequent alloSCT after R-BAC.
- Committee would welcome more data and clinical input to inform this estimate

Company

- Use 15% in its updated base case- but emphasise there is little evidence to inform this
- 31% from McCulloch (2020) accepted in TA677
- To estimate outcomes for people who did not have alloSCT after R-BAC, McCulloch study limited by small sample size (n=11), short follow up and limited number of events
- So, company use Liebers et al. (2025) to improve robustness of estimated outcomes

EAG comments

- For people who do not receive alloSCT, company aligns with EAG's approach from ACM1
- For people who did receive alloSCT, company's choice of data from Liebers et al. (2025) is improvement over subgroup from McCulloch due to longer follow-up and larger sample size
- High risk of bias comparing trial data (even if pooled with SACT) for brexu-cel, to real-world data for R-BAC - but this concern goes away if focusing extrapolations on the SACT data for brexu-cel
- Higher use of alloSCT, raises question of whether a cure should be modelled for this population

Does the committee still consider 15% alloSCT use after R-BAC appropriate?
Should a cure be considered for alloSCT? What source should inform outcomes for alloSCT?

alloSCT, allogeneic stem-cell transplant; ACM, appraisal committee meeting; SACT, Systemic Anti-Cancer Therapy

Key issues IVIg use

ACM1 conclusion

- 38% of people having IVIg for 1 year is appropriate (Wang et al. 2023), if RWE not available
- Clinical experts could not outline the exact populations in which IVIg would be used

Company

- Clinical experts at ACM1 estimated 10-20% of people have IVIg after brexu-cel for ~ 1 year
- ZUMA-2 clinical trial protocol (Wang et al. 2023: IVIg given based on presence of severe hypogammaglobulinemia alone) does not align with UK clinical practice (IVIg typically only given when both hypogammaglobulinemia and infection are present), so 38% is an overestimate
- Use midpoint of clinical expert estimates (15%) in updated base case
- SACT data shows rate of 16.5% and mean duration of 6.5 months, so 12 months is conservative

EAG comments

- Acknowledge uncertainty in estimating proportion of people requiring IVIg after CAR-T
- Wang et al. (2023) and previous NICE appraisals indicate rates consistently higher (30% - 40%)
- Previous appraisals have considered longer durations (up to 3 years) and uncertainty remains about the long-term need for IVIg, so EAG explores scenarios beyond 1 year
- SACT data quoted by company comes from R/R DLBCL - not MCL

- What % of IVIg use should be considered? For what duration?

NICE

IVIg, intravenous immunoglobulin; RWE, real-world evidence; SACT, Systemic Anti-Cancer Therapy; ACM, appraisal committee meeting

Company and EAG base case analyses (1)

Company and EAG base cases differ in key aspects

Area of change	Company's new approach	EAG's new approach
Population approach and extrapolation	Patient age - 66 years Intervention: Pooled dataset based on ZUMA-2 plus SACT for OS (limited to follow-ups from August 2022 onward) and ZUMA-2 plus UK RWE (O'Reilly 2024) for PFS Comparator: Updated R-BAC outcomes estimated separately for patients not having subsequent alloSCT (estimated from McCulloch 2020) and patients having subsequent alloSCT (data from Liebers 2025).	Patient age - 66 years Intervention: Same as company, but using all the SACT data Comparator: Same as company
Cure time point	48-month LTS timepoint	60-month LTS timepoint (for the brexu-cel arm and the SoC arm in patients who had alloSCT)

LTS, long-term survivorship; SACT, systemic anti-cancer therapies; RWE, real-world evidence; OS, overall survival; PFS, progression-free survival; SoC, standard of care; alloSCT, allogeneic stem-cell transplant

Company and EAG base case analyses (2)

Company and EAG base cases differ in key aspects

Area of change	Company's new approach	EAG's new approach
Costs of alloSCT	Including alloSCT in both arms ([redacted]% in brexu-cel and 15% in R-BAC) with updated costs	Same as company
Mortality Rate Adjustment Factor (MRAF)	MRAF of 1.09	MRAF of 3.00
IVIg Therapy Needs	15% IVIg post brexu-cel (clinician advice) for 1 year	38% IVIg post brexu-cel for 1 year
CAR T tariff costs	Outdated CAR-T tariff of £41,101	Latest CAR-T tariff of £60,462 plus ICU costs (probability of 27% requiring ICU)
Pre/Post-Progression, and LTS HRQoL Estimates	Pre-Progression; ZUMA-2 value ([redacted]) Post- Progression: weighted using relative difference between pre-progression and post-progression values from TA502 (13% lower)	Pre-Progression; GPU, Post-Progression: Direct TA502 value (0.68), LTS: GPU
Severity modifier	1.2 (make case for flexibility to use 1.7)	1.2

MRAF, mortality rate adjustment factor; alloSCT, allogeneic stem-cell transplant; IVIg, intravenous immunoglobulin; ICU, intensive care unit; GPU, general population mortality

Equality issues and uncaptured benefits

Equality issues

- Mantle cell lymphoma is more prevalent in men than women
- People from ethnic minorities have fewer donor options and are less likely to have alloSCT

Uncaptured benefits

- The company suggested the following uncaptured benefits:
  - Overestimation of R-BAC efficacy in McCulloch (2020) because of fitter patient population
  - Impact of Covid-19 with less favourable patient outcomes during this period (ZUMA-2)
  - New BSH guidelines aim to improve earlier identification and referral of high-risk MCL
  - O'Reilly (2024) shows improved infusion rates between 2022 and 2024
  - Boyle et al. (2023) shows improved infusion rates, 1-year PFS and OS, and ICU admission rates between 2019 and 2022

alloSCT, allogeneic stem cell transplant; BSH, British Society for Haematology; PFS, progression-free survival; OS, overall survival; ICU, intensive care unit

Cost-effectiveness results:

- Cost effectiveness results cannot be reported here because of confidential discounts for included technologies
- Company base case ICER is above £30,000 per QALY gained
- EAG base case ICER is above £30,000 per QALY gained

- All results are presented in Part 2 slides for committee

Abbreviations: ICER; incremental cost effectiveness ratio, QALY; quality adjusted life year

Brexucabtagene autoleucel for treating relapsed or refractory mantle cell lymphoma after 2 or more systemic treatments

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background on relapsed or refractory mantle cell lymphoma

Each subsequent treatment line for MCL is associated with worsening prognosis

Causes

- Rare fast-growing cancer of lymphatic system, caused by accumulation of abnormal B-cells in mantle zone of lymph nodes
- Relapsed/ refractory MCL returns after remission (a period of disease decline or disappearance) or if it didn't respond to initial treatment

Epidemiology

- Approximately 590 people are diagnosed with MCL each year (UK)
- Most commonly diagnosed at middle-age or older

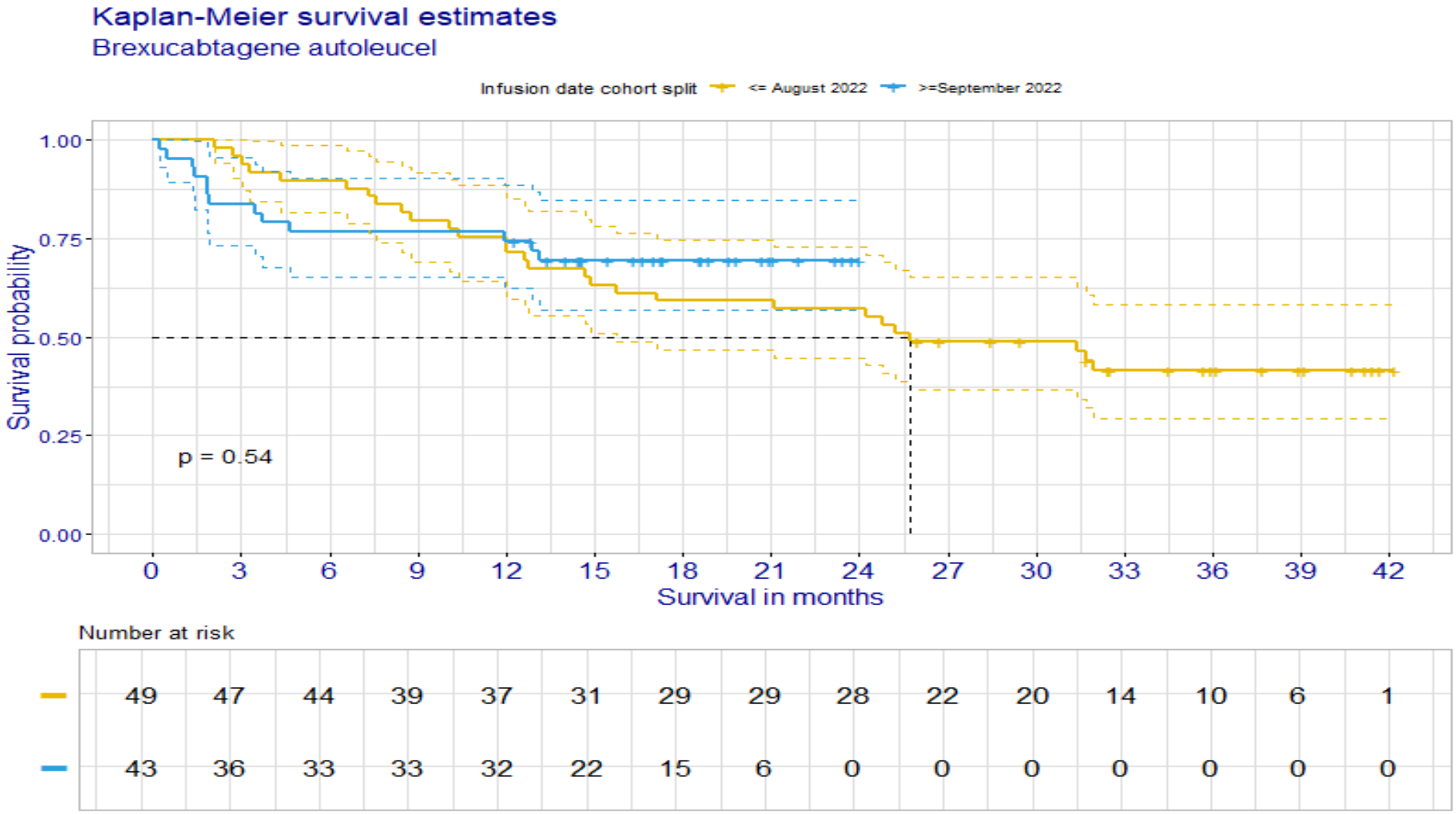
Symptoms and prognosis

- Painless swelling (because of enlarged lymph nodes), night sweats, high temperatures, weight loss and itching
- Aim of treatment for R/R MCL is disease management and prolonging survival
- Dependent on MCL International Prognostic Index risk category (low, medium or high), 5-year survival estimates at diagnosis are 60%, 40% and 15% respectively

MCL, mantle cell lymphoma; R/R, relapsed or refractory

Brexu-cel OS data from SACT

Dataset of people infused after August 2022 (n=43, blue line)



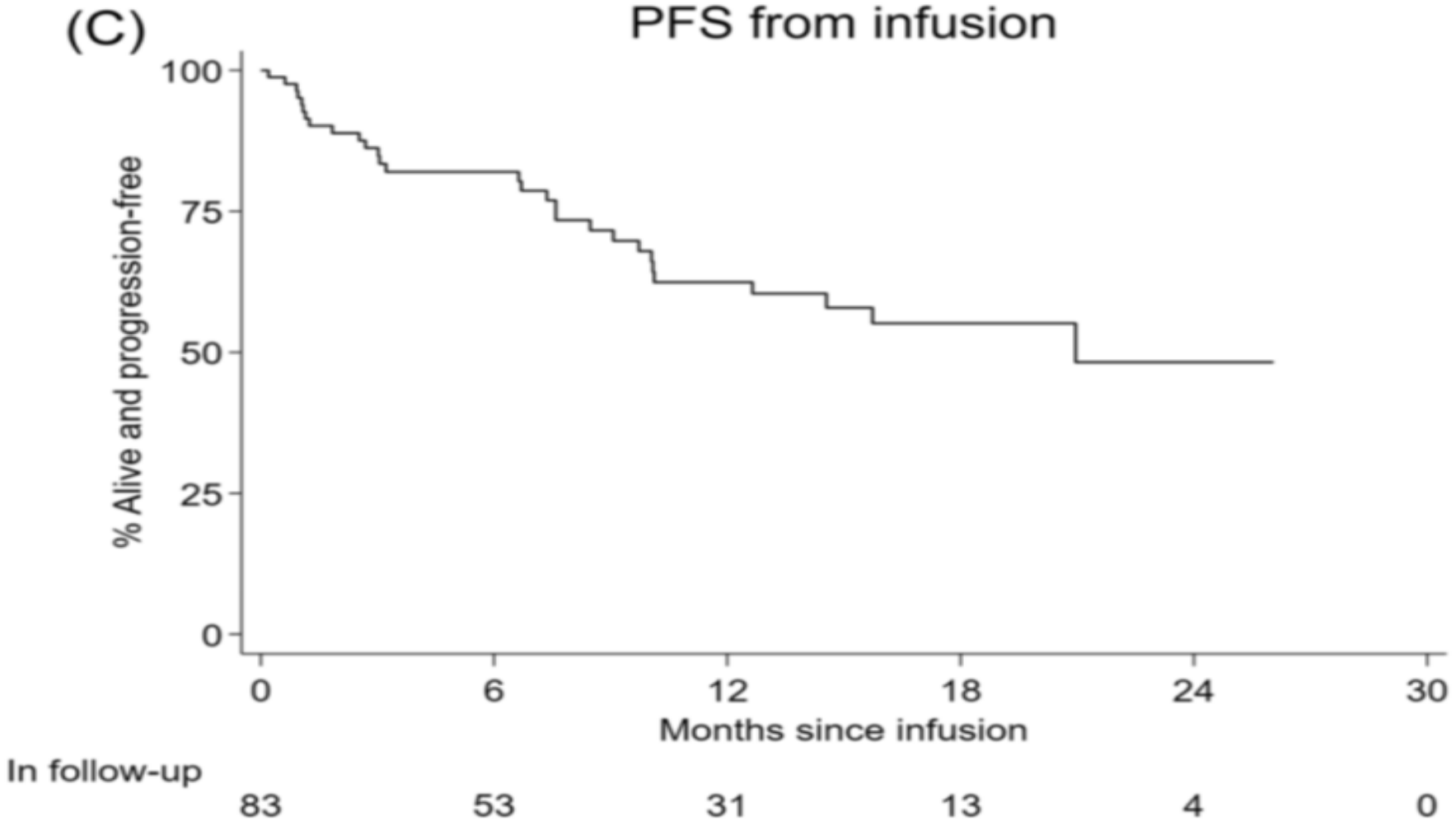
Brexu-cel pooled OS KM curves and extrapolations

Pooled OS using pseudo-IPD from ZUMA-2 (n=68) and SACT dataset enrolled from September 2022 onwards (n=43)

- Company chose log-normal for its base case, based on goodness of fit criteria

Brexu-cel PFS data from O'Reilly (2024)

RWE dataset of people infused with brexu-cel (n=83)



NICE

Brexu-cel pooled PFS KM curves and extrapolations

Pooled PFS using pseudo-IPD from ZUMA-2 (n=68) and O'Reilly (n=83)

- Company chose log-normal for its base case, based on goodness of fit criteria

OS and PFS for non-infused patients from ZUMA-2 (n=6)

People intended for treatment with brexu-cel, but who did not receive it (log-normal)

CAR-T drop-out rates

Comparison of drop-out rates between key CAR-T process steps

	ZUMA-2	O'Reilly Paper	Kite-Konnect	Company Preference	EAG preference
Drop out pre leukapheresis	NR	13% (of approved patients)	[redacted]% (of approved patients)	Not modelled	Not modelled
Drop out between leukapheresis and infusion	[redacted]% (of leukapheresed patients)	18% (of approved patients) 20% (of leukapheresed patients)	[redacted]% (of approved patients)	[redacted]% (scenario analysis)	20% (base case)

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Overview of landmark survival for outcomes

Estimated survival for company and EAG base cases

Population Outcome		24 months	48 months	60 months
Brexu-cel PFS:	Company	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]
Brexu-cel OS:	**Company**	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]
R-BAC PFS:	Company	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]
R-BAC OS:	Company	[redacted]	[redacted]	[redacted]
	EAG	[redacted]	[redacted]	[redacted]