NICE National Institute for Health and Care Excellence

[Public observer slides]

Lead team presentation - clinical

Blinatumomab for acute lymphoblastic leukaemia for people with minimal residual disease activity in remission [ID1036] - STA

Lead Team: Alex Cale, Nigel Langford, David Chandler

ERG: ScHARR, University of Sheffield

NICE technical team: Lyudmila Marinova and Alex Filby

5th February 2019

© NICE 2018. All rights reserved. Subject to notice of rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

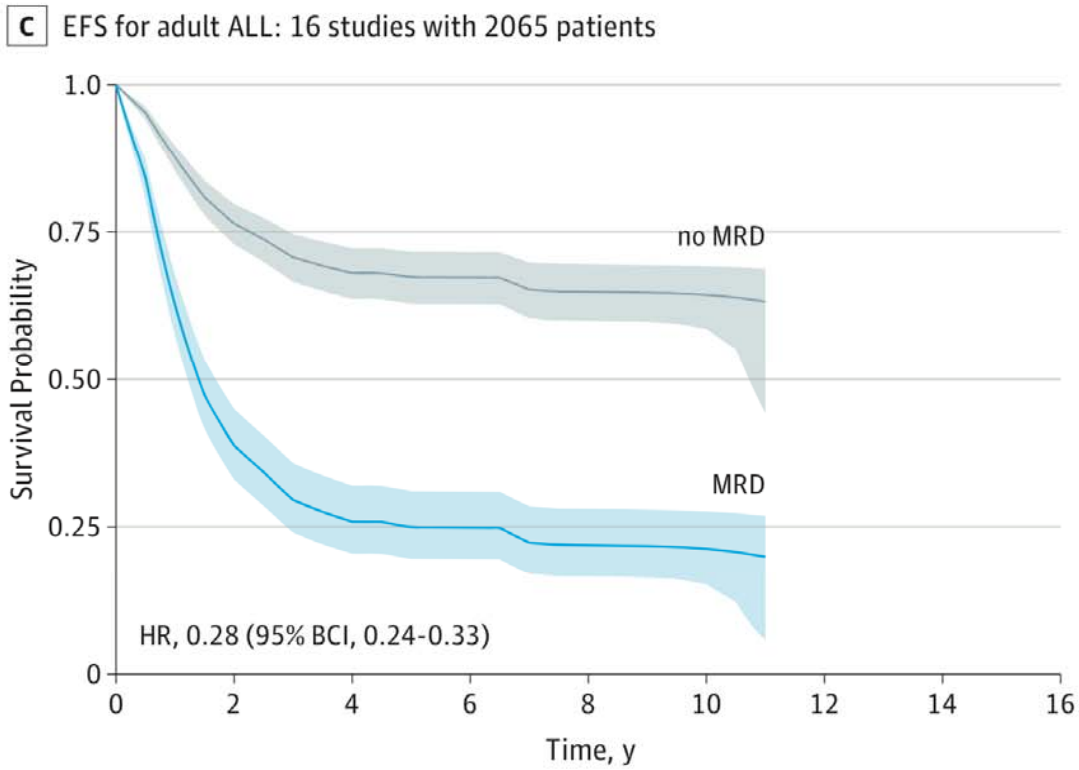
Key issues: clinical effectiveness

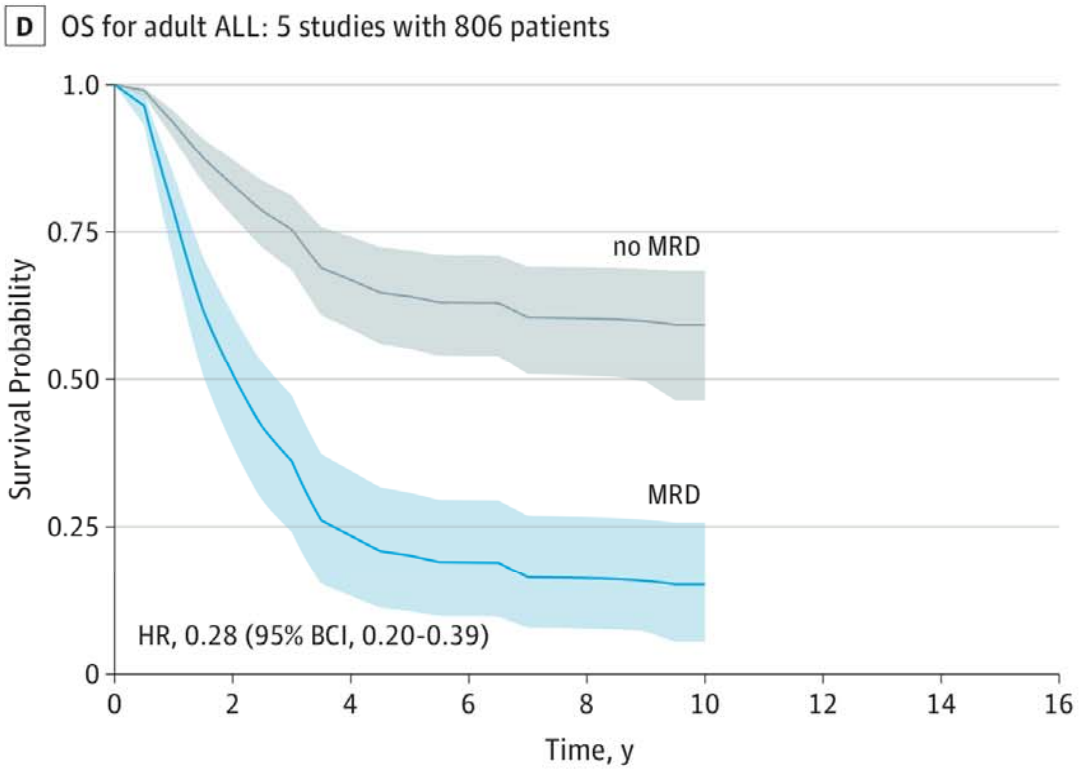
1. Where would blinatumomab (for MRD-positive) fit into NHS practice? Does the modelling reflect this?
2. Is the measurement and definition of ‘MRD’ standardised and available in the NHS? What level is ‘MRD-positive’?
3. Has the prognostic importance of MRD-positivity been clearly established?
4. Is it clear that eliminating MRD is beneficial?
5. Would patients who achieve MRD negativity with blinatumomab always *proceed* to HSCT?
6. What is the most relevant comparator in the marketing authorisation population?
7. Are results of the indirect comparison generalisable for the population in the MA, considering the absence of:
   - (i) patients unable to receive HSCT or tolerate chemotherapy,
   - (ii) patients in second complete remission (CR2)

Disease background

- ALL is a rapidly progressing form of cancer of the white blood cells
- Rare in adults - 0.2% of new cancers in UK
- 42% of ALL cases affect adults
- Common in children but children are not covered by the marketing authorisation
- Symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating. Patients with MRD activity in remission (licensed indication) may not have such extensive symptoms
- 75% of ALL is derived from precursor B-cells (B-cell ALL)
- Most B-cell ALL is Philadelphia chromosome negative (Ph-) (Ph- covered by MA)
- Approximately 44% of adult B-cell ALL patients are expected to relapse and 4% are refractory to available treatments
- MRD: residual ALL present at frequencies below the sensitivity of standard microscopy, but detectable by molecular means in the bone marrow of patients who have met the criteria for haematological complete response.
- No established MRD method for testing, so sensitivity may differ between tests

Estimated survival curves for adult patients with ALL

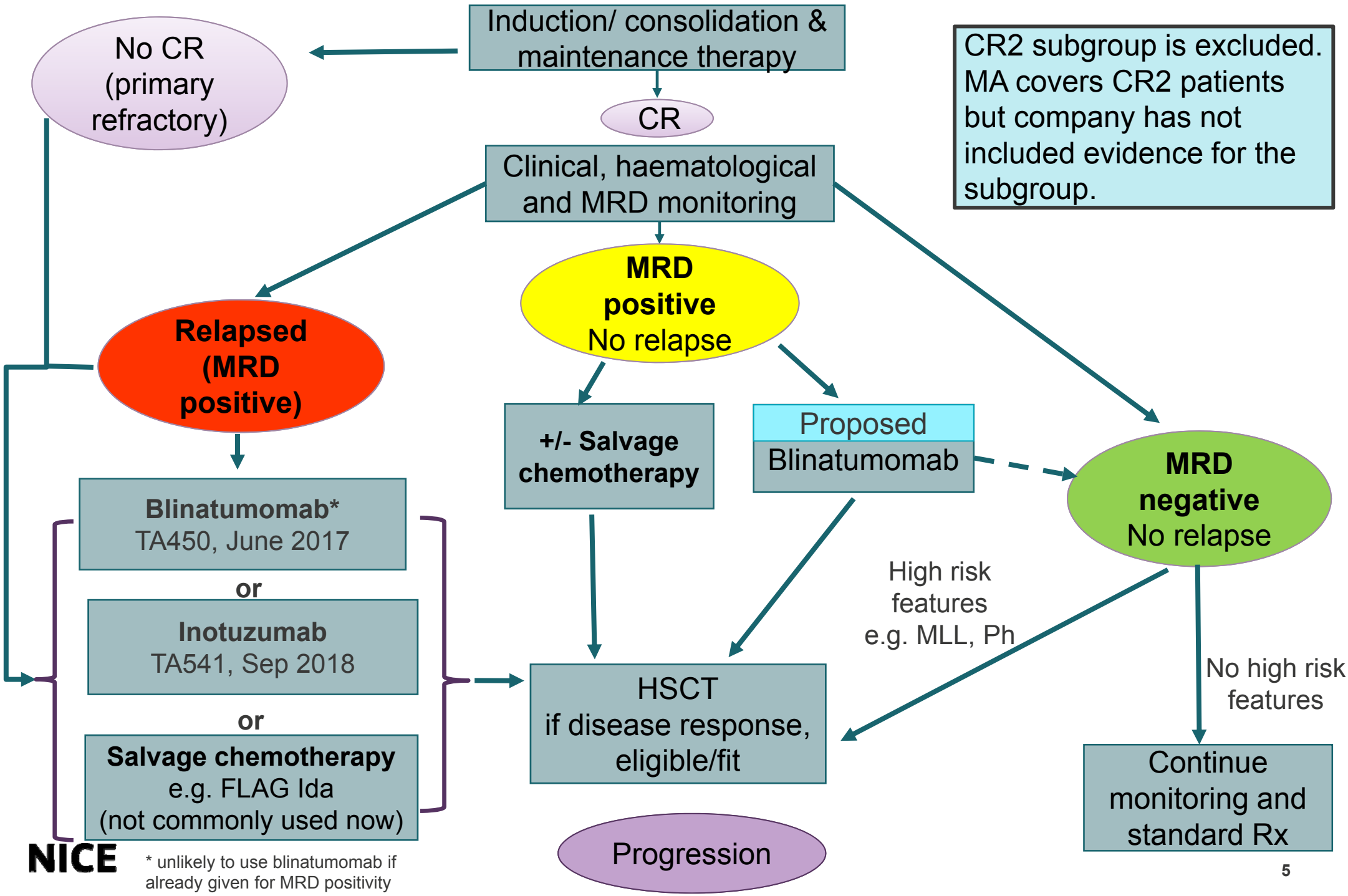




Reference: Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. Berry et al (2017); *JAMA Oncol*. 2017;3(7):e170580. doi:10.1001/jamaoncol.2017.0580

NICE

Treatment pathway for B cell precursor ALL



Blinatumomab (Amgen)

Marketing authorisation	"BLINCYTO is indicated as monotherapy for the treatment of adults with Philadelphia chromosome negative CD19 positive B-precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%." (i.e. $\geq 1 \times 10^{-3}$)
Mechanism of action	Blinatumomab is a T-cell engager targeting CD19 expressed on the surface of cells of B-lineage origin, and the CD3 expressed on the surface of T-cells. It activates endogenous T-cells by connecting CD3 expressed on the T-cell receptor complex with CD19 expressed on benign and malignant B-cells and through this mechanism it harnesses the immune system to kill the cancer cells.
Administration and dosage	It is administered by continuous intravenous infusion using an infusion pump for 28 days, followed by a 14 days treatment free period. Patients may receive 1 cycle of induction treatment followed by 3 additional cycles of consolidation treatment.
List price	The cost of blinatumomab is £2,017 per 38.5 µg vial (list price) The average cost of blinatumomab per cycle at the list price is: £56,476 (28 µg/day for Days 1–28, 28 vials) A simple discount Patient Access Scheme has been approved by NHS England

Decision problem (I)

	NICE scope	Company submission	ERG comments
Population	People with B-cell precursor ALL who have minimal residual disease (MRD) activity while in remission	Adults (≥ 18 years) with Philadelphia chromosome negative and MRD activity B-precursor ALL. Comparative effectiveness and cost-effectiveness evidence is only presented for first complete remission (CR1). The company considers that blinatumomab should be considered in its full marketing authorisation population (including second CR).	2 subgroups were excluded from indirect comparison and economic analysis: (i) patients who are in second haematological remission (CR2) (ii) patients who are unsuitable for HSCT or unable to tolerate chemotherapy.

Decision problem (II)

	NICE final scope	Company submission	ERG comments
Comparator	• Retreatment with combination chemotherapy • Monitor for relapse	• Retreatment with combination chemotherapy Expert opinion suggests that it is highly unlikely that people with MRD activity would only be monitored without any treatment. Therefore monitoring was not considered as a separate comparator, but was incorporated in ongoing chemotherapy regimens.	Blinatumomab may be a treatment option for people who are not eligible for HSCT or cannot tolerate chemotherapy, therefore monitor for relapse should have been included as a comparator for this subgroup
Outcomes	ERG comment: all relevant outcomes included		

NICE

Impact on patients – Living with ALL

Submission from Leukaemia CARE

- A rare rapidly progressive disease - most common in a younger population
- Diagnosis with ALL has huge emotional impact, placing a strain on families and friends
- Patients (and their families) experience feelings of:
  - *disbelief, denial, anger, fear, blame, guilt, isolation and depression.*
- Symptoms of active disease include:
  - *fatigue, feeling weak or breathless, sleeping problems, nausea or vomiting, memory loss or loss of concentration, tingling or numbness in extremities, bone or joint pain, bleeding or bruising and infections.*
- Therefore quality of life is affected extensively

Impact on patients – Views on treatments

Submission from Leukaemia CARE

- Patients assessed to be MRD positive following induction treatment, would be considered high-risk, with poor survival (a matter of months)
- There is an urgent need for access to treatments that can induce MRD negativity, prevent relapse and improve survival outcomes.
- Common side effects of blinatumomab:
  - *include fever, headaches, tremors, chills, fatigue, nausea and vomiting.*
- Not unusual for ALL treatment and blinatumomab is generally deemed manageable/tolerable
- In a recent survey, 76% of ALL patients reported that they would be willing to experience additional side-effects for a more effective treatment.
- Potential of outpatient administration is popular with patients
- Use as bridging therapy to stem cell transplant

Professional and clinical expert submissions

Royal College of Pathologists and Sheffield Teaching Hospital NHS Foundation Trust

- Main aim of treatment:
  - Induce remission (clear the majority of the leukaemia)
  - Consolidate remission to reduce relapse (chemotherapy, donor stem cell transplant)
- High unmet need - currently no good treatment of MRD positive patients
- Treatment options are repeating first line chemotherapy (rarely results in long term response) or HSCT, which is often ineffective
- Patients who are MRD positive after chemotherapy have a poor outlook
- Those successfully treated are often young and may go on to live long lives
- Blinatumomab is a safe and effective treatment option, tolerated better than second line chemotherapy
- Clinically meaningful benefits to patients:
  - less patients requiring second line chemotherapy treatment
  - more patients being cured. Increase in length of life more than current care
- Likely to be the only treatment option for people who cannot tolerate chemotherapy
- It can be delivered in outpatient setting

Clinical study evidence: single arm studies

	BLAST (n=116) (Used for economic model)	MT103-202 (n=20)
Design	Phase II, single-arm, open-label, international, multicentre	Phase II, single-arm, open-label, multicentre
Population	• Adult MRD+ BCP-ALL patients in haematological CR after front-line therapy • **Presence of MRD at a level of ≥10^{-3}** • Based in 10 European countries; 7 patients (6.0%) were enrolled in the UK	• Adult MRD+ BCP-ALL patients in haematological CR after front-line therapy • **Presence of MRD at a level of ≥10^{-4}** • 20 patients in Germany received at least one cycle and included in efficacy analysis
Intervention	• Blinatumomab 15 µg/m2/day continuous infusion	• Blinatumomab 15 µg/m^2/day continuous infusion
Primary outcome	• Proportion of patients with complete MRD response	• MRD response rate within 4 treatment cycles
Key secondary outcomes	• RFS at 18 months post initiation • OS; HRQoL	• MRD response after any cycle • MRD progression

NICE

ERG comments: Single-arm studies lead to performance bias, detection bias and selection bias.

Patient characteristics BLAST and MT103-202

Baseline characteristic	BLAST (n=116)	MT103-202 (n=20)
Male sex, n (%)	[redacted]	[redacted]
Median age (range), years	[redacted]	Mean age: [redacted]
Relapse history, n (%)		
First CR	[redacted]	NR
Second CR	[redacted]	NR
Third CR	[redacted]	NR
Baseline MRD levels, n (%)	[redacted]	NR
≥10^{-1} <1		
≥10^{-2} <10^{-1}	[redacted]	NR
≥10^{-3} <10^{-2}	[redacted]	NR
<10^{-3}	[redacted]	NR
Below LLQ or Unknown	[redacted]	NR
Philadelphia chromosome disease status, n (%)	Positive [redacted]	Positive [redacted]
	Negative [redacted]	Negative [redacted]

ERG comments: Majority of BLAST study patients (84%) had a baseline MRD level between 10^{-3} and 10^{-1}, where patients are classed as MRD+ when measurable to 10^{-4}. BLAST MRD levels may not necessarily reflect those of the UK population, but reflect the eligibility criteria for the blinatumomab studies.
Note: Red boxes indicate focus of model

OS and RFS outcomes in BLAST and MT103-202

Study	BLAST (n=116)		MT103-202 (n=20)
Outcome	OS/RFS not censored at HCST (CS primary analysis)	OS/RFS censored at HCST	NR
OS outcomes			
Events, n (%)	[redacted]	[redacted]	NR
Censors, n (%)	[redacted]	[redacted]	NR
OS % at 18 months, (95% CI)	[redacted]	[redacted]	NR
Median (months)	[redacted]	NR	NR
RFS outcomes			
Events, n (%)	[redacted]	[redacted]	NR
Censors, n (%)	[redacted]	[redacted]	NR
RFS % , (95% CI)	[redacted]	[redacted]	[redacted]
95% CI	[redacted]	[redacted]	
Median RFS(months)	[redacted]	[redacted]	[redacted]

NICE

ERG considers OS/RFS **not** censored at HSCT most appropriate (company's base case).

Overall survival results BLAST, Full trial population

OS censoring at HSCT, Full trial population, Median [redacted]

OS not censoring at HSCT, Full trial population, Median [redacted]

Company base case and ERG preferred

- Study MT103-202 did not include OS as an outcome measure

Relapse free survival results BLAST, Full trial population

RFS censoring at HSCT, Full trial population, Median [redacted]

RFS not censoring at HSCT, Full trial population , Median [redacted]

Company base case and ERG preferred

[redacted]

Results: MRD response and QoL in BLAST and MT103-202

	BLAST ([redacted])	MT103-202 (n=20)
Patients with complete MRD response after 1 cycle, n (%, 95% CI)	[redacted]	[redacted]
Patients with complete MRD response after ≥1 cycle, n (%, 95% CI)	[redacted]	[redacted]
Duration of median MRD response, months	without censoring [redacted] with censoring [redacted]	[redacted]

ERG comments: There was a higher rate of response for patients in CR1 82% (95% CI 72% to 90%), than in CR2 71% (95% CI 54% to 85%) or CR3 50% (95% CI 1% to 99%); but, only 2 patients in CR3. Hence results on subgroup should be treated with caution

- No significant difference for other subgroup analyses

- **EORTC QLQ-30:** Outcomes indicated some [redacted] in HRQoL, [redacted]. By the end of the BLAST study, [redacted]
- **EQ-5D:** Results did not change significantly by the end of the BLAST study

Comparative effectiveness vs chemotherapy

Comparator

- Data on the effectiveness of chemotherapy came from a historical control Study 20120148
- Covers blinatumomab MA population
- Exclusion criteria: use of blinatumomab within 18 months of MRD detection
- Primary endpoint: haematological RFS; secondary endpoints: OS, mortality rate
- Historical study subgroup of the population used in propensity score model to adjust for differences with BLAST population

BLAST subgroup and historical study subgroup are trimmed to match each other according to the following criteria:

- Ph- BCP- ALL;
- First complete haematological remission (CR1);
- MRD+ at a level of ≥1 x 10^{-3};
- ≥18 years old at MRD positivity (historical comparator) or first blinatumomab treatment (BLAST);
- Complete baseline covariate set;
- Time to relapse greater than 14 days from MRD detection (applied to historical study);
- Excludes patients in CR2 and CR3 because comparator doesn't cover them
- Trimming resulted in BLAST subgroup of [redacted] patients and historical study subgroup of [redacted] patients

Comparative effectiveness vs chemotherapy: Inverse probability of treatment weighting

- Due to differences between the populations of BLAST and the historical control study, comparative analyses were undertaken using subsets of the original study populations which were restricted to patients with Ph- disease in CR1 only: BLAST subgroup [redacted] and historical control [redacted]
- A propensity score model was constructed and used to generate weights which were applied to the historical control, with the aim of approximating the response to standard care chemotherapy that would be expected in a population with the same characteristics as the BLAST subgroup
- The resulting average treatment effect on the treated (ATT) estimates are applicable to Ph- and CR1 individuals only. This analysis suggested a hazard ratio (HR) [redacted]

ERG comments

- Method used by company is appropriate given limited data set
- Results are representative only of the CR1 population (narrower than MA)
- HSCT unobserved confounders: HSCT rate in BLAST (76%) is higher than the historical control study (37%)
- Limitations to non-randomised data: not possible to account for unobserved confounders and not clear if uncertainty surrounding the method use was accounted for
- Reported treatment effects likely to underestimate associated uncertainty – to be interpreted with caution
- Lack of clarity: stabilised weights presented in clinical effectiveness section, while standard (non-stabilised) weights used in economic model but clarified with company that there is no impact

OS results from propensity score method: BLAST subgroup [redacted] and historical study subgroup [redacted]

Blinatumomab [redacted]

Historical study subgroup [redacted]

Outcome	Median (months)		HR (95% CI)
	Standard care	Blinatumomab	Primary analysis
OS	[redacted]	[redacted]	[redacted]

RFS results from propensity score method:

BLAST subgroup [redacted] and historical study subgroup [redacted]

Outcome	Median (months)		HR (95% CI)
	Standard care	Blinatumomab	Primary analysis
RFS	[redacted]	[redacted]	[redacted]

Adverse events: Safety analysis

Pooled data from BLAST (n=116) and MT103-202 (n=20)

Event	Treatment-emergent AEs [redacted]	Treatment-related AEs [redacted]
All AEs, n (%)	[redacted]	[redacted]
Serious	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Grade ≥4	[redacted]	[redacted]
Fatal (occur within 30 days of blinatumomab treatment)	[redacted]	[redacted]
Leading to permanent discontinuation of blinatumomab	[redacted]	[redacted]
Serious	[redacted]	[redacted]
Grade ≥3	[redacted]	[redacted]
Grade ≥4	[redacted]	[redacted]
Fatal	[redacted]	[redacted]

- Events occurred in more than 20% of patients: [redacted] The most common treatment emergent AEs of blinatumomab were: [redacted]
  All patients experienced at least one treatment-emergent AE.
- Data included in economic model

Summary of ERG's comments on clinical evidence

Key areas of uncertainty:

- Only single-arm studies – these were well conducted but subject to inherent bias
- Absence of clinical evidence subgroups excluded from the comparative analysis (patients with CR2+)
- Generalisability to the full population in NICE scope and MA: the treatment effect estimates reflect a narrower population than NICE scope
- Excluded comparator: monitoring for relapse for a subgroup of patients unable to undergo HSCT or tolerate chemotherapy: unclear whether any relevant comparator data exist
- Treatment effects (HR) ignore uncertainty around estimated propensity score weights, and therefore it is likely that estimates underestimate the total uncertainty of the reported HR, resulting in erroneously narrow confidence intervals. HR results should be interpreted with caution.

Key issues: clinical effectiveness

1. Where would blinatumomab (for MRD-positive) fit into NHS practice? Does the modelling reflect this?
2. Is the measurement and definition of ‘MRD’ standardised and available in the NHS? What level is ‘MRD-positive’?
3. Has the prognostic importance of MRD-positivity been clearly established?
4. Is it clear that eliminating MRD is beneficial?
5. Would all patients who received blinatumomab proceed to HSCT?
6. What is the most relevant comparator in the marketing authorisation population?
7. Are results of the indirect comparison generalisable for the population in the MA, considering the absence of:
   - (i) patients unable to receive HSCT or tolerate chemotherapy,
   - (ii) patients in second complete remission (CR2)

NICE National Institute for Health and Care Excellence

[Public observer slides]

Lead team presentation - cost

Blinatumomab for acute lymphoblastic leukaemia for people with minimal residual disease activity in remission [ID1036] - STA

Lead Team: Alex Cale, Nigel Langford, David Chandler

ERG: ScHARR, University of Sheffield

NICE technical team: Lyudmila Marinova and Alex Filby

5th February 2019

© NICE 2018. All rights reserved. Subject to notice of rights. The content in this publication is owned by multiple parties and may not be re-used without the permission of the relevant copyright owner.

Key issues: cost effectiveness

1. Are cost-effectiveness results generalisable for the population in the MA, considering the absence of:

   (i) patients unable to receive HSCT or tolerate chemotherapy,

   (ii) patients in second complete remission (CR2)

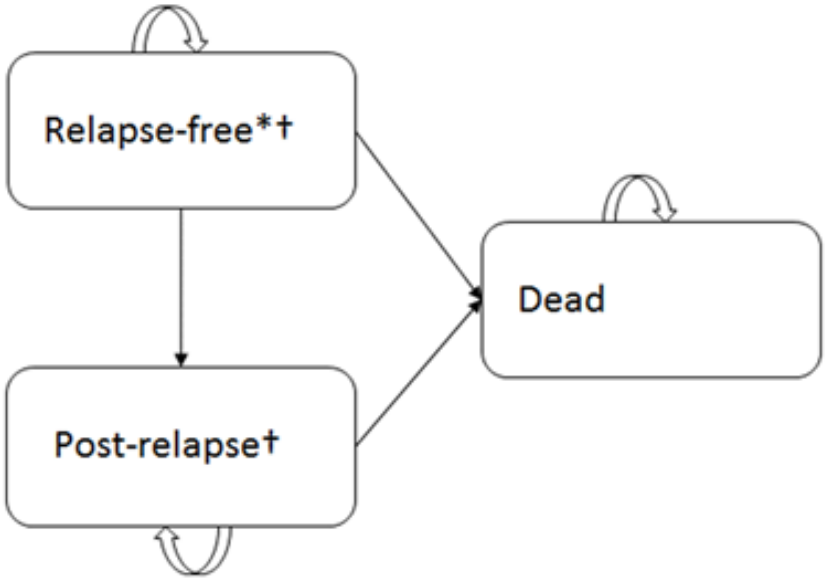
2. Which parametric curves for OS and RFS are most appropriate for extrapolation?
3. How should cure be modelled? What cure point should be included in the model?

   Company preferred: no fixed cure point; ERG preferred: fixed cure at 5 years in both arms

4. Which post-relapse HRQoL estimate should be used: (i) observed utility of 0.692 among BLAST patients with post-relapse assessment, assumed values of (ii) 0.50 and (iii) 0.25
5. Does the model structure appropriately incorporate HSCT? Should alternative modelling be used or will it have similar uncertainty issues?
6. Which is the most plausible ICER?
7. End of life criteria
8. Equality and innovation
9. Suitable for CDF?

Company's economic model: structure

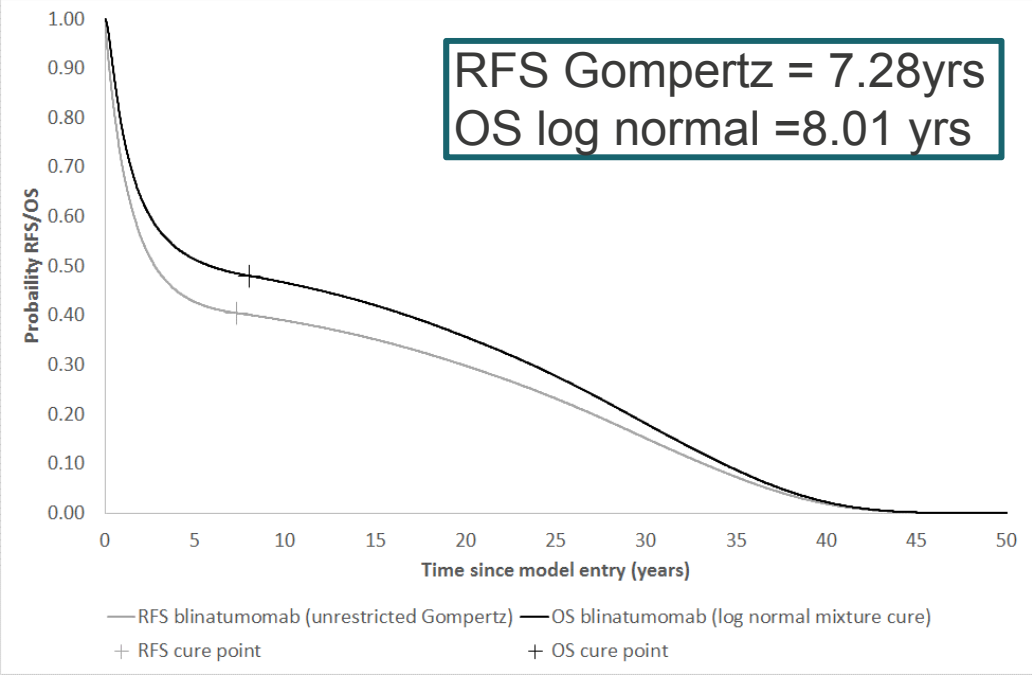
- Partitioned survival model based on RFS and OS. This structure does not allow for tracking of HSCT either before or after relapse.
- The principal benefits of HSCT in avoiding/delaying relapse are implicitly accounted for in the RFS and OS outcomes.
- The QALY losses and costs associated with the HSCT procedure and post-HSCT survival are reflected within two HSCT sub-models applied to the main partition survival structure. The pre-relapse HSCT sub-model is not causally related to RFS or OS, whilst the post-relapse HSCT sub-model is partially related to RFS.



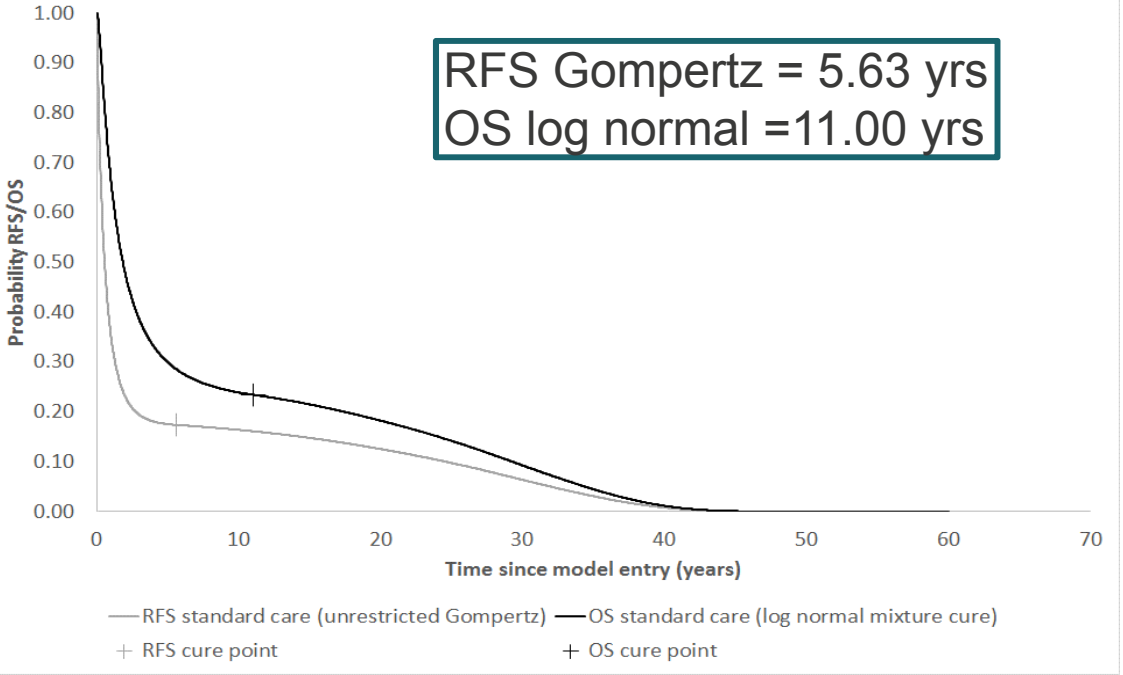
** RFS time divided into time on treatment and post-discontinuation*
† Patients may enter state-specific HSCT sub-model

Company's economic model: RFS/OS and cure point

Company base case: RFS and OS cure points blinatumomab arm



Company base case: RFS and OS cure points SoC arm



- RFS is based on a parametric (Gompertz) model fitted to the treatment-specific RFS time-to-event data
- OS is modelled using a parametric (log normal) mixture cure model fitted to the OS time-to-event data
- Distributions in company's model (RFS and OS) chosen based on a subset of models with best fit and good BIC
- Cure fraction is predicted by model and not fixed in time. Leads to different time points for cure as graphs show

NICE

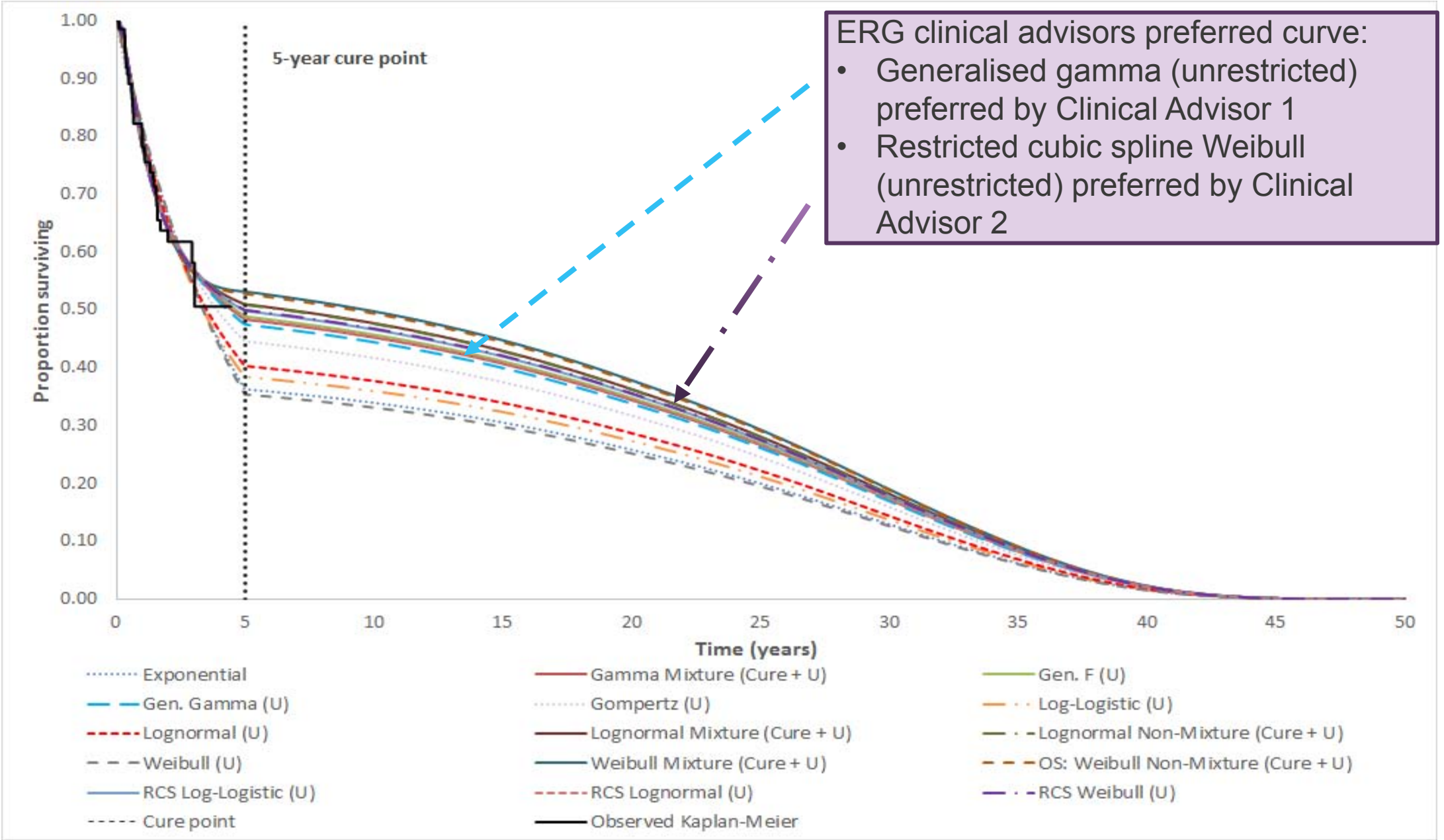
ERG comment: it is not clinically plausible to apply models which feature such a large gap between those achieving cure pre- and post-relapse

ERG critique of company model structure

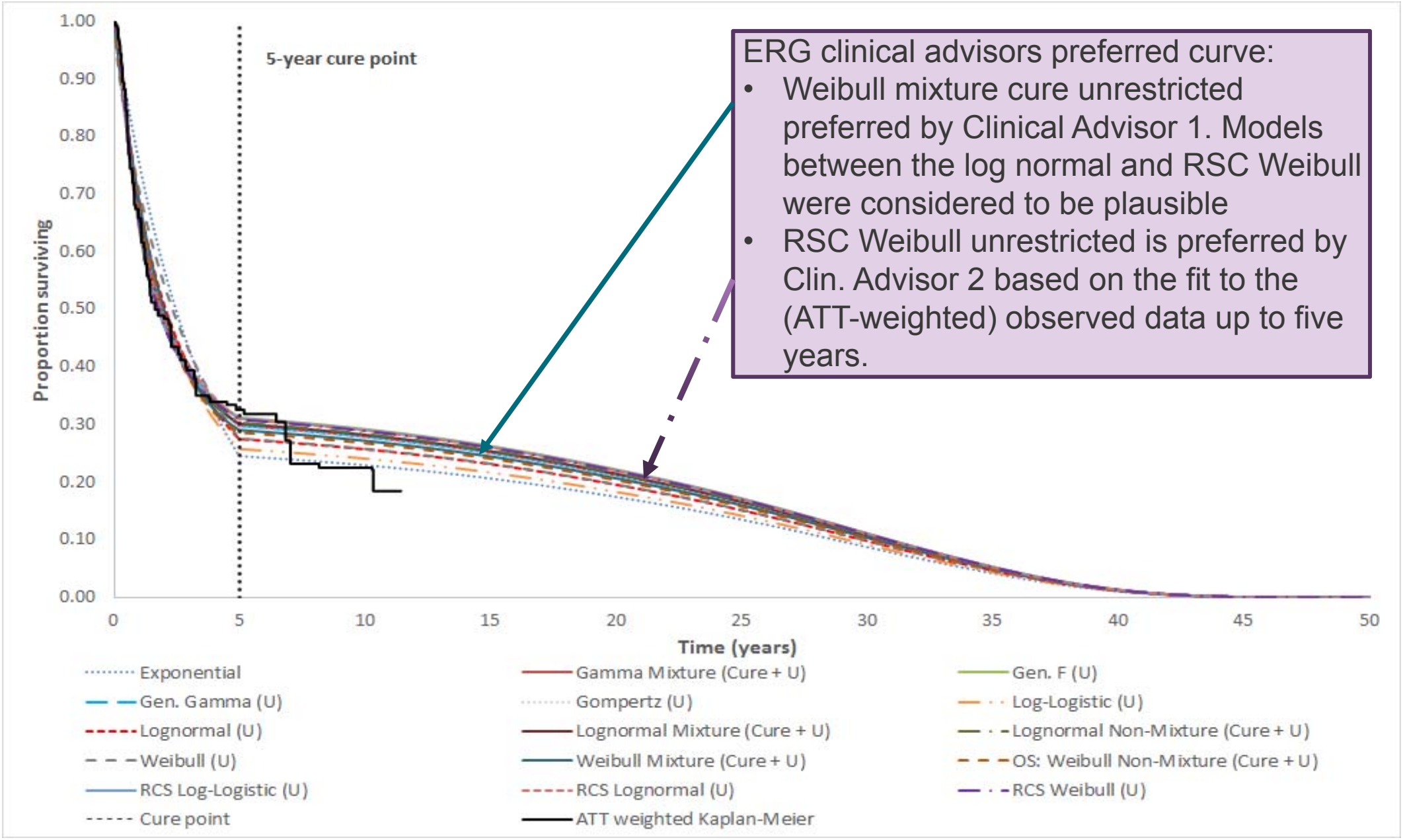
- Cure model appropriate: patient is considered cured if no relapse within 5-years
- Not clear if selected subset of RFS/OS models are clinically plausible (some do not predict a cure fraction and are inappropriate)
- Cure points with different time points (as company base-case) result in large gaps between cure pre- and post-relapse which is not clinically plausible
- Uncertainty regarding proportion of RFS deaths - decreasing them in the blinatumomab group leads to a less favourable ICER
- ERG think more appropriate to apply fixed cure at 5 years and prefers cure unrestricted model
- Model structure not appropriate for tracking HSCT due to:
    a. absence of causal link between HSCT uptake and its impact on RFS and OS outcomes;
    b. model does not estimate probability of receiving HSCT (cannot track patients who undergo HSCT post-relapse);
    c. adoption of questionable assumptions regarding HSCT receipt : BUT no substantial impact on ICER
    d. likely underestimation of post-HSCT costs – relied on survival data only for transplanted cohort; ERG testing shows that increasing post-HSCT costs and HRQoL decrements leads to increased ICER for blinatumomab vs SoC . Still not a big impact on ICER
    e. ERG suggests alternative model (eg. semi-Markov) to fully capture HSCT use

Although, ERG has explored alternative assumptions and models, it notes that data to populate transitions for other models may be limited and may be subject to selection bias and uncertainty.

ERG exploratory and preferred OS for blinatumomab



ERG exploratory and preferred OS for SoC



ERG clinical advisors preferred curve:

- Weibull mixture cure unrestricted preferred by Clinical Advisor 1. Models between the log normal and RSC Weibull were considered to be plausible
- RSC Weibull unrestricted is preferred by Clin. Advisor 2 based on the fit to the (ATT-weighted) observed data up to five years.

Company's model inputs and ERG comments

	Company	ERG comments
Population	Ph- MRD+ BCP-ALL in CR1 (MRD+ ≥1 x 10-3) (BLAST subgroup & historical comparator subgroup with ATT weights)	• Reflects patients likely to tolerate chemotherapy • Narrower than MA as it excludes CR2 patients (due to lack of data) • Cannot assess the cost-effectiveness of blinatumomab in these excluded population groups.
Comparator	SoC - chemotherapy regimen	• SoC chemotherapy regimen comprised of vincristine, prednisolone, mercaptopurine, methotrexate and prophylaxis against CNS relapse using intrathecal methotrexate (treatment up to 2 years) • Excludes "monitor for relapse" (may be relevant to patients unable to undergo HSCT or tolerate chemotherapy)
Costs	Active treatment costs (inpatient and out-patient setting, blinatumomab, HSCT, salvage chemotherapy)	No major issues with cost inputs
Dataset	BLAST subgroup and historical study subgroup with ATT weights	• IPTW propensity score methods appropriate given the absence of RCT evidence but introduce uncertainty

NICE

Company's model inputs: Utility values

Health state	Utility
Relapse-free utility [Blinatumomab, on-treatment, >6 months prior to death, cycle 1†; cycle 2+†]	0.792; 0.832
Relapse-free utility [Blinatumomab, off-treatment, >6 months prior to death, cycle 1†; cycle 2+†]	0.802; 0.842
SoC, relapse-free, >6 months prior to death	0.806
Post-relapse utility [Blinatumomab and SoC, >6 mos prior to death	0.692
General population utility decrement*	-0.02
HSCT utility decrement [1-12; 13-24; 25-60; 61+ months]	-0.170; -0.010; -0.020; 0.000

ERG concerns regarding plausibility of HRQoL estimates

- unrealistically high post-relapse utility estimate of 0.692 (per ERG clinical expert opinion)
- ERG ran exploratory analysis 7 and applied alternative post-relapse utility estimates (observed utility of BLAST patients with post-relapse assessment 0.819, assumed values of 0.50 and 0.25)
- Results show only a minor impact on ICER

Cost effectiveness results: company's base case (post-clarification submission, PAS included)

Option	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Probabilistic results (company's base case post clarification: unrestricted Gompertz function for RFS, log normal mixture cure model for OS, not-fixed cure point predicted by model)					
Blinatumomab	7.11	[redacted]	2.92	£83,634	£28,655
Standard care	4.19	[redacted]	-	-	-
Deterministic results (company's base case post clarification)					
Blinatumomab	7.23	[redacted]	3.02	£83,800	£27,779
Standard care	4.21	[redacted]	-	-	-

Company's updated model submitted post-clarification with the following amendments: (i) maximum annual mortality risk capped at 100%; (ii) pump costs included for all days after the first inpatient stay; (iii) general population utilities based on Ara and Brazier (2010), and (iv) post-relapse allogeneic HSCT not initiated after 5 years

Cost breakdown: company's base case

Cost Category	Blinatumomab (£)	SOC (£)	Incremental (£)
Pre-Relapse			
Blinatumomab and SOC maintenance treatment			
Medication	[redacted]	[redacted]	[redacted]
Administration			
Hospitalisation	[redacted]	N/A	[redacted]
Outpatient visits	[redacted]	[redacted]	[redacted]
Infusion pump	[redacted]	N/A	[redacted]
Total medication and admin.	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]	[redacted]
Other inpatient	[redacted]	[redacted]	[redacted]
Other outpatient	[redacted]	[redacted]	[redacted]
Total pre-relapse	[redacted]	[redacted]	[redacted]
Post-relapse			
Salvage therapy	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]	[redacted]
Other inpatient	[redacted]	[redacted]	[redacted]
Other outpatient	[redacted]	[redacted]	[redacted]
Total post-relapse	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Note: Mean number of blinatumomab cycles in BLAST= 1.86

Cost effectiveness results: ERG's corrected version of company's base case (PAS incl.)

Option	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Deterministic results (company's base case post clarification, used by ERG for expl. analyses)					
Blinatumomab	7.23	[redacted]	3.02	£83,800	£27,779
Standard care	4.21	[redacted]	-	-	-
ERG's rebuilt deterministic model (exploratory analysis 1: minor errors corrected)					
Blinatumomab	7.21	[redacted]	3.00	£83,264	£27,717
Standard care	4.21	[redacted]	-	-	-

ERG comment: PSA cost-effectiveness based on company's probabilistic model:

- Approx. 80% of ICER estimates lie below the £50,000/QALY threshold and 50% below the £30,000/QALY threshold.

ERG exploratory analyses results (I)
(deterministic results, PAS included)

Option	QALYs	Costs	Inc. QALYs	Inc. Costs	ICER
Company's base case deterministic version: RFS Gompertz (U) & OS lognormal mix cure					
Blinatumomab	7.23	[redacted]	3.02	£83,800	£27,779
Standard care	4.21	[redacted]	-	-	-
ERG exploratory analysis 1 – Correction of errors identified during model verification					
Blinatumomab	7.21	[redacted]	3.00	£83,264	£27,717
Standard care	4.21	[redacted]	-	-	-
ERG exploratory analysis 2 – Fixed cure point applied to all surviving patients at 5 years					
Blinatumomab	7.37	[redacted]	2.77	£83,803	£30,304
Standard care	4.61	[redacted]	-	-	-
ERG exploratory analysis 3 –Analyses 1 and 2 combined (ERG-preferred model)					
Blinatumomab	7.35	[redacted]	2.75	£83,268	£30,227
Standard care	4.59	[redacted]	-	-	-

- **ERG comment analysis 2**: 5-year cure point is applied to original model, hazard of death is switched to the general population at year 5 and beyond.
- **ERG comment analysis 3**: ERG's preferred model is company's updated model with corrected errors and added 5-year fixed cure point. The uncertainty based on original parametric RFS and OS still remains .

ERG exploratory analyses results (II)

(deterministic results, PAS included)

Option	Total QALYs	Total Costs	Inc. QALYs	Inc. Costs	ICER
Exploratory analysis 4: standard care costs doubled (based on ERG-preferred model)					
Blinatumomab	7.35	[redacted]	2.75	£82,222	£29,848
Standard care	4.59	[redacted]	-	-	-
Exploratory analysis 5: alternative HSCT survival probabilities (based on ERG-preferred model)					
Blinatumomab	7.29	[redacted]	2.73	£89,302	£32,667
Standard care	4.55	[redacted]	-	-	-

Exploratory analysis 4: Alternative SoC costs: drug acquisition costs were doubled to assess the impact of assuming alternative treatment regimens. No significant impact on ICER

Exploratory analysis 5: Assess impact of alternative HSCT survival probabilities

- Shows that HSCT survival probabilities lead to an increase ICER for blinatumomab vs SoC; but ERG notes there is uncertainty around survival trajectory of HSCT patients

ERG exploratory analyses results (II) Alternative cure fractions for SoC and utilities

(deterministic results, PAS included)

Blinatumomab vs SOC	Inc. QALYs	Inc. Costs	ICER
Exploratory analysis 6 – alternative cure fractions for SoC (based on ERG-preferred model)			
Cure fraction = 0.21 (company base case)	2.75	£83,268	£30,227
Cure fraction = 0.25	2.36	£81,402	£34,465
Cure fraction = 0.30	1.83	£78,883	£43,072
Cure fraction = 0.35	1.30	£76,363	£58,697
Exploratory analysis 7 - Impact of alternative post-relapse utility values			
Utility = 0.69 (company's base case)	2.75	£83,268	£30,227
Utility = 0.819 (BLAST post-relapse utility)	2.67	£83,268	£31,157
Utility = 0.50	2.88	£83,268	£28,930
Utility = 0.25	3.04	£83,268	£27,395

ERG comments:

- Results show cure fraction is a key driver of cost-effectiveness for blinatumomab vs SoC
- Utility values for the post-relapse state have a minor impact on the ICER

ERG exploratory analyses – alternative models (III)

(deterministic results, PAS included)

Exploratory analysis 8 - Impact of using ERG's clinical advisors' preferred OS models		
OS model (low-high ICER determined by RFS curve)	Low ICER	High ICER
(a) Generalised gamma (unrestricted) preferred for blinatumomab arm by Clinical Advisor 1	£32,800	£34,904
(b) Restricted cubic spline Weibull (unrestricted) preferred for blinatumomab arm by Clinical Advisor 2	£30,868	£32,857
(c) Weibull mixture cure (unrestricted) selected for SoC by Clinical Advisor 1	£25,810	£27,492

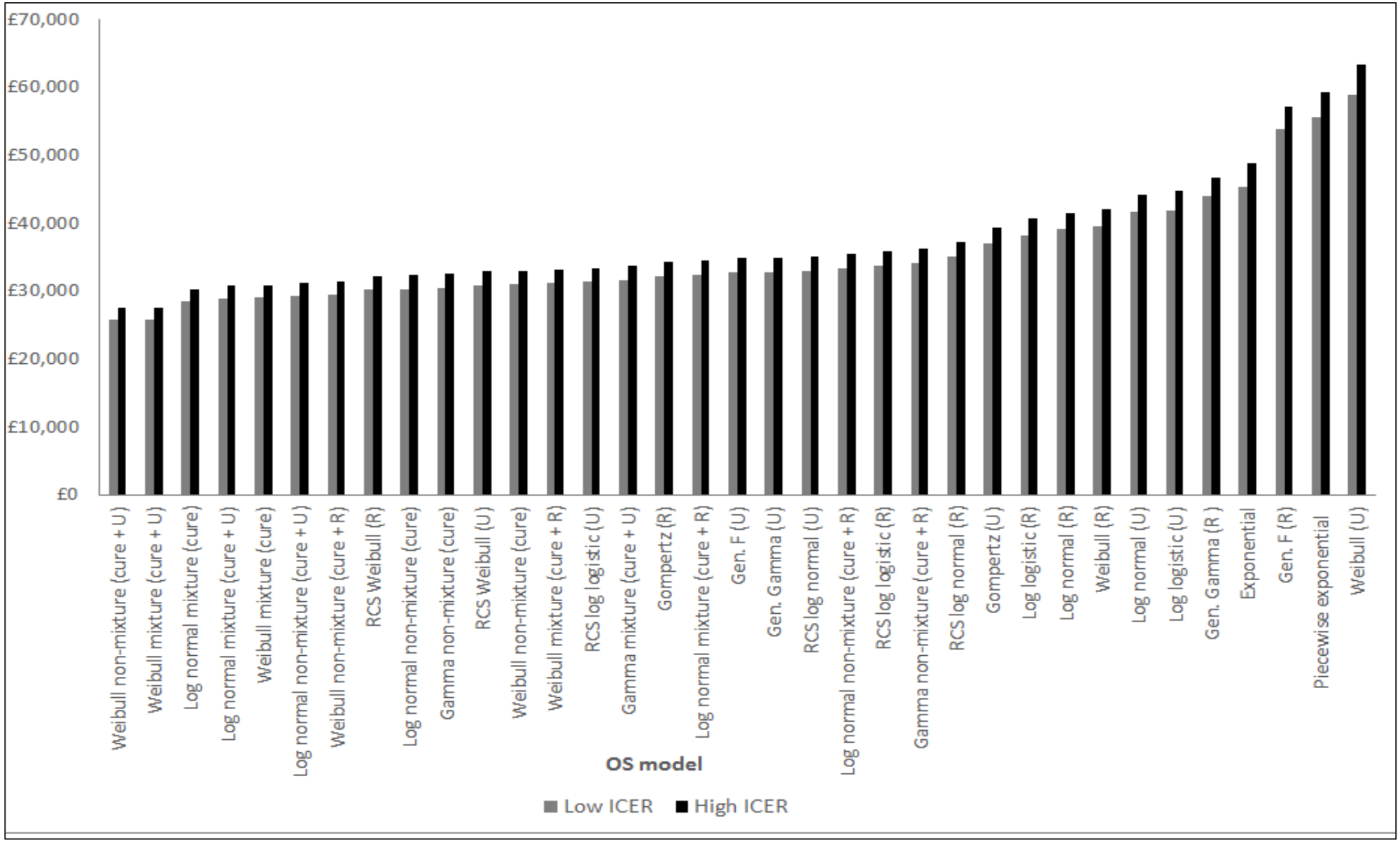
ERG comment: Cure rate is driving cost-effectiveness. Inclusion of the 5-year cure assumption reduces variation in ICERs across the OS models considered (cure models also produce lower ICERs vs other OS forms)

- Range of low and high ICERs reflects the impact of assuming alternative RFS functions
- Only the Weibull non-mixture cure model (unrestricted) and the Weibull mixture cure model (unrestricted) produced ICERs below £30,000 per QALY gained

ERG Clinical experts: Cure point at 5 years is acceptable

- The distributions above were chosen based on:
  - (a) OS at 50% at 5 years data matched observed data from BLAST and MT103-202
  - (b) Provides clinically expected changes in OS between years 4 and 5
  - (c) The predicted 5-year OS probability
  - (d) RSC Weibull is preferred based on the fit to the (ATT-weighted) observed data up to five years.
- The clinical advisors' 3 preferred OS models result in ICERs in the range £25,810- £34,904 per QALY gained.

ERG exploratory analysis 8: Impact of alternative parametric RFS and OS models on the ICER for blinatumomab



Innovation and equality

- Clinicians consider it innovative and a step-change in the management of ALL with MRD activity (Professional expert submission)
- Currently no targeted treatment option is available for people with MRD positive B-cell precursor positive ALL (Professional expert submission)
- Novel mechanism of action facilitates transient connection of malignant cells with T cells, thereby inducing T-cell-mediated killing of the bound malignant cell. By bringing T cells into close proximity with tumour cells much more frequently than without blinatumomab, the surveillance and cytotoxic abilities of the patient's own T cells are greatly increased (Company submission, B.2.12)
- No equality issues raised during scoping or company submission/ patient professional statements.

End of life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS for the historical control group (using ATT-weighted propensity score matching analyses) for standard care chemotherapy was [redacted] The estimated mean survival (undiscounted) in the economic analysis was almost 5x greater than the median survival ([redacted] years) in the SoC arm; however, this is reflective of the small proportion of patients who achieve long-term survival (~20%).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median OS (using ATT-weighted propensity score matching analyses), was [redacted] after more than 40 months follow-up for blinatumomab thus demonstrating a [redacted] OS survival [redacted] when compared to standard care. The estimated mean survival (undiscounted) in the economic analysis was [redacted] years in the blinatumomab arm, resulting in an incremental survival benefit of [redacted] years.
ERG comment	ERG disagrees with using median values to determine whether the end of life criteria are met. Medians represent the middle patient and don't take into account the skewness in the distribution of patient outcomes ERG's exploratory analyses show a lowest mean OS for the standard of care group of 7.69 years and a mean OS gain with blinatumomab of 2.12 years.

End of life considerations:
Landmark OS based on company's base case updated post-clarification

Landmark OS vs. BLAST				
Month	Blinatumomab		SOC	
	BLAST	Model	Historical Control	Model
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
53.5	[redacted]	[redacted]	[redacted]	[redacted]
60*		[redacted]	[redacted]	[redacted]
120*		[redacted]	[redacted]	[redacted]

**Input obtained from company model v0.4 by NICE technical team*

Key issues: cost effectiveness

1. Are cost-effectiveness results generalisable for the population in the MA, considering the absence of:

   (i) patients unable to receive HSCT or tolerate chemotherapy,

   (ii) patients in second complete remission (CR2)
2. Which parametric curves for OS and RFS are most appropriate for extrapolation?
3. How should cure be modelled? What cure point should be included in the model?

   Company preferred: no fixed cure point; ERG preferred: fixed cure at 5 years in both arms
4. Which post-relapse HRQoL estimate should be used: (i) observed utility of 0.692 among BLAST patients with post-relapse assessment, assumed values of (ii) 0.50 and (iii) 0.25
5. Does the model structure appropriately incorporate HSCT? Should alternative modelling be used or will it have similar uncertainty issues?
6. Which is the most plausible ICER?
7. End of life criteria
8. Equality and innovation
9. Suitable for CDF?