NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Blinatumomab for treating minimal residual B-precursor acute lymphoblastic leukaemia in remission [ID1036]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Second committee meeting presentation slides**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Leukaemia Care
   - The Royal College of Pathologists
   - The Royal College of Pathologists-British Society of Haematology
   - The Royal College of Physicians-The Royal College of Radiologists

   Comments on the Appraisal Consultation Document from experts:
   No comments

   Comments on the Appraisal Consultation Document received through the NICE website
   No comments

4. **Appendix of new evidence –** submitted by Amgen
   - ACD response form
   - ACD response appendix 1
   - ACD response appendix 2
   - Additional clarification response
   - HSCT post-relapse costing
   - Post-relapse OS Tower patients
   - KM estimates by events

5. **New evidence submission by Professor Adele Fielding - UKALL14**

6. **Evidence Review Group critique of company response** – prepared by School of Health and Related Research

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

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Amgen	**Executive summary** **We have carefully reviewed the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) of blinatumomab (Blincyto®) in the treatment of acute lymphoblastic leukaemia (ALL) in remission with minimal residual disease (MRD). Importantly, the Committee has recognised that patients with ALL who achieve haematological complete remission (CR) but have MRD remain at significantly greater risk for relapse and have poorer survival than those without MRD. Blinatumomab is a highly innovative therapy and is unique in being the only therapy approved to address the significant unmet needs of patients with this ultra-orphan disease.** **Blinatumomab was recommended by NICE in June 2017 for use in patients with ALL who have relapsed following prior therapy (TA450). Since then, blinatumomab has also demonstrated unprecedented high MRD response rates, relapse-free survival (RFS) and overall survival (OS) benefits compared with standard of care (SOC) chemotherapy in the earlier setting in patients in CR with MRD, despite the many challenges presented by the rarity of the condition and the lack of effective treatments. These benefits translate into a high likelihood of blinatumomab being cost effective when used earlier in the treatment pathway in patients in CR with MRD compared with its currently recommended use in patients after they have experienced frank relapse. We are therefore disappointed that the Committee was minded not to recommend the earlier use of blinatumomab as a treatment option in these patients due to perceived uncertainties regarding the exact size of its treatment benefits relative to chemotherapy, and its cost effectiveness in this setting.** We are committed to working with NICE to address the concerns of the Committee expressed in the ACD. We have responded to the Committee's specific requests by: • providing the latest BLAST trial data cut to address concerns regarding uncertainty in the long-term survival benefit with blinatumomab; and • conducting extensive cost-effectiveness analyses including a new model structure to address	Comments noted. Individual comments addressed below.

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			concerns regarding uncertainty in the cost effectiveness of blinatumomab. We believe our response will sufficiently address the concerns of the Committee, demonstrate there is little uncertainty in the size of the treatment benefits with blinatumomab relative to chemotherapy, establish that blinatumomab is highly likely to be cost effective, and allow a positive recommendation for the appropriate, earlier use of blinatumomab in the MRD setting. 1. **ALL patients in CR with MRD remain at high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to approve blinatumomab use earlier in the treatment pathway before relapse.** As acknowledged in the ACD, patients who achieve CR but have MRD are at increased risk of relapse and have poorer survival than those without MRD. Blinatumomab is the only therapy approved for use in MRD and, as indicated in the scope, the only relevant comparator is continued chemotherapy. However, as MRD is an indicator of chemotherapy resistance, patients with MRD are predicted to have a poor response to subsequent chemotherapy. Blinatumomab is currently recommended as a treatment option in relapsed/refractory ALL patients based on NICE TA450. However, patients who experience relapse experience poorer survival outcomes. There are therefore robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients with MRD, to reduce their risk of relapse and optimise their outcomes, rather than requiring these patients to first experience frank relapse before accessing blinatumomab (or inotuzumab) as salvage therapy. 2. **The clinical benefit of blinatumomab when used early in the treatment pathway in patients in CR with MRD is clearly established and is unprecedented; there is a high degree of certainty in the size and durability of the clinical effects of blinatumomab relative to chemotherapy.** **Trial data:** The BLAST and pilot study were single-arm trials, which is appropriate given the rarity of the condition, lack of standard effective treatments and the highly innovative nature of blinatumomab in this setting. There was a very small proportion (<5%) of patients in the BLAST trial who did not meet the subsequent licensed indication for blinatumomab, and these are highly unlikely to have positively biased the estimated efficacy of blinatumomab. Results of the BLAST trial and pilot study are therefore generalisable to patients meeting the licensed indication. Blinatumomab achieved very high MRD response rates of around 80%, which is unprecedented in this condition. The pilot study demonstrates a relapse-free survival (RFS) rate of 53% over almost 6 years of follow-up, and the latest data cut from the BLAST trial, which was requested by the Committee, confirms the interim data	

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			provided in our submission: median overall survival (OS) with blinatumomab was 36.5 months over a median follow-up of 4.5 years. **Indirect treatment comparison:** Given the need to evaluate the efficacy of blinatumomab in single-arm trials, an indirect treatment comparison was required to demonstrate the treatment effects of blinatumomab relative to standard of care (SOC) chemotherapy. The ERG confirmed that the methods of our indirect treatment comparison were appropriate. We confined the indirect treatment comparison to patients in their first CR (CR1) in order to match to and improve the robustness of these comparative data. This is aligned with the MRD patient population in which blinatumomab is expected to be used in clinical practice as patients in later remission states (CR2) are expected to be a small and declining pool given that they would have access to blinatumomab as relapsed patients before CR2. Additionally, patients' ineligible for HSCT or chemotherapy were by definition excluded from the indirect comparison; however, these patients represent a very small minority of given the substantial risk of relapse with MRD and the resulting clinical need to provide some form of active treatment. The results of the indirect comparison are therefore robust, reliable and highly generalisable to patients anticipated to use blinatumomab in the MRD setting in clinical practice. Given the median RFS was [redacted] with blinatumomab compared with SoC chemotherapy ([redacted]; HR[redacted]), and median OS with blinatumomab was [redacted] after more than 40 months of follow-up, compared to a median OS of [redacted] for SoC chemotherapy (suggesting at least [redacted] of the median OS with blinatumomab), there is also a high degree of certainty in the unprecedented size and durability of the clinical benefit provided by blinatumomab when used early in the treatment pathway for patients in CR with MRD. **3. The uncertainties in the economic evaluation have been fully explored by conducting a range of analyses in line with the Committee's request. All analyses demonstrate that blinatumomab is highly likely to be cost effective when used earlier in the treatment pathway in patients in CR with MRD.** **Our original partitioned survival model:** The Committee raised concerns that our original model and base case analyses did not reflect the current treatment pathway following relapse. At the time of our submission (October 2017), blinatumomab had only recently received its positive recommendation for use in the relapsed/refractory setting, and inotuzumab had not been recommended by NICE. We presented an **alternative base case analysis** in our submission, which included blinatumomab as salvage therapy in patients who relapse following treatment with SOC and so reflected the existing treatment pathway at the time. However, this alternative base case was not reported in the ACD. It should be noted that, compared with our original submitted base case ICER of £28,524/QALY, the incorporation of salvage therapy significantly reduced the ICER to £17,420/QALY. This demonstrates that the ICERs in our original base case analysis were highly conservative, as were the results of all sensitivity and scenario analyses that were conducted by Amgen and the ERG.	

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			The ACD also highlighted specific concerns regarding our modelling of cure points and the link between HSCT and outcomes. Whilst accepting there is inevitable uncertainty in some elements of our modelling, we note the ERG analyses demonstrated the ICER estimates were reassuringly close to our base case model estimates when alternative assumptions on cure points and HSCT outcomes were explored. These uncertainties therefore relate to the *precision* of the ICER estimates, rather than the *magnitude*. Had these analyses been conducted using the alternative base case model, which incorporated salvage therapy following relapse, all ICERs would have been well within the thresholds of cost effectiveness. **Additional analyses to address the Committee's concerns on the appropriate treatment pathway using our original partitioned survival model:** We acknowledge that the NICE approval of inotuzumab in September 2018 changed the relapsed pathway from that at the time of our submission. To resolve the Committee's concerns that our model did not fully reflect the current treatment pathway following relapse, we have revised the original model to provide a comparison of blinatumomab in the MRD setting followed by inotuzumab salvage therapy, versus SOC chemotherapy in the MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split). This pathway, which was informed by clinical expert opinion and has been validated as relevant to clinical practice, confirms that early use of blinatumomab in MRD remains cost effective with an ICER of £18,818/QALY. Sensitivity and scenario analyses indicate these results are robust, and confirm blinatumomab is highly likely to be cost effective. **A new Markov model structure to address all the Committee's concerns and specific requests regarding the structural elements of our original model**: We have developed a new, combined decision-tree and Markov cohort model which: • reflects the current treatment pathway in relapsed/refractory setting – by including blinatumomab and inotuzumab as salvage therapy; • provides the link between MRD status, HSCT and survival – using data from re-analysis of BLAST and the historical comparator trial; • models a specific cure point of 5 years – which given the availability of trial data with almost 5 years of follow-up requires little survival curve extrapolation; • includes the different positions in the treatment pathway at which HSCT might be given – as it explicitly models time to transplant in remission and post-relapse states, and • reflects the latest data cut from the BLAST trial – data from the latest BLAST data cut with a	

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			median follow-up of 53.1 months has been used to estimate parameters. In the new model, early use of blinatumomab in ALL patients in CR1 with MRD remains highly cost effective with a base case ICER of £25,645/QALY compared with current SOC. This supports the conclusion that, although there are uncertainties in the *precision* of the ICER estimate, the *magnitude* of the ICER is highly likely to be within the thresholds of cost effectiveness. It is important to note that to address the Committee's specific requests on structural relationships between MRD, HSCT and outcomes, post hoc analyses of small subgroups of the clinical trials are necessary; therefore, some uncertainty in the estimation of the required parameters is expected. As a result, our original partitioned survival model structure may better reflect the observed clinical trial data as parameters are estimated based on larger sample sizes and event rates. Collectively, the range of analyses conducted to address the Committee's concerns all point to the same conclusion: **blinatumomab is highly likely to be cost effective when used earlier in the treatment pathway in patients in CR with MRD.** **4. Blinatumomab in the treatment of patients in CR with MRD clearly fulfils the criteria for consideration under NICE's end-of-life policy based on compelling clinical data and expert opinion.** Blinatumomab clearly fulfils the criteria for consideration under NICE's end-of-life policy based on compelling OS data from the clinical trials and expert opinion. SOC chemotherapy in the historical comparator study had a median OS of [redacted] months, and the clinical expert quoted in the ACD suggested survival at 2 years would be around 20%, clearly fulfilling the short life expectancy criterion. Mature BLAST OS data show a median OS of 36.5 months with blinatumomab, clearly indicating an OS gain of over 3 months. We note the ERG rejected our conclusions that blinatumomab meets the end-of-life criteria due to the use of median rather than mean estimates of OS. However, given the compelling median OS gain of [redacted] for blinatumomab versus the historical control in our robust indirect comparison, we believe there is little doubt that patients with MRD treated with SOC chemotherapy have a short life expectancy less than 24 months, and that blinatumomab provides a substantial gain in OS that is highly likely to be in excess of 3 months. We refer the Committee to the pragmatic approach taken in previous appraisals, in which treatments were accepted for consideration under NICE's end-of life policy using median OS data to demonstrate fulfilment of the criteria (e.g. TA366 and TA396). We suggest that a similar pragmatic approach is warranted for blinatumomab in the treatment of people with MRD, not least to avoid the introduction of inconsistencies that would inappropriately penalise the considerations of blinatumomab's cost effectiveness when used earlier in the treatment pathway compared with the later use of blinatumomab or inotuzumab as salvage therapy, which were accepted as cost effective with higher ICERs under NICE's end of life policy.	

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			Conclusion • ALL patients in CR with MRD remain at very high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to use of blinatumomab earlier in the treatment pathway in these patients, to reduce their risk of relapse and optimise outcomes, rather than treating later (i.e. requiring these patients to first experience unnecessary frank relapse before accessing blinatumomab as salvage therapy.) • We have comprehensively addressed the Committee's requests for additional data and modelling analyses. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, we have demonstrated that there is a high degree of certainty around the unprecedented clinical benefit that blinatumomab brings over SOC chemotherapy when used earlier in the treatment pathway. Importantly we have demonstrated, using different modelling approaches, that earlier use of blinatumomab in patients in CR with MRD remains highly cost effective compared with treating later. Further, compelling survival data and clinical expert opinion support the case that blinatumomab for the treatment of MRD fulfils the end-of-life criteria, which bolsters the conclusion that blinatumomab in this setting provides strong value for money. • Based on this body of compelling evidence of clinical effectiveness and robust additional analyses demonstrating consistently cost-effective ICERs, we propose that blinatumomab is recommended within its full licensed indication for use earlier in the treatment pathway in patients in CR with MRD, to reduce their risk of relapse and optimise outcomes.	
2	Company	Amgen	***Section 1:*** ***1.The relevant comparator for blinatumomab is continued treatment with chemotherapy. HSCT is not a relevant comparator*** The ACD states that *'...the position of blinatumomab in the treatment pathway is more complex than is implied by a comparison with …chemotherapy because some patients may have HSCT'* (ACD section 3.5). ALL treatment protocols are complex and variable across countries, but patients typically receive induction chemotherapy with the aim of achieving a complete response (CR), after which they may be eligible for haematopoietic stem cell transplantation (HSCT), with or without intensification chemotherapy. Patients ineligible for transplant may receive consolidation treatment, which aims to ensure the clearance of leukemic cells from sanctuary sites such as the central nervous system (CNS), followed by maintenance therapy[1].	Comment noted. The comparators have been amended to reflect the positioning of blinatumomab. See FAD section 3.5. However, at the first committee meeting, it was

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			Patients who achieve CR but have MRD are at increased risk of relapse and have poorer survival than those without MRD, as acknowledged in the ACD. Blinatumomab has demonstrated unprecedent response rates in patients with MRD (see section 2 below) and is the only therapy approved for the treatment of patients with MRD. In the absence of blinatumomab, the only other options for patients with MRD are to proceed to HSCT (if well enough and a donor is available), despite the known risks of suboptimal outcomes, or continued treatment with poorly effective chemotherapy. However, if blinatumomab is made available, HSCT would *not* be replaced by blinatumomab; in those able and willing to undergo the procedure, HSCT would still occur *after* treatment with blinatumomab. Therefore, as agreed at the scoping stage and as reflected in the final scope for this appraisal, HSCT is not a comparator for blinatumomab. In contrast, in those awaiting or unable to undergo HSCT, blinatumomab would replace continued chemotherapy. Therefore, the only relevant comparator is continued treatment with chemotherapy, as indicated in our submission.	agreed that it is still possible for some patients to proceed to directly to HSCT even if there is no relapse.
3	Company	Amgen	***Section 1:*** ***2. The ACD misrepresents the treatment pathway: salvage chemotherapy is not a comparator for blinatumomab in the treatment of MRD*** Throughout the ACD reference is made to "salvage chemotherapy" as the comparator for blinatumomab. This is incorrect – only patients who relapse after achieving CR receive salvage chemotherapy. As the indication under appraisal is for the use of blinatumomab in patients who are in complete remission with MRD, salvage chemotherapy is not relevant. We therefore request that the inappropriate term "salvage chemotherapy" is replaced in the FAD with "continued chemotherapy" as the standard of care comparator.	Comment noted. The FAD has been amended to reflect the suggested wording by the company. See FAD section 1.
4	Company	Amgen	***Section 1:*** ***3. Chemotherapy has poor efficacy in MRD. It is clinically, ethically and economically appropriate to use blinatumomab earlier in the treatment pathway to avoid exposing patients to unnecessary relapses and poorer outcomes*** As acknowledged in the ACD (ACD section 3.2), MRD is a marker of chemotherapy resistance and is therefore a predictor of poor response to subsequent chemotherapy. Blinatumomab is currently recommended as a treatment option in relapsed/refractory ALL patients (TA450). However, patients who experience relapse experience poorer outcomes and a reduced likelihood of success with subsequent treatment.[2, 3] We demonstrate in sections 2 and 3 of this response that there is a high degree of certainty that blinatumomab is clinically effective and cost effective when used earlier in patients in CR with MRD compared with its later use in patients who have relapsed. There are therefore robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients with MRD to reduce their risk of relapse, rather than requiring these patients to first experience frank relapse before accessing blinatumomab (or inotuzumab) as salvage therapy.	Comment noted. See section 3.2 of the FAD. No further action required.

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			<u>Conclusion</u> • **Our comparisons against continued chemotherapy are relevant and appropriate to address the decision problem. HSCT and salvage chemotherapy are not relevant comparators for blinatumomab in the MRD setting.** • **There are robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients in CR with MRD to reduce their risk of relapse, rather than requiring these patients to first experience frank relapse before accessing this therapy.** • **As demonstrated in sections 2 and 3 of this response, there is a high degree of certainty that blinatumomab is clinically effective and cost effective when used earlier in patients in CR with MRD compared with its later use in patients who have relapsed.** • **Permitting patient and clinician access to blinatumomab earlier in the treatment pathway is therefore clinically and ethically appropriate.**	
5	Company	Amgen	**Section 2:** The ACD makes several references to uncertainty in the size of the clinical benefit with blinatumomab due to a lack of direct comparative data and long-term survival data, and uncertainty in the methods of the indirect treatment comparison. It also notes that the population in the BLAST trial is wider than the licensed indication and the population in the indirect treatment comparison is narrower than the licensed indication. We address these issues below and demonstrate that the uncertainty in the clinical evidence implied in the ACD is somewhat overstated. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, there is a high degree of certainty in the magnitude and durability of the clinical effects of blinatumomab relative to chemotherapy as presented in our submission. The latest data cut from the BLAST trial, requested by the Committee, further confirms the long-term effectiveness of blinatumomab. **1. The MT103-202 pilot study and the BLAST trial clearly demonstrate the unprecedented, durable clinical efficacy of blinatumomab** The ACD states "*there are no data directly comparing blinatumomab with … chemotherapy … This means that the exact size of the benefit of blinatumomab is unknown*" (ACD section 1.2). It further notes "*The MT103-202 study had a follow-up of about 4 years, but included only 20 patients and did not record overall survival*"; "*The Committee concluded that blinatumomab is clinically effective, but immature survival data and the lack of direct comparative data means the size of this benefit is*	Comment noted. The committee considered the clinical evidence and agreed blinatumomab is clinically effective; however, the size of the benefit is still unclear. See FAD section 3.6. No further action required.

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			unclear" (ACD section 3.7) , and "*The study population in BLAST was wider than the population outlined in the marketing authorisation*". ALL is an ultra-orphan disease, with an incidence in the UK of around 1.2 per 100,000,[4] and MRD is even more rare; only 36% of ALL patients have MRD after induction therapy.[5] With no approved treatments specifically for people with MRD, blinatumomab is a highly innovative treatment in an area of great unmet need. MRD is itself a marker of resistance to chemotherapy, as acknowledged by the Committee, and as continued treatment with chemotherapy is the only relevant comparator for blinatumomab (see section 1) there are substantial ethical and logistical challenges in conducting large randomised clinical trials within this patient population. Given these challenges, and the highly innovative nature of blinatumomab in this indication, the single-arm design of the MT103-202 pilot study and the BLAST trial was appropriate and was agreed with the regulator (European Medicines Agency) during development. Uncertainty is an inherent feature of single-arm trials; however, the collective, consistent evidence of unprecedented response rates with blinatumomab in this population, from the pilot study and the BLAST trial, gives confidence that blinatumomab is a highly effective treatment for patients in CR with MRD. *MT103-202 pilot study* The pilot study demonstrated that blinatumomab induced a complete MRD response in 80% of patients within one cycle. Overall survival (OS) was not specified as an endpoint, as noted by the Committee; however, **median haematological relapse-free survival (RFS) had not been reached after more than 4 years of treatment, and the final RFS estimate was 53% after 5.9 years.** Considering that the adjusted median RFS with SOC chemotherapy in the historical comparator study was only 6.5 months, and median OS was only 19.6 months, the comment by the Committee regarding the lack of formal OS data collection in the pilot blinatumomab study seems unwarranted; the RFS data from the pilot study are in themselves a strong and clear indication of the prolonged OS benefit achievable with blinatumomab in the long-term in this patient population. *BLAST trial* In our submission we presented analyses of the BLAST trial from the most recent data cut that was available at the time (after the last Ph-negative patient completed an 18-month follow-up period - 5th August 2015). Blinatumomab induced a complete MRD response in 78% of patients within the first cycle of treatment, and in 80% within 2 cycles of treatment, which confirmed the unprecedented high response rates observed in the pilot study. Median haematological RFS had not been reached after more than 40 months and median OS was 36.5 months (95% CI: 19.8 to not estimable), which far exceed the survival estimates for SOC chemotherapy in the historical comparator study.	

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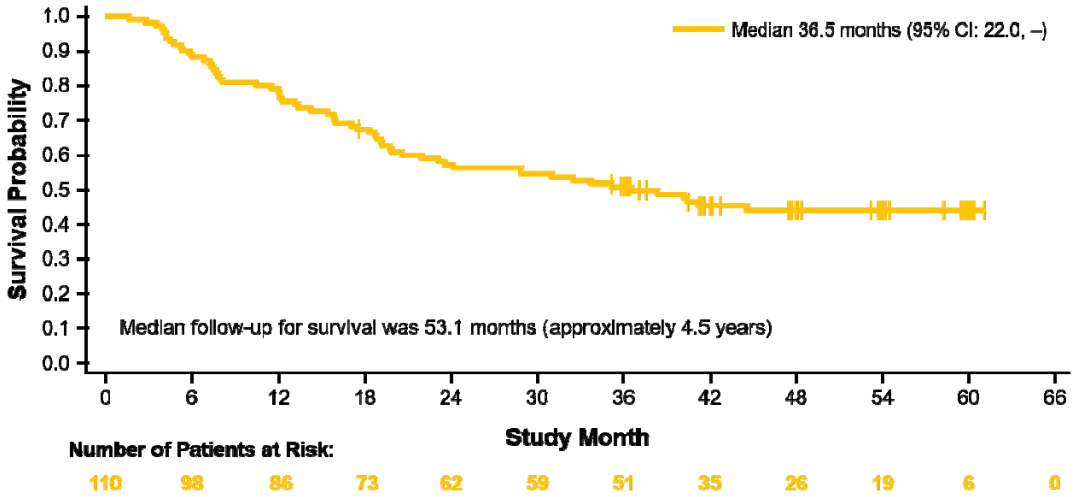
			The latest BLAST data cut was taken on 1st June 2017, and analyses were presented at the American Society of Hematology 60th Annual Meeting, December 1–4 2018. OS was evaluated for the 110 patients with Philadelphia chromosome-negative (Ph−) BCP-ALL and less than 5% blasts at enrolment (i.e. aligned with the licensed indication for blinatumomab), including 74 who received HSCT while in continuous complete remission (CCR) after blinatumomab. Over a median follow-up of 53.1 months, median OS was 36.5 months (95% CI: 22.0 to not estimable) (Figure 1). [6] These mature OS data are highly consistent with and confirm the OS data that were presented in our submission. Furthermore, these findings, including the plateau observed in the Kaplan-Meier curve post 42 months, support the survival curve extrapolations used in our original company model and submission. There is therefore a high degree of certainty in the long-term efficacy of blinatumomab in this patient population; blinatumomab is a highly effective treatment that clearly improves overall survival substantially in the long-term in patients who are, by virtue of their MRD positive status, resistant to chemotherapy. **Figure 1. Median overall survival after 53.1 months in Ph- patients with BCP-ALL and MRD**  Includes patients analyzed for overall survival (N = 110). BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CI, confidence interval. Goekbuget N, et al. Slides presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.[6] The BLAST trial was designed and initiated before blinatumomab was granted its licensed indication in patients in CR with MRD. Patients in first or second CR (CR1 and CR2) account for 98% of the BLAST population, with only 2 patients in their third CR (CR3). [7] As such the licensed indication	

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			excluded patients in CR3 on the basis of limited data. In addition, more than 95% of patients in BLAST were Philadelphia-chromosome-negative (Ph−), and so Philadelphia-chromosome-positive (Ph+) patients were excluded from the licensed indication. Whilst the Committee is correct that the BLAST population was wider than the subsequent licensed population, given the very small number of patients not meeting the subsequent licensed indication it is highly unlikely that the full BLAST trial data are positively biased. Indeed, it is more likely that the full BLAST data provide a conservative estimate of effectiveness of blinatumomab within the licensed population. There are therefore no material uncertainties in the generalisability of the data from the full BLAST trial population to the licensed indication.	
6	Company	Amgen	**2. The indirect comparison against SOC chemotherapy is robust and generalisable to the expected use of blinatumomab in clinical practice** *The methods employed for the indirect comparison are robust and results are reliable; contrary reference in the ACD should be removed* The Committee accepted that the indirect comparison of blinatumomab against SOC chemotherapy presented in our submission was appropriate in the absence of randomised controlled trial data, but concluded the methods were subject to uncertainty: "*The ERG noted that there were inconsistencies in efficacy data presented by the company and the data used to inform the economic model. The Committee noted that it would have been helpful to see the range of weights used in the model, as an indicator of the model reliability and the appropriateness of using stabilised weights.*" (ACD section 3.10). Although the data presented in the clinical and economic sections differed in our original submission, due to an editorial oversight, we addressed this issue in our response to the ERG clarification questions and provided an addendum which clearly demonstrated there was no material difference in the results when the stabilised or unstabilised weights were used. It is clearly stated in the ACD that the ERG noted the method of applying weights to balance the datasets was appropriate (ACD section 3.10, p11). As such, the methods used in the indirect comparison have been shown to be appropriate and robust, and are not a material source of uncertainty. We therefore request that reference to this point is removed from the FAD. *The indirect comparison provides robust comparative data that are highly generalisable to the anticipated use of blinatumomab in clinical practice and underscore that blinatumomab is recommended within its full licensed indication* The Committee concluded the results of the indirect comparison were not generalisable to the full	Comment noted. The committee considered the company's response but concluded that it could only make recommendations based on the evidence presented to it See FAD section 3.8

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			licensed indication: "*…the population in the indirect comparison was narrower than the marketing authorisation and excluded the following groups: patients who could not have HSCT or tolerate chemotherapy; patients whose disease is in second complete remission*" (ACD section 3.9). The indirect comparison focused on the CR1 subgroup because these data were available in the historical comparator dataset, and were within the licensed indication. Confining the indirect comparison to data from patients in BLAST in CR1 provided a more robust comparison than would have been achieved if data from the (minority) of CR2 patients in BLAST had also been included. Given that blinatumomab is expected to be used in MRD as early in the treatment pathway as possible (i.e. in patients in CR1 with MRD), the indirect comparison provides comparative data specifically in the most relevant patient population in clinical practice. Patients in CR2 are expected to be a small and declining proportion of eligible patients as blinatumomab becomes more established as the standard of care in the CR1 MRD setting; given the positive NICE recommendation for blinatumomab (and inotuzumab) in the relapsed setting, patients who have not received blinatumomab in CR1 would be expected to receive blinatumomab (or inotuzumab) at relapse following CR1 rather than waiting further until a hoped-for CR2 occurs in order to receive blinatumomab under its MRD indication. The exclusion of CR2 patients from the indirect comparison reflects blinatumomab's anticipated use in practice and *reduces* the uncertainty regarding the effectiveness of blinatumomab in its anticipated use in practice. **However, on equity grounds, the prevalent population of patients in CR2 with MRD who have not previously received blinatumomab should be afforded the opportunity to benefit from this highly effective treatment.** Regarding the exclusion from the indirect comparison of patients who are ineligible for HSCT, it should be noted that HSCT eligibility was not restricted in the protocol for the BLAST study – eligibility for and receipt of HSCT is multi-factorial, and as HSCT is the main route to cure for patients with ALL, it would have been unethical to determine enrolment in BLAST on the basis of HSCT eligibility. The indirect comparison therefore does potentially exclude patients who are ineligible for HSCT. However, as noted in the ACD, even patients with known suboptimal characteristics for HSCT are offered HSCT in practice where possible (ACD section 3.2). Therefore, patients who are ineligible for HSCT represent a small minority sub-population of patients within this ultra-orphan disease. Pre-specified analyses of the BLAST trial, in which data were censored at HSCT, indicate that blinatumomab improves survival outcomes irrespective of receipt of HSCT (see section B.2.6 of our submission). Therefore, it is likely that the very small number of patients who are ineligible for HSCT would benefit from blinatumomab therapy. The exclusion of this subgroup of patients from the BLAST trial and the indirect comparison does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication. **And on equity grounds, patients who have the misfortune to be ineligible for potentially lifesaving HSCT should not also be**	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			denied the opportunity to benefit from the only effective non-transplant therapy. Regarding the exclusion from the indirect comparison of patients who are intolerant of chemotherapy, as the aim of the historical comparator study was to provide a SOC chemotherapy arm against which to compare blinatumomab, patients enrolled were, by definition, eligible for chemotherapy. The indirect comparison is therefore not able to provide specific comparative data on the use of blinatumomab in patients who are intolerant of chemotherapy which, according to clinical experts, is only likely to represent a very minor sub-population of patients within this ultra-orphan disease given the substantial risk of relapse with MRD and the resulting need to not withhold active treatment. Nevertheless, the results of the single-arm BLAST trial would likely be more indicative of blinatumomab's efficacy in these patients, and use of the indirect comparative data to represent the relative treatment effects of blinatumomab in this population would be conservative, rather than biased in favour of blinatumomab. The lack of data specifically in patients who are intolerant of chemotherapy does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication. **And on equity grounds, patients who have the misfortune to be intolerant of chemotherapy should not also be denied the opportunity to benefit from the only effective non-transplant therapy.**	
7	Company	Amgen	**3. Results of the indirect comparison clearly demonstrate the substantial clinical benefit of blinatumomab compared with SOC chemotherapy in patients in CR with MRD** Given the appropriate methodology and generalisability of the data to the patients expected to be eligible for blinatumomab in clinical practice, the results of the indirect treatment comparison are robust and reliable. The median RFS was [redacted] with blinatumomab compared with SoC chemotherapy ([redacted]; HR[redacted]), and median OS with blinatumomab was [redacted] after more than 40 months of follow-up, compared to a median OS of [redacted] for SOC chemotherapy, suggesting at least [redacted] of the median OS with blinatumomab. There is therefore little uncertainty in the unprecedented clinical benefit provided by blinatumomab relative to SOC chemotherapy when used early in the treatment pathway for patients in CR with MRD. **Conclusion: There is a high degree of certainty in the size and durability of clinical benefit with blinatumomab when used early in the treatment pathway in patients in CR with MRD** • The single-arm design of the BLAST trial and pilot study is entirely appropriate given the rarity of the condition, lack of standard, effective treatments and the highly innovative nature of blinatumomab. • The very small number of patients in the BLAST trial not meeting the subsequent licensed indication for blinatumomab is highly unlikely to have positively biased the estimated efficacy	Comment noted. Committee considered clinical evidence and agreed blinatumomab is clinically effective but considers that the indirect comparison is still subject to uncertainty. See FAD section 3.6 and 3.9.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			of blinatumomab. Results are therefore generalisable to patients meeting the licensed indication. • The pilot study and BLAST trial both demonstrate high MRD response rates of around 80% with blinatumomab, which is unprecedented in this condition. The pilot study provides RFS data out to almost 6 years, and the latest data cut from the BLAST trial provides OS data from patients followed-up for a median of 4.5 years, confirming the median OS with blinatumomab that was presented in our submission. There is therefore a high degree of certainty in the size and durability of the clinical benefit of blinatumomab. • The ERG confirmed that the methods of our indirect treatment comparison were appropriate. The results of this indirect comparison are robust and reliable, and clearly demonstrate the significant magnitude of the RFS and OS benefit blinatumomab provides compared with SOC chemotherapy. Despite the lack of direct comparative data, there is therefore little uncertainty in the size of the clinical benefit provided by blinatumomab. • The indirect comparison provides comparative effectiveness data specifically in those patients anticipated to use blinatumomab in clinical practice. The exclusion of small subgroups of patients from the analysis does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication.	
8	Company	Amgen	**Section 3:** The ACD makes references to what the Committee perceive to be several sources of uncertainty in our original economic model and the estimated cost effectiveness of blinatumomab. We address these issues below and demonstrate that, whilst there may be some uncertainty in the *precision* of the ICER estimates from our original economic model, there is a high degree of certainty in the *magnitude* of the ICER estimates, which are within the usual thresholds for cost effectiveness. To address the Committee's specific concerns regarding the appropriate modelling of the relapsed/refractory treatment pathway, we have provided revised analyses incorporating salvage therapy with blinatumomab and inotuzumab in our original partitioned survival model. We have also provided a new decision tree/Markov cohort model to address the Committee's concerns regarding the structural elements of our original model. ***1. Our original economic model and the alternative base case analysis reflected the anticipated use of blinatumomab in clinical practice at that time*** The ACD states: *"Clinical experts highlighted that this model is not reflective of current practice or the treatment pathway. They clarified that the treatment pathway has recently changed and now includes inotuzumab ozogamicin or blinatumomab for treating relapses."* (ACD section 3.10); and: *"The population in the cost-effectiveness model cannot be generalised to the full population in the marketing authorisation."* (ACD section 3.12)	Comment noted. Committee considered the revised original model and acknowledged that the model reflects current treatment pathway. However, because the model did not include all amendments requested by the committee, it was not acceptable

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Our original model reflected the appropriate and anticipated use of blinatumomab early in the treatment pathway in ALL patients in CR with MRD. The robust comparative effectiveness data for blinatumomab versus continued chemotherapy (the relevant comparator) described in section 2 above are congruent with this positioning of blinatumomab in the treatment pathway. The exclusion of CR2 patients from the analysis, and patients ineligible for HSCT or intolerant of chemotherapy, would not introduce uncertainty regarding the clinical or cost effectiveness of blinatumomab in its anticipated use in practice, and on grounds of equity, should not preclude a recommendation for this use. At the time of our submission (October 2017), blinatumomab had only recently received its positive recommendation for use in the relapsed/refractory setting, and inotuzumab had not been recommended by NICE. Our base case analysis therefore represented the clinical pathway at the time of development of our submission and, although completely omitted from the ACD, we presented an alternative base case analysis that incorporated blinatumomab as salvage therapy in the SOC chemotherapy arm, which represented the direction of movement in the clinical pathway given the advent of blinatumomab as an alternative to chemotherapy in the relapsed/refractory setting. As blinatumomab became established as standard of care in the relapsed setting our alternative base case analysis presented in our submission was more reflective of the clinical pathway than our original base case analysis. Compared with our original base case ICER of £28,524/QALY, the incorporation of blinatumomab as salvage therapy significantly reduced the ICER to £17,420/QALY. Although the ERG notes some limitations with this approach (i.e. cost and benefits are not structurally linked within the partition survival model), this nevertheless demonstrates that the ICER in the original base case analysis was highly conservative and therefore so were the results of all sensitivity and scenario analyses that were conducted by Amgen and the ERG. Inotuzumab is now also recommended as an option alongside blinatumomab in relapsed/refractory patients (TA541, Sep 2018). We therefore acknowledge that inotuzumab should be incorporated appropriately in our modelling to reflect the current clinical pathway following relapse. To address this, we have provided revised analyses incorporating blinatumomab and inotuzumab as salvage therapy. These analyses are discussed in detail in sections below.	for decision making. See FAD section 3.13.
9	Company	Amgen	**Section 3:** ***2. Our original modelling approach is appropriate to address the decision-problem*** The ACD states: "*The company's model is not acceptable for decision-making*", noting particular	Comment noted. Committee considered the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			issues with the modelling of the cure point, and the link between HSCT and outcomes. However, the impact of the uncertainty in these elements of our modelling approach relates to the *precision* of the ICER estimates and not the *magnitude*, which is highly likely to be within the thresholds of cost effectiveness. Our original modelling approach was and remains appropriate and sufficiently reliable to inform decision-making. <u>Uncertainty in the modelled cure point relates to the precision of the ICER estimates, not the magnitude</u> The Committee rejected our approach to modelling the cure point on the basis that this resulted in different cure points between the RFS and OS extrapolation. The ACD notes that the assumptions around the cure fraction and cure point were a key driver in the cost effectiveness analysis and an explicitly modelled cure point was required (ACD section 3.13). The ERG provided analyses assuming a 5-year cure point in line with clinical expert opinion. While this introduced bias in favour of the SOC chemotherapy arm and against blinatumomab, the ICER increased from £27,700 to only £30,200 per QALY. These ICERs are compatible with our original base case ICER estimate (£28,524/QALY), and do not incorporate salvage therapy in the clinical pathway, which would significantly reduce these ICERs to well below £30,000/QALY (see section above). The ERG also provided analyses exploring cure fractions for SOC chemotherapy in the range 25-35%.[8] No basis is provided for this range of cure fractions, which increases the proportion of patients achieving a cure whist on SOC chemotherapy by up to 67% compared with the ERG's preferred base case. Given that MRD is acknowledged in the ACD as an indicator of resistance to chemotherapy, and given that patients with MRD are at increased risk of relapse and have poorer survival compared with those without MRD, we feel these analyses are unjustified. Clinical expert opinion sought during the development of our original submission consistently verified that the survival analyses presented in the base case model were reasonable and indeed this was reiterated during the 1st Appraisal Committee Meeting. The ERG also conducted an independent validation exercise on the survival extrapolations – the ERG's clinical advisors' preferred OS models resulted in ICERs in the range £25,810 per QALY gained to £34,904 per QALY gained, without incorporating the impact of salvage therapy in the clinical pathway. These results confirm the appropriateness of the original assumptions and underline that the modelled cure point is unlikely to meaningfully impact on the magnitude of ICERs presented. <u>Uncertainty in the modelling of HSCT relates to the precision of the ICER estimates, not the magnitude</u> ALL is an ultra-orphan disease, and whilst the magnitude of the clinical benefit of blinatumomab is	revised original model and acknowledged that the model reflects current treatment pathway. However, because the model did not include all amendments requested by the committee, it was not acceptable for decision making. See FAD section 3.13.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>clearly and robustly established from the BLAST and historical control trial data, these trials were not sufficiently powered or designed to provide complete analyses of the incidence of HSCT both pre- or post-relapse, or by MRD status. Our approach to modelling HSCT reflected these data limitations.

The ERG performed exploratory analysis using alternative HSCT survival probabilities, which increased the ICER from its preferred base case of £30,200/QALY to only £32,667/QALY.[8] Whilst we acknowledge these analyses were conducted within the constraints of our model structure, the fact the increase in the ICERs is marginal suggests the uncertainty in the approach to modelling HSCT outcomes is of limited impact. These ICERs are reassuringly similar to our original base case ICER estimate (£28,524/QALY), and do not incorporate salvage therapy in the clinical pathway, which would significantly reduce these ICERs to well below £30,000/QALY (see section above). Any uncertainty in the modelling of HSCT outcomes may therefore lead to uncertainty in the precision of the ICER estimate, but not the magnitude of the ICER estimate, which is highly likely to be within the thresholds of cost effectiveness.</td><td></td></tr>
<tr><td>10</td><td>Company</td><td>Amgen</td><td>Section 3:

3. Revised analyses reflecting the relapsed treatment pathway in our original model confirm the cost effectiveness of early use of blinatumomab in patients in CR with MRD

Given the above, which leads to the conclusion our original modelling approach was sufficient to address the decision problem at the time of our submission, we have used our original partitioned survival model to address the Committee’s concerns on the appropriate treatment pathway following relapse. We have therefore provided revised analyses for comparison of:

• blinatumomab in the MRD setting followed by inotuzumab salvage therapy, versus

• SOC chemotherapy in the MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split).

This comparison has been validated by clinical experts as reflective of the current clinical pathway. Further details of this revised partitioned survival model are provided in Appendix 1.

In this setting, the early use of blinatumomab in MRD was shown to be highly cost effective with an ICER of £18,818/QALY (Table 1).

Table 1: Revised Partitioned Survival Model – Base Case Analysis
<table><tr><th>Treatment</th><th>Total Cost, (£)</th><th>Total QALYs</th><th>Incremental Costs (£)</th><th>Incremental QALYs</th><th>ICER (£)</th></tr></table></td><td>Comment noted. Committee considered the revised original model and acknowledged that the model reflects current treatment pathway. However, because the model did not include all amendments requested by the committee, it was not acceptable for decision making. See</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			<table><tr><td>Blinatumomab</td><td>[redacted]</td><td>7.79</td><td>39,720</td><td>2.11</td><td>18,818</td></tr><tr><td>SOC</td><td>[redacted]</td><td>5.68</td><td></td><td></td><td></td></tr></table> Consistent with clinical expert opinion as to the importance of achieving MRD-negativity, the use of blinatumomab earlier in the treatment pathway results in a substantial increase in the proportion of patients remaining relapse free at 5-years (42.7% vs.17.5% for blinatumomab and SOC, respectively). The highly cost effective ICER is also driven by the ability of blinatumomab to reduce the need for subsequent salvage treatment, realising a reduction in post-relapse costs of £[redacted] in the base case analysis. One-way deterministic sensitivity analyses and scenario analyses are presented in **Appendix 1** and indicate that the base case results are robust when considering parameter uncertainty. Of note, when implementing the Committee's preferred fixed cure-point at 5-years, the ICER only marginally increases to £21,340/QALY and remains well within standard cost effectiveness thresholds. Probabilistic sensitivity analysis generated a mean ICER of £20,024/QALY with a 71.9% and 85.5% probability of being cost-effective at willingness-to-pay thresholds of £30k- and £50k/QALY, respectively. These analyses therefore confirm that early use of blinatumomab in the treatment pathway in patients in CR with MRD is highly likely to be cost effective compared with later use of blinatumomab (or inotuzumab) as salvage therapy following relapse.	FAD section 3.13.
11	Company	Amgen	**Section 3:** **4. New Markov modelling approach as requested by the Committee confirms that early use of blinatumomab in patients in CR with MRD is highly likely to be cost effective** To further address the Committee's concerns regarding the structural elements of our original partitioned survival model we have developed a new, combined decision-tree and Markov cohort model, which incorporates the Committee's specific requests:[1] • it reflects the current treatment pathway in relapsed/refractory setting – by including blinatumomab and inotuzumab as salvage therapy as per clinical expert guidance;	Comment noted. Committee considered the new semi-Markov model and acknowledged that the model

[1] The ACD also referred to the latest available evidence on survival outcomes after HSCT. These data, highlighted by the clinical expert at the Committee meeting, are unpublished

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			• it provides the link between MRD status, HSCT and survival – using data from re-analysis of BLAST and the historical comparator trial; • it models a specific cure point of 5 years – which given the availability of trial data with almost 5 years of follow-up requires little survival curve extrapolation; • it includes the different positions in the treatment pathway at which HSCT might be given – as it explicitly models time to transplant in remission and post-relapse states, and • it reflects the latest data cut from the BLAST trial – data from the latest BLAST data cut with a median follow-up of 53.1 months has been used to estimate parameters (see section 2). In addition to the above, the new Markov modelling approach addresses the limitation of the partitioned survival model by providing a structural link between costs and QALYs generated when incorporating blinatumomab or inotuzumab as salvage therapies. The ERG acknowledged that a revised model structure using the available data to populate specific transitions would be limited by very small sample sizes, may be subject to selection bias, and would be associated with considerable uncertainty.[8] It was for these reasons that we adopted a partitioned survival modelling approach in our original submission, and we maintain that the revised partitioned survival model incorporating blinatumomab and inotuzumab salvage therapy discussed above (section 3 above) better reflects the observed data from the clinical trials. The combined decision-tree and Markov cohort model was informed by previous modelling approaches in this disease area.[8-10] However, building on these approaches, it was deemed necessary to implement a Markov structure to fully address the Committee requests around a causal link between MRD status, HSCT and survival, in addition to reflecting the current treatment pathway. It is important to note that *post hoc* analyses of small subgroups of the clinical trials are necessary in this model structure, therefore, some uncertainty in the estimation of the required parameters is expected. Full details of the new model structure and parameter estimation are provided in Appendix 2, along with the results of scenario analyses and one-way deterministic sensitivity analyses. Probabilistic sensitivity analyses (PSA) are not yet implemented at the time of submission but will be provided in full for consideration by the Committee. *Base Case Results* The base case ICER of £25,645/QALY (Table 2) supports the conclusion of the revised partitioned survival model in that blinatumomab is highly likely to be cost-effective when used in the MRD setting. **Table 2: New Modelling Approach – Base Case Results**	reflects current treatment pathway and includes the committee's request (see ACD section 1.2). The model was suitable for decision making. See FAD section 3.14.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

Treatment	Total Cost, (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£)
Blinatumomab	[redacted]	6.56	54,264	2.12	**25,645**
SOC	[redacted]	4.44			

The main clinical outcomes generated by the model are RFS and OS which are causally linked to MRD status and receipt of HSCT, as requested by the Committee. Survival projections from the model are compared with the Kaplan-Meier estimates from BLAST and the historical control data in Figure 2 and

Figure 3, below.

Figure 2: Relapse Free Survival

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Figure 3: Overall Survival  Based on visual inspection of the RFS plot compared to the Kaplan-Meier data, both projections are highly consistent with observed data and demonstrate an excellent fit. The proportion of patients estimated to be relapse-free at 5-years (Committee preferred cure time point) was 40% and 18.1% for blinatumomab and SOC, respectively. Because fewer patients receiving blinatumomab are projected to relapse, salvage therapy costs were notably higher in the SOC arm than with blinatumomab (£[redacted]), as were post-relapse HSCT and hospitalisation costs (£[redacted]). Therefore, in total, the early use of blinatumomab in the MRD setting resulted in a reduction in post-relapse costs of £[redacted] when compared with SOC in the base case analysis. Similarly, visual inspection of the OS plot suggests a slight underestimation of long-term survival in the blinatumomab arm and overestimation of long-term survival in the SOC arm. The fact that the modelled OS projections are higher than the KM data in the SOC arms is to be expected given the	

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Markov model incorporates blinatumomab/inotuzumab as salvage treatment, with greater efficacy than SOC chemotherapy received on trial. This effect points to a conservative estimate of the magnitude of survival benefit with blinatumomab and its ICER compared with SOC chemotherapy.

<u>Key Scenario Analyses</u>
The results of scenario analyses and one-way deterministic sensitivity analyses are presented in full in Appendix 2 and underline that blinatumomab is highly likely to be cost-effective even when considering the inherent uncertainty in this modelling approach.

Key scenario analyses exploring limitations in parameter estimation, internal consistency of the MRD-response based modelling approach, the impact of varying HSCT rate and the robustness of the base case model results to the cure time point, are presented in Table 3. These results demonstrate that the ICER remains reasonably stable with respect to changes in key parameters and robust to alternative data sources informing transitions.

Table 3: Key Scenario Analyses
<table>
<tr><th>Scenario</th><th>Rationale</th><th>ICER</th></tr>
<tr><td>SOC survival curves to inform survival in MRD+ patients receiving blinatumomab</td><td>Given the low number of MRD non-responders in BLAST, parameters estimated from the historical cohort were used to inform MRD+ transitions in the blinatumomab arm</td><td>24,852</td></tr>
<tr><td>Blinatumomab MRD Response</td><td></td><td></td></tr>
<tr><td>74.17% MRD response rate (lower CI)</td><td rowspan="2">Explore sensitivity to MRD response rate for blinatumomab</td><td>31,210</td></tr>
<tr><td>91.17 MRD response rate (upper CI)</td><td>22,457</td></tr>
<tr><td>SOC estimated based on BLAST data:</td><td></td><td></td></tr>
<tr><td>8% MRD response rate</td><td rowspan="3">Consistency of MRD-response based modelling approach utilising BLAST data (with varying MRD response rates) to model SOC arm</td><td>26,829</td></tr>
<tr><td>15% MRD response rate</td><td>29,515</td></tr>
<tr><td>0% response rate</td><td>24,311</td></tr>
<tr><td>Impact of varying HSCT rate:</td><td></td><td></td></tr>
<tr><td>HSCT rate for MRD+ based on SOC (historical control) data</td><td rowspan="3">Exploration of impact of HSCT rates by setting all arms to use the time to HSCT survival distributions</td><td>11,695</td></tr>
<tr><td>HSCT rate based on SOC (historical control) for all</td><td>31,851</td></tr>
<tr><td>HSCT based on MRD-</td><td>25,936</td></tr>
</table>
</td><td></td></tr>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>(BLAST) for all</td><td></td><td></td></tr>
<tr><td>Impact of Cure Timepoint:</td><td></td><td></td></tr>
<tr><td>Cure time point 3 years</td><td rowspan="2">Exploration of the cure time point on modelled results, based on assumptions in other models in this disease area (e.g. inotuzumab in TA541)</td><td>25,551</td></tr>
<tr><td>Cure time point 4 years</td><td>25,479</td></tr>
</table>

In conclusion, the combined decision-tree and Markov cohort model, developed specifically to address the Committee's concerns around the structural limitations of the original partitioned survival model, produces ICER estimates that are broadly consistent with the original modelling approach when the current clinical pathway is reflected. This supports the conclusion that blinatumomab is highly likely to be cost-effective when used earlier in the treatment pathway. Scenario and sensitivity analyses demonstrate that the ICERs in both models are reasonably stable to alternative assumptions for key parameters. In particular, the new Markov model is shown to be robust when implementing the Committee's preferred fixed cure point and assessing the impact of varying the timepoint at which this occurs. Taken together, these results support the conclusion that, although there are uncertainties in the precision of the ICER estimate, the magnitude of the ICER is highly likely to be within the thresholds of cost effectiveness.</td><td></td></tr>
<tr><td>12</td><td>Company</td><td>Amgen</td><td>Section 3:

5. Blinatumomab clearly meets the criteria for consideration under NICE's end-of-life policy based on expert opinion and compelling survival data

The ACD states: "Blinatumomab does not meet the criteria to be considered a life-extending treatment at the end of life"; "It concluded that it was plausible that blinatumomab offered more than 3-months' additional survival but they could not be certain because of flaws in the modelling." (ACD section 3.18)

The clinical experts quoted in the ACD "suggested that for patients with MRD, survival at 2 years would be around 20%," clearly indicating that the short life expectancy criterion was met. While we acknowledge the perspective of the Committee with regards to the results of the model, consideration of the clinical data alone provides compelling evidence that SOC chemotherapy is associated with a short life expectancy of less than 24 months, and that blinatumomab provides an OS gain that is substantially greater than 3 months. Mature data from the BLAST trial confirms a median OS of 36.5 months, and our robust indirect treatment comparison in patients in CR1 (discussed in our submission and above in section 2) demonstrates that the median OS in patients treated with blinatumomab had not been reached after more than 40 months of follow up, in comparison to [redacted] months with standard of care chemotherapy (i.e. at least a doubling of OS with blinatumomab, and a life expectancy with SOC therapy less than 24 months).

In addition to these compelling trial data, emerging real-world evidence confirms the substantial</td><td>Comment noted. The evidence was considered by the appraisal committee. The committee agreed that only one of the two end-of-life criteria were met. See FAD section 3.21.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			survival gains in clinical practice associated with achieving MRD negative status compared with MRD positive status, after front-line treatment. Results from a chart review in Belgium, Greece and Switzerland demonstrate that in patients who achieve MRD negativity (n=50), the median OS was [redacted] ([redacted]) after a median follow-up of [redacted] compared to [redacted] months ([redacted]) after a median follow-up of [redacted] in MRD positive patients (n=17).[11] These real-world data confirm and support our trial-based estimates of short life expectancy for patients who do not achieve MRD-negativity and the substantial increase in survival for those who do. We note the ERG rejected our conclusions that blinatumomab meets the end-of-life criteria due to the use of median rather than mean estimates of OS.[8] Given the compelling median OS data above we feel there is little doubt that patients with MRD treated with SOC chemotherapy have a short life expectancy less than 24 months, and it is not only plausible that blinatumomab provides a substantial gain in OS in excess of 3 months compared with SOC chemotherapy, it is highly likely. We refer the Committee to the pragmatic approach taken in the appraisals of blinatumomab (TA450)[8] and inotuzumab (TA541)[10] in the relapsed/refractory setting, both of which were accepted for consideration under NICE's end-of life policy using trial-based median OS data to demonstrate fulfilment of the criteria. This approach has also been adopted in NICE technology appraisals in other cancer types, where the specific issue of long tails in the survival curve that skews the mean OS estimates have been recognised and median OS estimates accepted (e.g. TA366[12] and TA396[13]). We suggest that a similar pragmatic approach is warranted for blinatumomab in the treatment of people with MRD, not least to avoid the introduction of inconsistencies that would inappropriately penalise the considerations of blinatumomab's cost effectiveness when used earlier in the treatment pathway compared with the later use of blinatumomab or inotuzumab as salvage therapy, which were accepted as cost effective with higher ICERs under NICE's end of life policy. ***Conclusion: All evidence indicates blinatumomab is highly likely to be cost effective when used early in the treatment pathway in patients in CR with MRD*** • Although the Committee had highlighted specific uncertainties relating to our original modelling approach, the impact of the uncertainty in these elements related to the precision of the ICER estimates and not the magnitude. • We have demonstrated using our original model, revised to reflect the current treatment pathway in relapsed/refractory patients, and the new model, requested by the Committee to address the structural relationships between MRD, HSCT and survival outcomes, that the ICER estimates are highly likely to be within the thresholds for cost effectiveness. • Our models, driven by compelling clinical data, clearly demonstrate that early use of blinatumomab in these patients leads to higher response rates, fewer relapses requiring salvage therapy and improved survival compared with SOC chemotherapy, which translates into a high likelihood of blinatumomab being cost effective.	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			• Given that blinatumomab clearly fulfils the criteria for consideration under NICE's end-of-life policy, and should therefore be assessed against a higher threshold of cost effectiveness, there is little doubt that the early use of blinatumomab in the treatment pathway for patients in CR with MRD is cost effective compared with the later use of blinatumomab (or inotuzumab) as salvage therapy in the relapsed setting.	
13	Company	Amgen	**Section 4: Conclusion** ALL patients in CR with MRD remain at very high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to use of blinatumomab earlier in the treatment pathway in these patients, to reduce their risk of relapse and optimise outcomes, rather than treating later (*i.e. requiring these patients to first experience unnecessary frank relapse before accessing blinatumomab as salvage therapy*.) We have addressed the Committee's requests for additional data and analyses and believe we have resolved all areas of uncertainty highlighted in the ACD. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, we have demonstrated that there is a high degree of certainty around the unprecedented clinical benefit that blinatumomab brings over SOC chemotherapy when used earlier in the treatment pathway. Importantly, we demonstrate using different modelling approaches which address the specific concerns and requests of the Committee in the ACD, that the earlier use of blinatumomab in patients in CR with MRD remains highly cost effective compared with treating later. Further, compelling survival data and clinical expert opinion support the case that blinatumomab for the treatment of MRD fulfils the end-of-life criteria, which bolsters the conclusion that blinatumomab in this setting provides strong value for money. **Based on this body of compelling evidence of clinical effectiveness and comprehensive additional analyses of cost effectiveness demonstrating highly cost-effective ICERs, we propose that blinatumomab is recommended within its full licensed indication for use earlier in the treatment pathway in patients in CR with MRD, to reduce their risk of relapse and optimise outcomes.**	Comment noted. No action required.
14	Company	Amgen	In addition to the responses above, we request that the following points of clarification should be noted and considered for the FAD: **i. Throughout**	Comment noted. Text amended to reflect this suggestion. See

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Throughout the ACD reference is made to salvage chemotherapy as a comparator to blinatumomab. This is incorrect, as discussed in section 1 of our response. Amgen requests this is corrected within the FAD	FAD section 1, 3.5.
15	Company	Amgen	**i. Section 1.1, page 3** *Context: "The Committee was minded not to recommend blinatumomab as an option for treating acute lymphoblastic leukaemia in adults with Philadelphia-chromosome-negative CD19-positive B-precursor whose disease is in first or second complete remission with minimal residual disease (MRD) of at least 0.1%."* The indication provided is worded unusually; Amgen requests that the full approved indication is given, and the section updated as follows: "as an option for treating 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%".	Comment noted. Text aligned with marketing authorisation text. See FAD section 1.
16	Company	Amgen	**i. Section 1.2, page 4** *Context: "Evidence from 2 studies suggests that blinatumomab may help people have longer without their disease relapsing. Also, their disease responds well to treatment."* Amgen requests that for clarity, this statement is reworded as follows: "Evidence from two studies suggests that blinatumomab may provide a longer period of disease remission, and may lead to a greater number of patients achieving a cure."	Comment noted. Text amended. See FAD section 1.
17	Company	Amgen	**v. Section 3.1, pages 5–6** *Context: "About 44% of adults have acute lymphoblastic leukaemia that is expected to relapse."* Amgen believes that this statement is ambiguous and suggests that it be reworded for clarity, as follows: "Although more than 80% of patients achieve complete remission, up to 44% of patients will ultimately relapse.[14]"	Comment noted. Text amended. See FAD section 3.1.
18	Company	Amgen	**v. Section 3.2, page 6**	Comment noted. Text amended.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Context: "Once patients have had induction, consolidation and maintenance therapy and their disease is in complete remission, they will be monitored for the presence of MRD." Amgen does not believe that this statement aligns with the current treatment pathway for ALL; ESMO guidelines for the treatment of ALL recommend MRD testing immediately following achievement of a CR after induction therapy, and subsequently in the post-induction phase, and every 3 months in the follow-up of asymptomatic patients.[1] Indeed, in a survey of MRD testing patterns in the UK, 79% of clinicians performed an initial MRD test 4–8 weeks after commencing induction therapy when CR is first observed; it is not current practice to wait until after consolidation and maintenance therapy.[15] Amgen therefore suggests rewording as follows: "In the NHS, patients are routinely monitored for the presence of MRD 4–8 weeks after beginning induction when complete remission is first observed."	See FAD section 3.2.
19	Company	Amgen	**i. Section 3.7, page 9** Table 1 (Clinical effectiveness results for blinatumomab) refers to progression-free survival; Amgen suggests that this be reworded to "relapse-free survival", in order to align with the terminology used in the rest of the ACD. In addition, the final row of Table 1 ("Progression-free survival"), for consistency the cell in the BLAST column should be updated to "53.0% (95% CI 44 to 62) at 18 months", in line with the cell in the MT103-202 column.	Comment noted. Text amended in FAD. See FAD section 3.7, table 1.
20	Company	Amgen	**i. Section 3.15, page 14** *Context: "The company's post-relapse utility value is too high"* The ACD includes this unqualified bold heading; however, it is clearly noted that the ERG ran exploratory analyses using a wide range of alternative values, which clearly demonstrate that the model is insensitive to this parameter and the committee concluded this was not a key driver of the model results. We further note that, despite a high utility value, based on clinical expert opinion sought by the ERG, our base case may nevertheless be conservative. The prominence of this section of the ACD, including the unqualified bold heading, implies a level of uncertainty that is not warranted.	Comment noted. This is still relevant text because the value is used in the newly submitted models. NO action required. See FAD section 3.12.
21	Company	Amgen	References 1. Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.	Comment noted. No further action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(suppl 5):v69-v82. 2. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120(9):1868-76. 3. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA oncology. 2017:e170580. 4. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence statistics 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero. 5. Amgen Inc. ALL epidemiology estimates. 2017. 6. Goekbuget N, Dombret H, Zugmaier G, Bonifacio M, Graux C, Faul C, et al. Blinatumomab for Minimal Residual Disease (MRD) in Adults With B-Cell Precursor Acute Lymphoblastic Leukemia: Median Overall Survival Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months. American Society of Hematology Annual Meeting 20182018. 7. Gokbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522-31. 8. National Institute for Health and Care Excellence. Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804] - Committee papers. 2017. 9. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health technology assessment. 2017:1-204. 10. National Institute for Health and Care Excellence. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (TA451). 2018. 11. Pharmerit International. Disease Management and Outcomes in B-Precursor ALL Patients: Greece, Belgium, Switzerland. 2019. 12. National Institute for Health and Care Excellence. Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366]. 2015. 13. National Institute for Health and Care Excellence. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma [TA396]. 2016. 14. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944-50. 15. Amgen I. Data on File: Minimal residual disease testing patterns and healthcare utilization for	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			adults with B-precursor acute lymphoblastic leukemia - results of a physician survey in the UK. 2017.	
22	Consultee	Leukaemia Care	Overall, we are disappointed that an ACD has been produced, as both the company and ERG base-case ICERs fall within the cost-effectiveness threshold. The further analyses and clarification requested is unlikely to yield significant insights for the committee, but has delayed access for patients. To paraphrase the clinical expert, the committee face a 'pay now or pay later' situation. Blinatumomab has been already been recommended by NICE for use in relapsed patients (TA 450) and is now being assessed earlier in the pathway for patients with MRD activity. We are pleased that the committee has recognised the clinical importance of MRD (3.2) and that people with untreated MRD activity are likely to need subsequent treatment for relapse (3.4). As noted in 3.2, MRD activity is a "marker of chemotherapy resistance", therefore it would be unfair not to recommend Blinatumomab for these patients, as their alternative treatment option would be chemotherapy. This forces patients to knowingly undergo ineffective treatment, before likely receiving blinatumomab anyway (per TA 450). This is unethical and cannot be a cost-effective use of NHS resources. Blinatumomab has already obtained its marketing authorisation for this indication, so the production of an ACD in this instance has delayed access for NHS patients with a huge unmet need. Hopefully a positive recommendation will be urgently made.	Comment noted. No action required.
23	Consultee	Leukaemia Care	We are concerned by recommendation 3.18, regarding the life-extending treatment and the end of life criterion. As outlined by the clinical experts, for patients with MRD activity, 20% of patients would be alive at 2 years (3.18), clearly satisfying the short life-expectancy requirement (normally less than 24 months). NICE committees have frequently accepted that median OS satisfies the 'normal' requirement (e.g. TA 450 or TA451) where a proportion of patients proceed to successful transplant (with long term survival), rendering the mean OS an unreasonable interpretation of 'normal' survival. It would be unfair not to make the same interpretation in this appraisal. Based on the BLAST study, patients with MRD activity have a median OS of 12.5 months compared to a median OS of at least 27.3 months (not yet reached) for those who are MRD negative at this stage. It is an unreasonable and clinically implausible interpretation of the	Comment noted. The evidence was considered by the appraisal committee. The committee agreed that only one of the two end-of-life criteria were met. See FAD section 3.21.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			evidence to suggest that this would not translate to at least 3-months' additional survival. As such, we strongly suggest that the committee revises its recommendation on this point.	
24	Consultee	NCRI-ACP-RCP-RCR	We hope that this issue will be reviewed sooner than the mandatory 3 years - additional data and modelling has been requested and it would be good to know that the committee will review these data and make a definitive decision in the next few months	Thank you for your comment. The additional evidence was considered at the second appraisal committee meeting.
25	Consultee	NCRI-ACP-RCP-RCR	The uncertainty about whether this drug will or not be available for this setting creates a huge difficulty for designing clinical trials for patients with ALL as the 'high risk' arm would be very different if blin were standard of care for MRD + ALL (or not). Whilst this is not a problem for NICE, per se, it is a potential problem for patient who have a right to expect the NCRI to offer them appropriate trials. The NCRI adult ALL subgroup is about to start the process of funding UKALL15 - submission to CRUK planned June 2019. We have already put off submission in March 2019, pending the outcome of this process., We'd be very keen for a resolution, as a community	Comment noted. The committee considered your comment. No further action required.
26	Consultee	NCRI-ACP-RCP-RCR	We plan to supply NICE with data, in confidence, from the academic trial UKALL14	Thank you for your comment.
27	Consultee	RCPth (same submission has been received by RCPth-BSH)	I am concerned that since this appraisal was initiated subsequent appraisals have changed the treatment landscape for this disease and therefore the assumptions for the modelling are no longer correct.	Thank you for your comment. The additional evidence included the recent changes in treatment landscape. See FAD sections 3.10 and 3.14
28	Consultee	RCPth	On behalf of the patients diagnosed with Acute Lymphoblastic Leukaemia I am keen to see a swift resolution of this issue.	Thank you for your comment.
29	Consultee	RCPth	I am involved in the design and set up of the next major frontline study for Acute Lymphoblastic Leukaemia (known as the UKALL15 study) and the outcome of this appraisal	Thank you for your comment.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			will affect the design of the trial. I am concerned that delays in resolving this will delay the design, submission and set up of this study ultimately impacting patient care.	The committee considered your comment.

There were no web comments to the ACD.

NICE National Institute for Health and Care Excellence [Public observer slides - redacted]

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

2nd appraisal committee meeting

Chair's presentation

Lead Team: Alex Cale, Nigel Langford, David Chandler

ERG: ScHARR, University of Sheffield

NICE technical team: Lyudmila Marinova and Alex Filby

8th May 2019

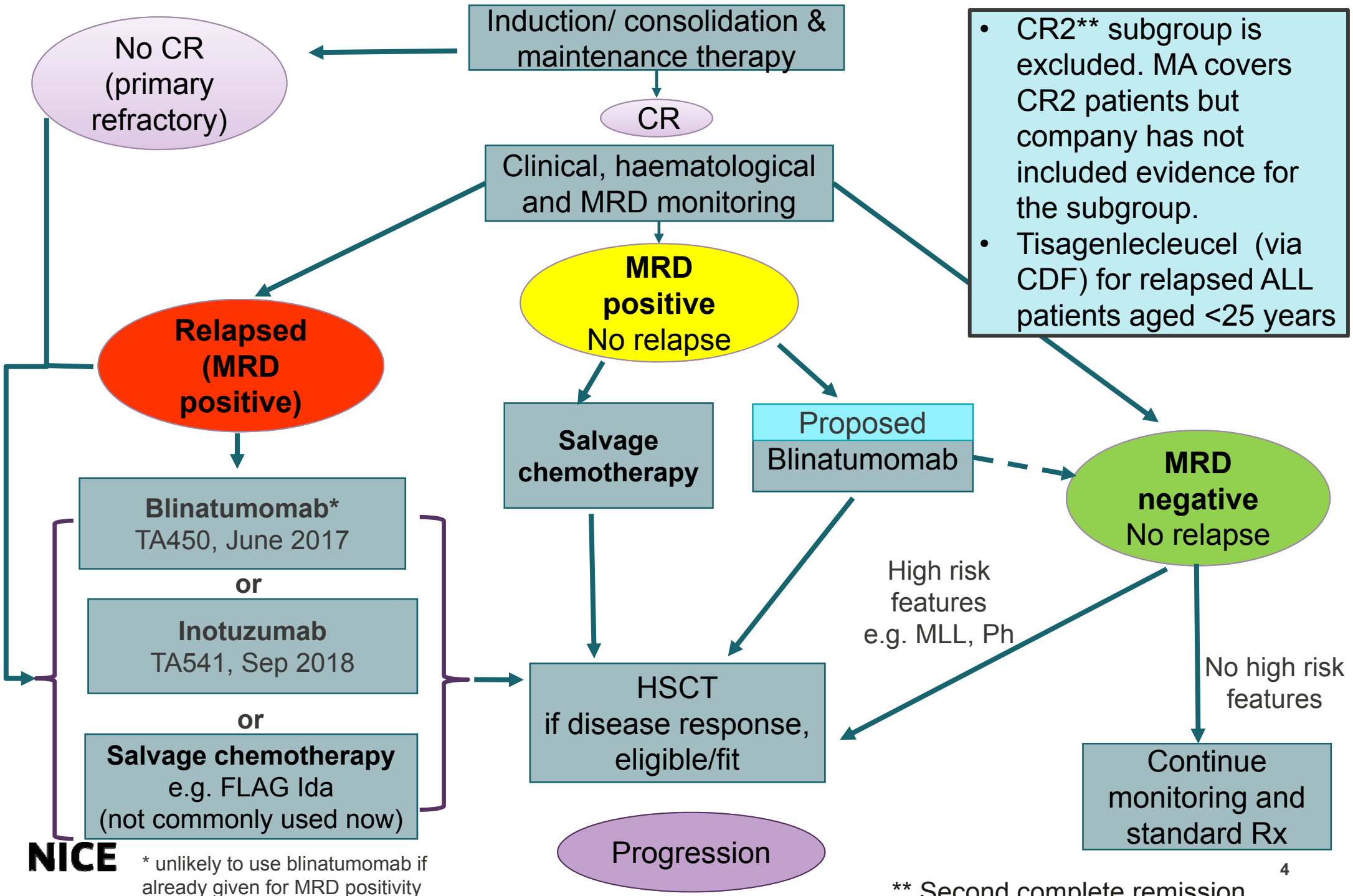
Key issues for consideration

- Does the additional evidence improve the clinical plausibility of the results?
- Does the revised partitioned survival and/or semi-Markov model accurately reflect the current treatment pathway – in particular the inclusion of blinatumomab/inotuzumab for people with minimal residual disease activity in remission?
- Is the cure point plausible (5 years in semi-Markov model)?
- Is the model(s) structure adequate for decision-making?
- What is the most plausible ICER?
- Are EoL criteria met?

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

Treatment pathway for B cell precursor ALL (ACM1)



NICE

* unlikely to use blinatumomab if already given for MRD positivity

** Second complete remission

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

ACD preliminary recommendation

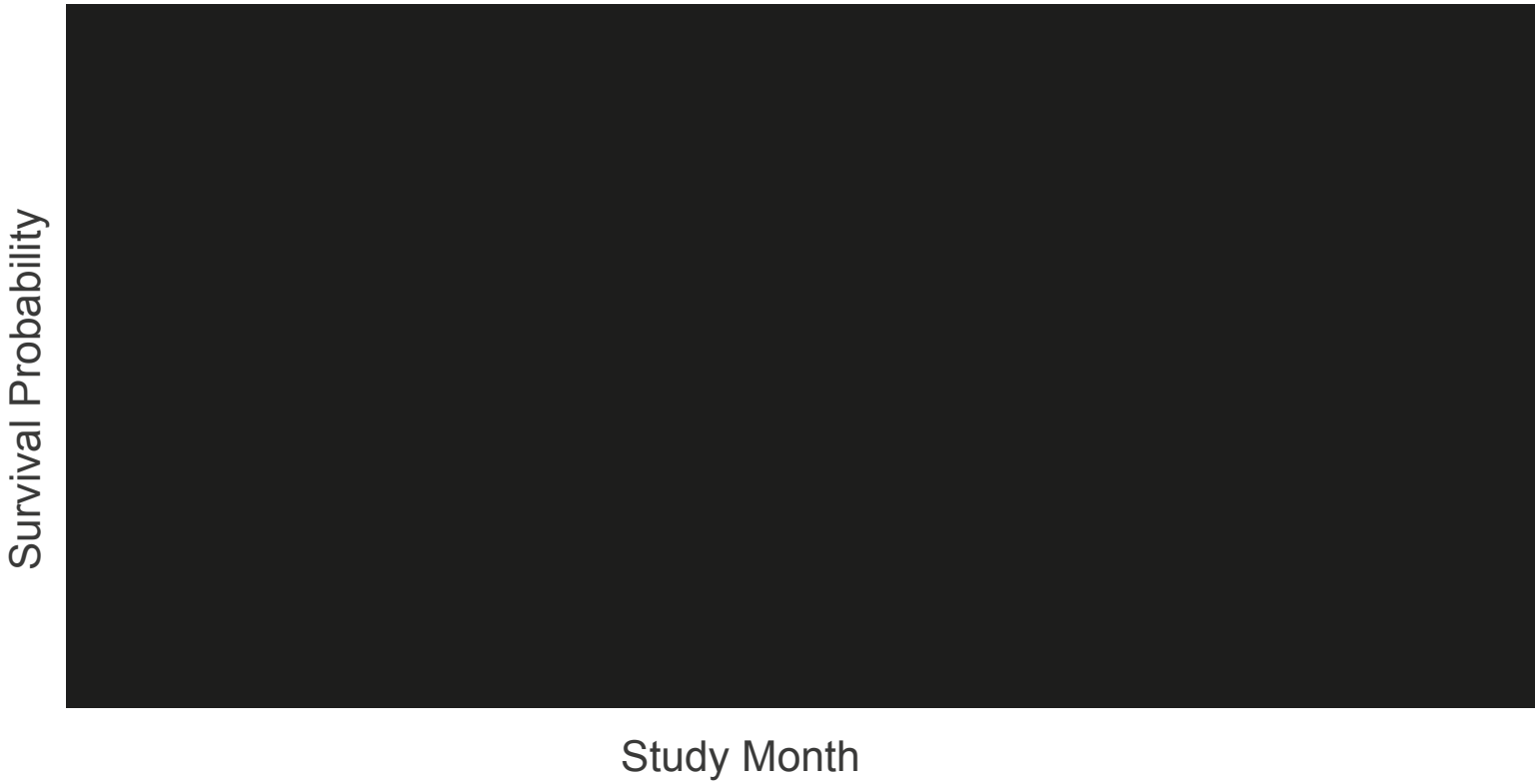
Committee minded not to recommend blinatumomab

- The committee requests a revised cost-effectiveness analysis reflecting the current treatment pathway and comparing blinatumomab with standard care. The revised economic model should:
  - include costs, health-related quality-of-life estimates and outcomes associated with the current treatment pathway for people with relapsed or refractory acute lymphoblastic leukaemia
  - include the proportion of people with and without MRD after blinatumomab treatment and how many have haematopoietic stem cell transplantation (HSCT)
  - incorporate an explicit causal link between the probability of HSCT and relapse-free survival and overall survival in both groups
  - explicitly model a cure for people whose disease is expected to be cured and include scenario analyses considering different cure fractions and cure points
  - factor in the different positions in the treatment pathway at which HSCT might be given
- the latest available evidence on survival outcomes after HSCT
- the latest trial data cut.

Conclusions from ACD [ACM1]:

Overall survival results BLAST

Full trial population (August 2015 data cut)



OS censoring at HSCT, Full trial population, Median XXXX

OS not censoring at HSCT, Full trial population, Median XXX

Company base case and ERG preferred

ACD conclusion:

- There is a plateau in the KM curves for both the OS and RFS but there are very few patients at risk in that part of the curve
- Blinatumomab is clinically effective but the size of benefit is unclear due to immature survival data

Committee's conclusions from ACD

Issue	Committee's conclusion
Treatment pathway	Current model does not reflect accurately the treatment pathway and the position of blinatumomab
Comparator	Relevant comparator is salvage treatment including chemotherapy and HSCT
Clinical effectiveness	Blinatumomab is clinically effective but immature survival data and the lack of direct comparative data means the size of the benefit is unclear
Indirect comparison	Appropriate but subject to uncertainty and the results are not generalisable to the full MA population. The comparison excluded the following groups: (a) patients who could not have HSCT or tolerate chemotherapy and (b) patients whose disease is in second complete remission
Cost effectiveness	Cure point assumption is not clinically plausible. Parametric curves for OS & RFS should be re-evaluated. Model results are uncertain.
Utility values	Not key drivers of the cost-effectiveness results Post-relapse quality-of-life estimates included in the model are too high
CDF	Does not meet the criteria for CDF
End of life	Did not meet the criterion for extension to life (at least 3 additional months). It is possible that blinatumomab is a life-extending treatment but this could not be verified due to flaws in the modelling.

ACD consultation responses

- Consultee comments from:
  - Leukaemia CARE
  - NCRI-ACP-RCP-RCR
- Clinical and patient experts:
  - 1x Clinical expert
- NHSE
  - Statement from Peter Clark
- Commentator comments from:
  - None
- Web comments from:
  - None
- Additional evidence from UKALL14 provided by Prof. Adele Fielding

Patient and professional group comments

- Disagree with the ‘minded no’ recommendation (Leukaemia CARE)
- Blinatumomab appears to be a cost-effective option as the ICERs fall below the threshold of other recommended technologies (Leukaemia CARE)
- Since the appraisal was initiated subsequent appraisals have changed the treatment landscape and therefore assumptions for the modelling are no longer correct (clinical expert)
- The outcome of the appraisal will impact the study design of UKALL15 study and timing is key (RCP-RCR)
- Uncertainty about whether blinatumomab will or not be available for this setting creates difficulty for designing trials for patients with ALL as the ‘high risk’ arm would be very different if blinatumomab were SoC for MRD+ ALL (or not) (clinical expert)
- Concern regarding the end-of-life criterion due to proportion alive at 2 years (20%) and the median OS values from BLAST (Leukaemia CARE)
- NHS England comments
  - Inotuzumab would be used at relapse if patients had previously had blinatumomab
  - NHSE likely to widen recommendations to patients ages less than adults
  - NHSE will consider widening for use in Ph+ MRD+ patients if NICE recommends in Ph-

Additional evidence: UKALL14 clinical trial data [1]

Trial population: XX patients aged 25-65 years with B-cell Ph- ALL

1. Proportion of patients (N=XX) who were MRD positive and proceeded to SCT

- Overall, XX (XX %) patients had received SCT. Potential increase to maximum of XX (XX %) when all data available
  - XX Myeloablative Conditioned (MAC) SCT
  - XX Reduced Intensity Conditioned (RIC) SCT

2. EFS, OS and RR for patients undergoing any time of HSCT

	Events/N	HR (95% CI)	p-value	3 year rate
EFS (Events are relapse or death)				
MRD negative	XX	XX	XX	XX
MRD positive	XX	XX		XX
OS				
MRD negative	XX	XX	XX	XX
MRD positive	XX	XX		XX
Relapse risk				
MRD negative	XX	XX	XX	XX
MRD positive	XX	XX		XX

Additional evidence: UKALL14 clinical trial data [2]

Overall survival for people undergoing HSCT any time per MRD status

Overall survival for people who do not proceed to HSCT per MRD status

Committee preferences and company's response

Committee preferred assumptions	Company updated analyses
Updated model reflecting current treatment pathway & relevant cost, utilities and outcomes	Yes - includes blinatumomab and inotuzumab as salvage therapy (both models)
Proportion of people with MRD response	Yes (semi-Markov model)
Proportion of people who undergo HSCT	Yes (semi-Markov model)
Incorporate causal link between HSCT and OS/RFS	Yes for pre-relapse HSCT (semi-Markov model). Post-relapse not explicitly captured.
Explicitly model cure and consider different cure fractions & cure points	Explicitly modelled cure using a 5 year cure point and looked at different cure point in the scenario analyses
Factor in different positions for HSCT in the treatment pathway	HSCT only explicitly modelled for pre-relapse (semi-Markov model)
Latest available evidence on survival after HSCT	Yes (TOWER study in both models but semi-Markov is explicitly modelling OS curve within the structure)
Latest trial data cut	Yes in semi-Markov model/ No in partitioned survival

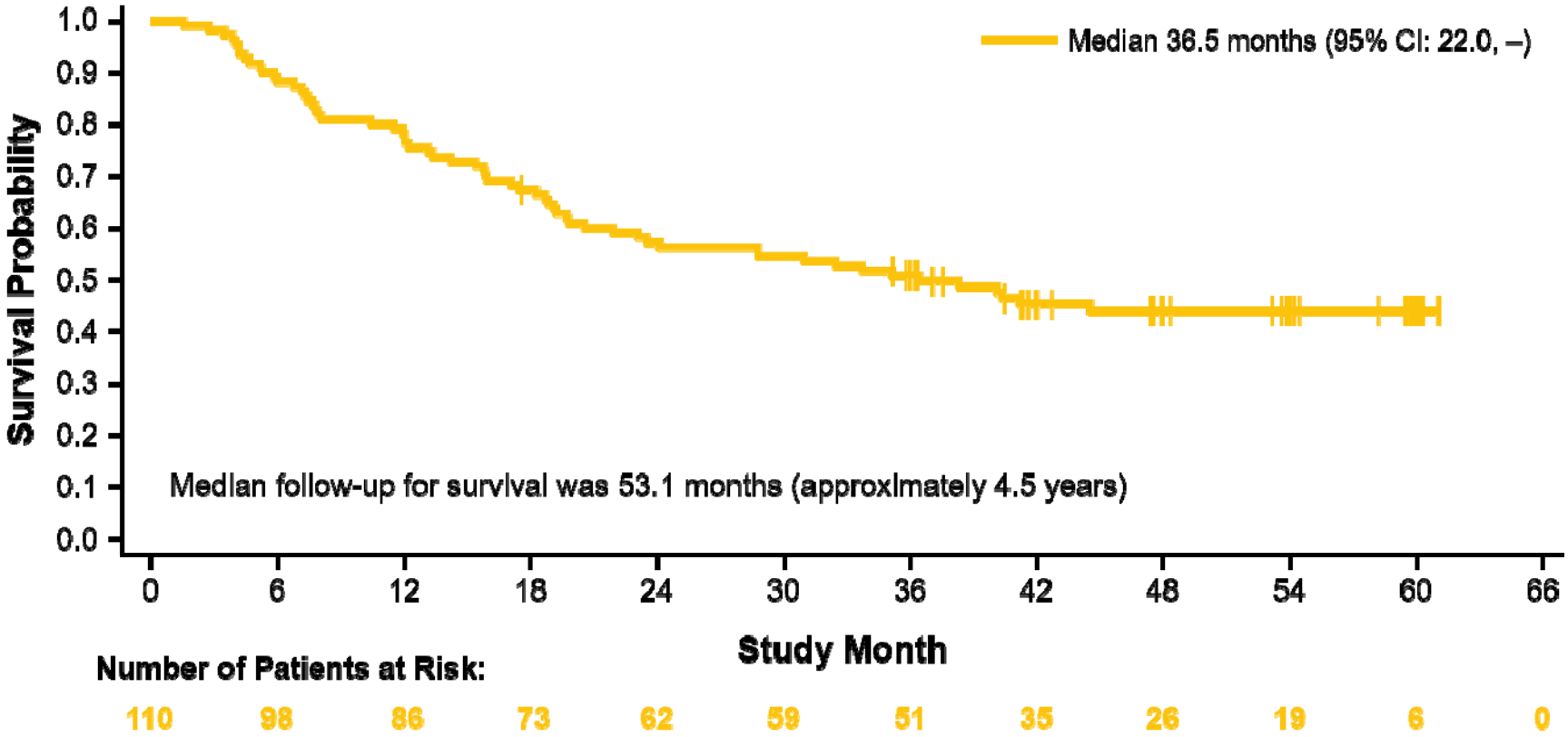
Company's ACD comments

- Relevant comparator for blinatumomab is continued chemotherapy
  - HSCT and salvage chemotherapy are not relevant comparators
- Clinical evidence suggests blinatumomab should be used prior to overt relapse in the treatment pathway in patients in CR with MRD to reduce risk of relapse
- The clinical benefit of blinatumomab in patients in CR with MRD is clearly established - CR1 and CR2 account for 98% of BLAST patients and only 2 patients in CR3. Therefore, the small number of patients not meeting the licensed indication are unlikely to have biased the estimated efficacy of blinatumomab. The results are generalisable to patients meeting the licensed indication.
- Results of indirect comparison are robust and demonstrate substantial clinical benefit of blinatumomab compared with SoC
- The two new models show that blinatumomab is cost effective if used prior to overt relapse in the treatment pathway

ERG comment: No evidence provided on CR2+ population

Company's new evidence: OS last data cut-off

Median follow up of 53.1 months in Ph- patients with BCP-ALL and MRD



- Last cut-off date for BLAST June 2017 (Aug 2015 in original submission)
- CR (CR1 and CR2) account for 98% of BLAST population

NICE

Company's new evidence: two models[1]

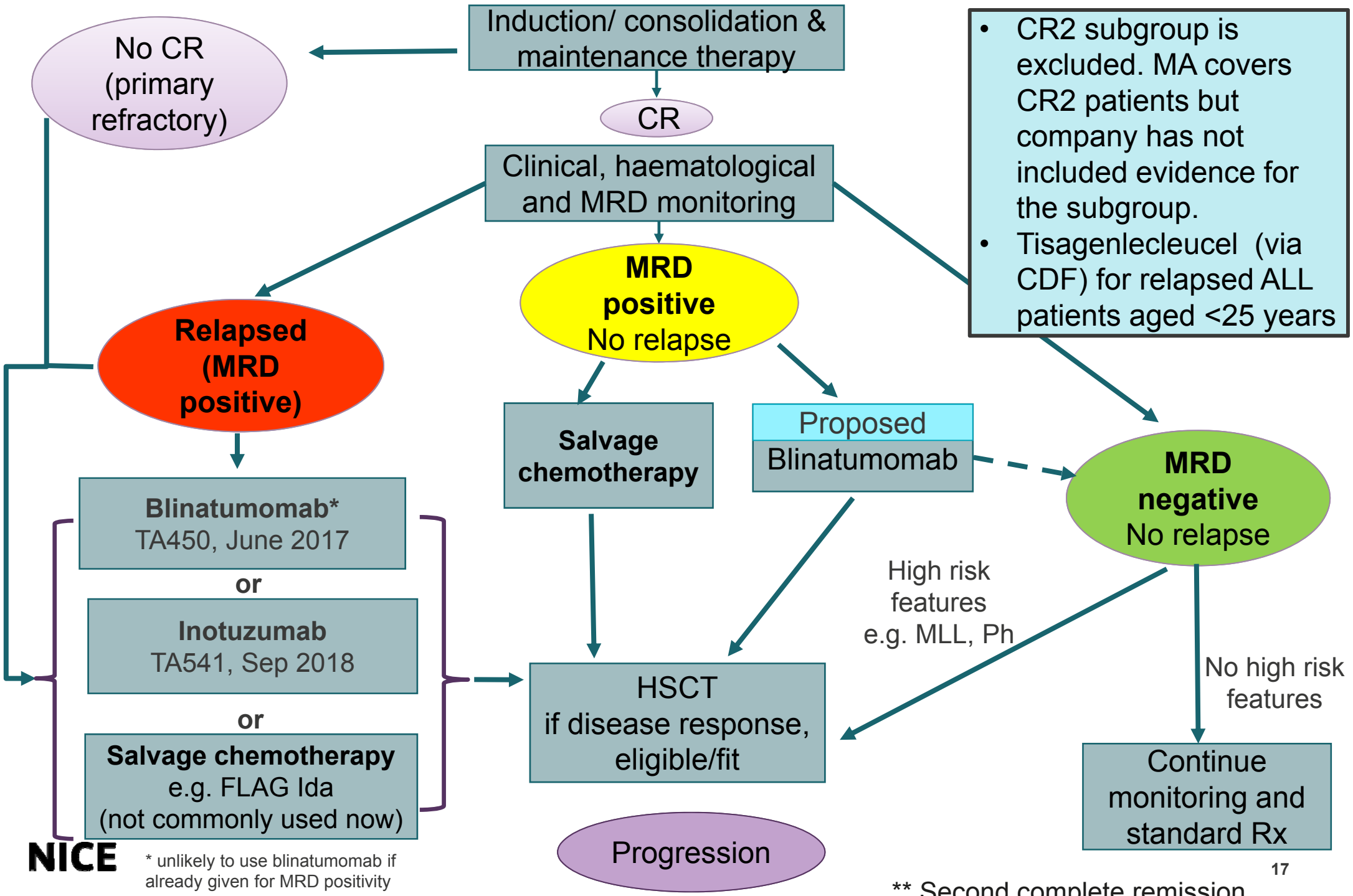
1. Semi-Markov cohort model

- Population: Ph-negative MRD-positive B-precursor ALL in CR1 with MRD
- Reflects latest data cut from BLAST trial (June 2017)
- Transition probabilities: estimated from BLAST (June 2017) and historical control (HC) from original submission; TOWER

2. Revised partitioned survival model

- Same structure as model from the original submission but amended treatment pathway to compare blinatumomab in MRD setting followed by inotuzumab salvage therapy vs. SoC chemotherapy in MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split)
- Cost of IO salvage therapy is a new parameter; cost of blinatumomab salvage therapy with updated value
- No causal link between MRD status, HSCT and OS/RFS
- Uses BLAST data from original submission (cut-off date August 2015)

Treatment pathway for B cell precursor ALL (ACM1)

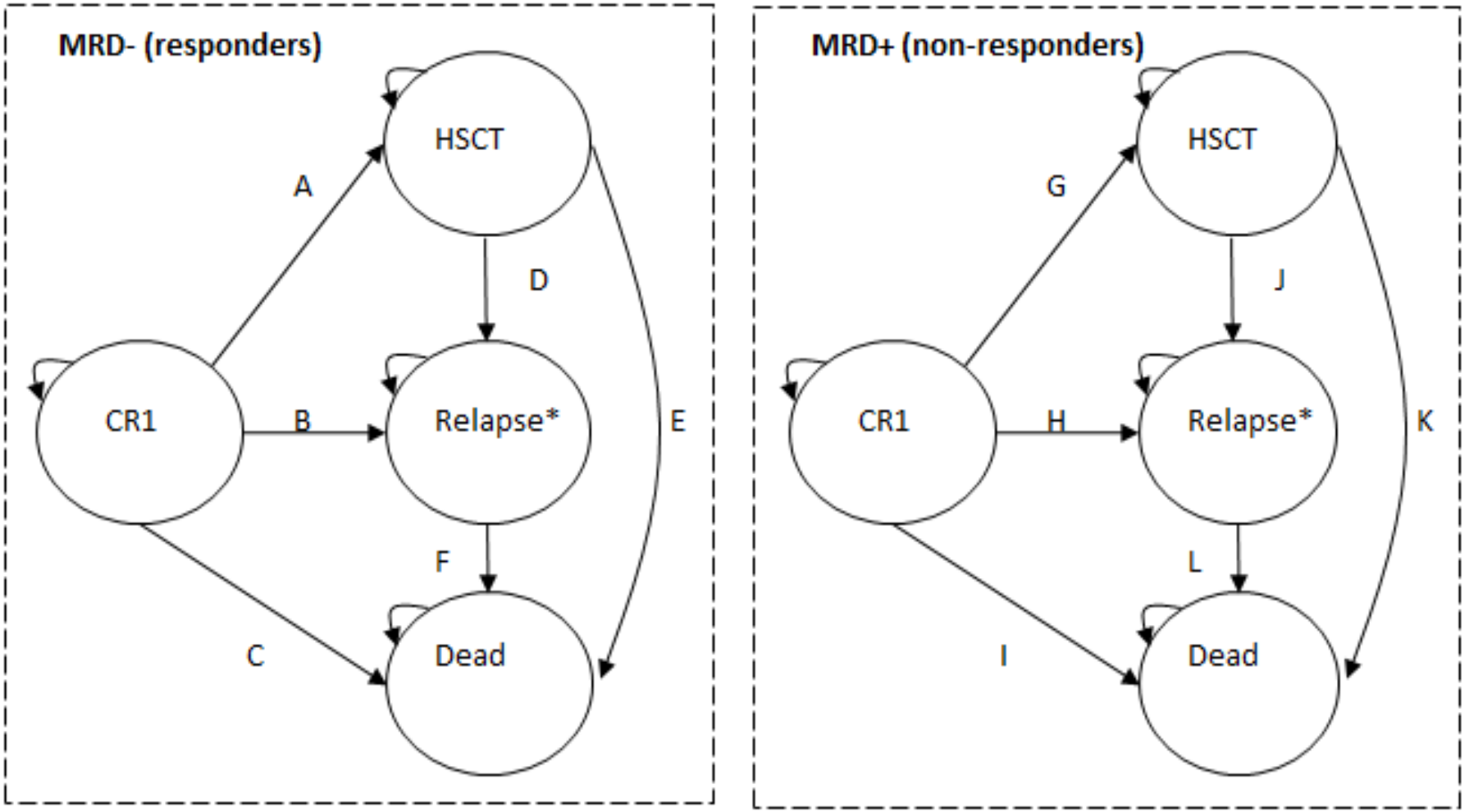


NICE

* unlikely to use blinatumomab if already given for MRD positivity

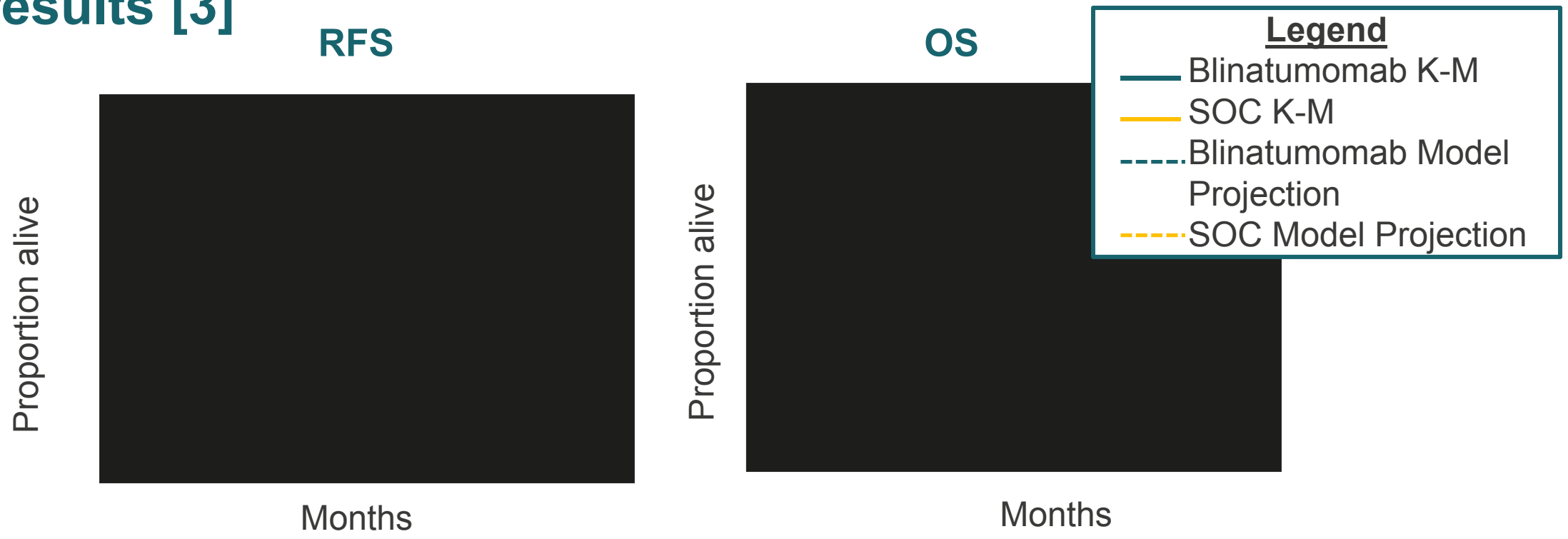
** Second complete remission

Company's new evidence: semi-Markov model [2]



- Includes committee's requests (slide 15)
- Adapted from ERG addendum
- For the exact number of patients at risk at each health state transition, please refer to Table 6 from the ERG addendum.

Company's new evidence: semi-Markov model RFS & OS results [3]



Company comments

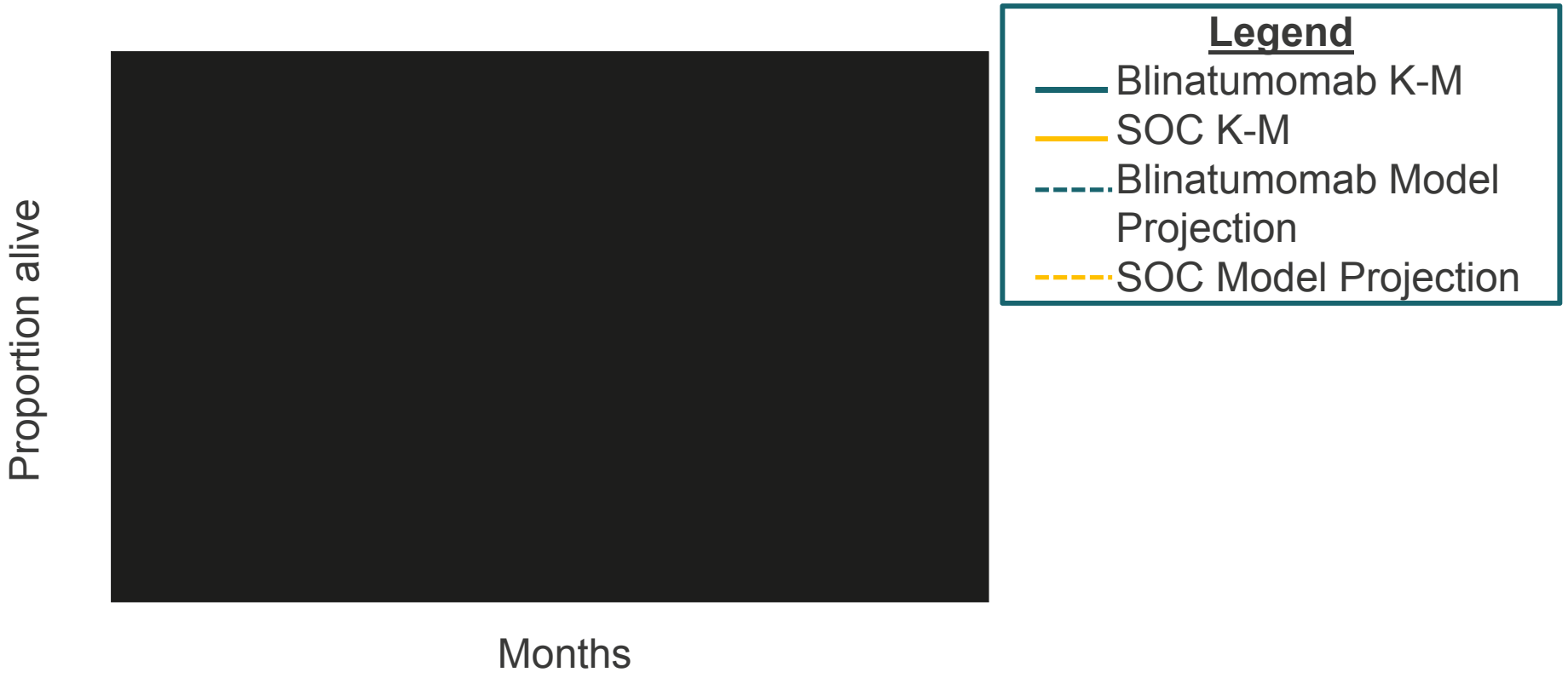
- The survival curves projected by the model fit both the BLAST and the historical control data very well.
- Post-relapse OS estimated with a matching exercise between BLAST [n=13] & TOWER (Blinatumomab patients [n=78] & SOC patients [n=39])
- The percentage of total patients achieving a cure as predicted by the model is 43.59% for blinatumomab vs 26.78% for SoC

ERG comments: semi-Markov model [1]

- The semi-Markov model addresses the majority of concerns from the ACD
- However, patients who undergo pre-relapse HSCT are penalised for a later cure point than that applied to the CR1 state
- The use of cure points of 5 years in each health state may be overly conservative; ERG is unsure whether this is clinically plausible
- The model structure only explicitly links HSCT to cure in those patients who receive HSCT prior to relapse. It doesn't reflect the fact that using IO for relapse will probably increase HSCT costs
- Inappropriate method for handling competing risks, which is likely to inflate the risk of each event
- Small numbers of events and patients risks, which increases uncertainty
- Questionable rationale for curve selection. May be better to select curves using BIC
- Concerns regarding model-predicted OS.

ERG comment: semi-Markov model OS predictions[2]

Company's semi-Markov model – overall survival, model excludes blinatumomab/IO as downstream treatments for relapsed ALL



Historical SoC comparator study is unlikely to have included blinatumomab/IO post-relapse (treatments not approved until 2018). Therefore, the model is likely under-predicting survival in both groups but more so in the SoC group. The company's base case OS projections (including downstream blinatumomab/IO) should not match the curves, they are expected to be higher.

Company's new evidence: updated base case and scenario analyses based on the two new models

Scenarios for semi-Markov model		Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case Deterministic model	Blinatumomab	XXXX	6.56	54,264	2.12	**25,645**
	SOC	XXXX	4.44			
DSA range (largest change from baseline is cost of blinatumomab as salvage therapy)						14,735-36,556
PSA mean results	Blinatumomab	XXXX	6.48	56,619	2.08	27,257
	SOC	XXXX	4.40			
Scenarios for revised partitioned survival model		**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**
Base case Deterministic model	Blinatumomab	XXXX	7.79	39,720	2.11	**18,818**
	SOC	XXXX	5.68			
DSA analysis (largest change from baseline is proportion of blinatumomab patients receiving HSCT)						1,721-41,644
PSA mean results	Blinatumomab	XXXX	7.67	40,023	2.00	20,024
	SOC	XXXX	5.67			

Company: The two new models show that blinatumomab is cost effective if used early in the treatment pathway (prior to overt relapse)
NICE comment: There is a difference in total QALYs between the two models

Company's new evidence: semi-Markov model key scenario analyses

Scenario	ICER (£/QALY)
Base case semi-Markov model	25,645
SOC survival curves to inform survival in MRD+ patients receiving blinatumomab	24,852
Blinatumomab MRD Response	
74.17% MRD response rate (lower CI)	31,210
91.17 MRD response rate (upper CI)	22,457
SOC estimated based on BLAST data:	
8% MRD response rate	26,829
15% MRD response rate	29,515
0% response rate	24,311
Impact of varying HSCT rate:	
HSCT rate for MRD+ based on SOC (historical control) data	11,695
HSCT rate based on SOC (historical control) for all	31,851
HSCT based on MRD- (BLAST) for all	25,936
Impact of Cure Timepoint:	
Cure time point 3 years	25,551
Cure time point 4 years	25,479

ERG exploratory analyses with semi-Markov model (deterministic)[2]

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (£/QALY)
Semi-Markov model – company's curve selections, 5-year cure timepoint							
Blinatumomab	12.14	6.56	XXXX	4.06	2.12	£54,264	£25,645
Standard care	8.08	4.44	XXXX	-	-	-	-
Semi-Markov model – company's curve selections, 4-year cure timepoint							
Blinatumomab	12.50	6.72	XXXX	4.05	2.11	£53,847	£25,479
Standard care	8.44	4.61	XXXX	-	-	-	-
Semi-Markov model – company's curve selections, 3-year cure timepoint							
Blinatumomab	13.13	7.03	XXXX	4.00	2.09	£53,403	£25,551
Standard care	9.13	4.94	XXXX	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 5-year cure timepoint							
Blinatumomab	10.39	5.75	XXXX	4.57	2.39	£59,916	£25,106
Standard care	5.81	3.37	XXXX	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 4-year cure timepoint							
Blinatumomab	11.41	6.23	XXXX	4.87	2.52	£58,618	£23,237
Standard care	6.54	3.71	XXXX	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 3-year cure timepoint							
Blinatumomab	12.69	6.84	XXXX	5.03	2.60	£56,940	£21,874
Standard care	7.66	4.24	XXXX	-	-	-	-

Undiscounted LYG

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental

ERG comments: updated partitioned survival model [3]

- Cure points determined separately for RFS and OS based on parametric models
- Concerns regarding the curves selected for the company's base case model
- Latest BLAST data-cut not used
- Concerns regarding the incorporation of downstream costs and benefits for patients with relapsed disease
- Concerns regarding the included costs of downstream treatments for relapsed disease

ERG exploratory analyses with partitioned survival model [4]

Company's updated partitioned survival model – cure point determined by parametric curves probabilistic model							
	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (£/QALY)
Blinatumomab	13.23	7.67	XXXX	5.47	2.00	£40,023	£20,024
Standard care	7.76	5.67	XXXX	-	-	-	-
Company's updated model with fixed 5-year cure point							
Blinatumomab	13.72	7.89	XXXX	4.95	1.78	£39,894	£22,433
Standard care	8.77	6.12	XXXX	-	-	-	-

*Undiscounted LYG

Company's updated partitioned survival model, ERG exploratory analysis 2 – ICER ranges using ERG clinical advisors' preferred OS functions, deterministic model		
OS model	Low ICER	High ICER
Generalised gamma (U)	£21,742	£26,753
RCS Weibull (U)	£20,976	£24,562
Weibull Mixture (Cure + U)	£15,176	£18,991

End of life criteria

Company's evidence	Median OS for the historical control group (using ATT-weighted propensity score matching analyses) for standard care chemotherapy was XXXX (XXXX). Median OS (using ATT-weighted propensity score matching analyses), was XXXX after more than 40 months follow-up for blinatumomab thus demonstrating a XXXX OS survival XXXX when compared to standard care. Real-world evidence from Belgium, Greece and Switzerland demonstrate that in patients who achieve MRD negativity (n=50), the median OS was XXXX (XX) after a median follow-up of XX compared to XX months (XX) after a median follow-up of XXXX in MRD positive patients (n=17).
ERG comments	Median and mean OS estimates from the model diverge considerably due to the inclusion of an assumption of cure for a proportion of patients. The ERG notes that the company's partitioned survival and semi-Markov models produce mean OS estimates for the standard care group of XX years and XX years, respectively. The company's partitioned survival and semi-Markov models (probabilistic versions) produce incremental LYGs for blinatumomab versus SoC of 5.47 and 3.98, respectively. ATT-adjusted historical control study suggests the following survival probabilities: after 1 year – 65%; after 2 years – 48%

Key issues for consideration

- Does the additional evidence improve the clinical plausibility of the results?
- Does the revised partitioned survival and/or semi-Markov model accurately reflect the current treatment pathway – in particular the inclusion of blinatumomab/inotuzumab as for people with minimal residual disease activity in remission?
- Is the cure state (5 years in semi-Markov model) plausible?
- Is the model(s) structure adequate for decision-making?
- What is the most plausible ICER?
- Are EoL criteria met?

NICE National Institute for Health and Care Excellence

Blinatumomab for treating minimal residual B-precursor acute lymphoblastic leukaemia in remission [ID1036]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**n/a**
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Example 1	We are concerned that this recommendation may imply that ……..
1	Overall, we are disappointed that an ACD has been produced, as both the company and ERG base-case ICERs fall within the cost-effectiveness threshold. The further analyses and clarification requested is unlikely to yield significant insights for the committee, but has delayed access for patients. To paraphrase the clinical expert, the committee face a 'pay now or pay later' situation. Blinatumomab has been already been recommended by NICE for use in relapsed patients (TA 450) and is now being assessed earlier in the pathway for patients with MRD activity. We are pleased that the committee has recognised the clinical importance of MRD (3.2) and that people with untreated MRD activity are likely to need subsequent treatment for relapse (3.4). As noted in 3.2, MRD activity is a "marker of chemotherapy resistance", therefore it would be unfair not to recommend Blinatumomab for these patients, as their alternative treatment option would be chemotherapy. This forces patients to knowingly undergo ineffective treatment, before likely receiving blinatumomab anyway (per TA 450). This is unethical and cannot be a cost-effective use of NHS resources. Blinatumomab has already obtained its marketing authorisation for this indication, so the production of an ACD in this instance has delayed access for NHS patients with a huge unmet need. Hopefully a positive recommendation will be urgently made.
2	We are concerned by recommendation 3.18, regarding the life-extending treatment and the end of life criterion. As outlined by the clinical experts, for patients with MRD activity, 20% of patients would be alive at 2 years (3.18), clearly satisfying the short life-expectancy requirement (normally less than 24 months). NICE committees have frequently accepted that median OS satisfies the 'normal' requirement (e.g. TA 450 or TA451) where a proportion of patients proceed to successful transplant (with long term survival), rendering the mean OS an unreasonable interpretation of 'normal' survival. It would be unfair not to make the same interpretation in this appraisal. Based on the BLAST study, patients with MRD activity have a median OS of 12.5 months compared to a median OS of at least 27.3 months (not yet reached) for those who are MRD negative at this stage. It is an unreasonable and clinically implausible interpretation of the evidence to suggest that this would not translate to at least 3-months' additional survival. As such, we strongly suggest that the committee revises its recommendation on this point.
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Insert extra rows as needed

Checklist for submitting comments

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Royal College of Pathologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**I have no past or current direct or indirect links to the tobacco industry**
Name of commentator person completing form:	[redacted]

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2	On behalf of the patients diagnosed with Acute Lymphoblastic Leukaemia I am keen to see a swift resolution of this issue.
3	I am involved in the design and set up of the next major frontline study for Acute Lymphoblastic Leukaemia (known as the UKALL15 study) and the outcome of this appraisal will affect the design of the trial. I am concerned that delays in resolving this will delay the design, submission and set up of this study ultimately impacting patient care.
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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We hope that this issue will be reviewed sooner than the mandatory 3 years - additional data and modelling has been requested and it would be good to know that the committee will review these data and make a definitive decision in the next few months
2	The uncertainty about whether this drug will or not be available for this setting creates a huge difficulty for designing clinical trials for patients with ALL as the 'high risk' arm would be very different if blin were standard of care for MRD + ALL (or not). Whilst this is not a problem for NICE, per se, it is a potential problem for patient who have a right to expect the NCRI to offer them appropriate trials. The NCRI adult ALL subgroup is about to start the process of funding UKALL15 - submission to CRUK planned June 2019. We have already put off submission in March 2019, pending the outcome of this process., We'd be very keen for a resolution, as a community.
3	We plan to supply NICE with data, in confidence, from the academic trial UKALL14

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- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Blinatumomab for treating minimal residual B-precursor acute lymphoblastic leukaemia in remission [ID1036]

Consultation on the appraisal consultation document – deadline for comments on **Wednesday 27 March 2019 email:** TACommC@nice.org.uk/NICE DOCS

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Amgen Ltd

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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Executive Summary	**We have carefully reviewed the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) of blinatumomab (Blincyto®) in the treatment of acute lymphoblastic leukaemia (ALL) in remission with minimal residual disease (MRD). Importantly, the Committee has recognised that patients with ALL who achieve haematological complete remission (CR) but have MRD remain at significantly greater risk for relapse and have poorer survival than those without MRD. Blinatumomab is a highly innovative therapy and is unique in being the only therapy approved to address the significant unmet needs of patients with this ultra-orphan disease.** **Blinatumomab was recommended by NICE in June 2017 for use in patients with ALL who have relapsed following prior therapy (TA450). Since then, blinatumomab has also demonstrated unprecedented high MRD response rates, relapse-free survival (RFS) and overall survival (OS) benefits compared with standard of care (SOC) chemotherapy in the earlier setting in patients in CR with MRD, despite the many challenges presented by the rarity of the condition and the lack of effective treatments. These benefits translate into a high likelihood of blinatumomab being cost effective when used earlier in the treatment pathway in patients in CR with MRD compared with its currently recommended use in patients after they have experienced frank relapse. We are therefore disappointed that the Committee was minded not to recommend the earlier use of blinatumomab as a treatment option in these patients due to perceived uncertainties regarding the exact size of its treatment benefits relative to chemotherapy, and its cost effectiveness in this setting.** We are committed to working with NICE to address the concerns of the Committee expressed in the ACD. We have responded to the Committee's specific requests by: • providing the latest BLAST trial data cut to address concerns regarding uncertainty in the long-term survival benefit with blinatumomab; and • conducting extensive cost-effectiveness analyses including a new model structure to address concerns regarding uncertainty in the cost effectiveness of blinatumomab. We believe our response will sufficiently address the concerns of the Committee, demonstrate there is little uncertainty in the size of the treatment benefits with blinatumomab relative to chemotherapy, establish that blinatumomab is highly likely to be cost effective, and allow a positive recommendation for the appropriate, earlier use of blinatumomab in the MRD setting. 1. **ALL patients in CR with MRD remain at high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to approve blinatumomab use earlier in the treatment pathway before relapse.** As acknowledged in the ACD, patients who achieve CR but have MRD are at increased risk of relapse and have poorer survival than those without MRD. Blinatumomab is the only therapy approved for use in MRD and, as indicated in the scope, the only relevant comparator is continued chemotherapy. However, as MRD is an indicator of chemotherapy resistance, patients with MRD are predicted to have a poor response to subsequent chemotherapy. Blinatumomab is currently recommended as a treatment option in relapsed/refractory ALL patients based on NICE TA450. However, patients who experience relapse experience poorer survival outcomes. There are therefore robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients with MRD, to reduce their risk of relapse and optimise their outcomes, rather than requiring these patients to first experience frank relapse before accessing blinatumomab (or inotuzumab) as salvage therapy.

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	2. The clinical benefit of blinatumomab when used early in the treatment pathway in patients in CR with MRD is clearly established and is unprecedented; there is a high degree of certainty in the size and durability of the clinical effects of blinatumomab relative to chemotherapy. **Trial data:** The BLAST and pilot study were single-arm trials, which is appropriate given the rarity of the condition, lack of standard effective treatments and the highly innovative nature of blinatumomab in this setting. There was a very small proportion (<5%) of patients in the BLAST trial who did not meet the subsequent licensed indication for blinatumomab, and these are highly unlikely to have positively biased the estimated efficacy of blinatumomab. Results of the BLAST trial and pilot study are therefore generalisable to patients meeting the licensed indication. Blinatumomab achieved very high MRD response rates of around 80%, which is unprecedented in this condition. The pilot study demonstrates a relapse-free survival (RFS) rate of 53% over almost 6 years of follow-up, and the latest data cut from the BLAST trial, which was requested by the Committee, confirms the interim data provided in our submission: median overall survival (OS) with blinatumomab was 36.5 months over a median follow-up of 4.5 years. **Indirect treatment comparison:** Given the need to evaluate the efficacy of blinatumomab in single-arm trials, an indirect treatment comparison was required to demonstrate the treatment effects of blinatumomab relative to standard of care (SOC) chemotherapy. The ERG confirmed that the methods of our indirect treatment comparison were appropriate. We confined the indirect treatment comparison to patients in their first CR (CR1) in order to match to and improve the robustness of these comparative data. This is aligned with the MRD patient population in which blinatumomab is expected to be used in clinical practice as patients in later remission states (CR2) are expected to be a small and declining pool given that they would have access to blinatumomab as relapsed patients before CR2. Additionally, patients' ineligible for HSCT or chemotherapy were by definition excluded from the indirect comparison; however, these patients represent a very small minority of given the substantial risk of relapse with MRD and the resulting clinical need to provide some form of active treatment. The results of the indirect comparison are therefore robust, reliable and highly generalisable to patients anticipated to use blinatumomab in the MRD setting in clinical practice. Given the median RFS was [redacted] with blinatumomab compared with SoC chemotherapy ([redacted]; HR [redacted]), and median OS with blinatumomab was [redacted] after more than 40 months of follow-up, compared to a median OS of [redacted] for SoC chemotherapy (suggesting at least [redacted] of the median OS with blinatumomab), there is also a high degree of certainty in the unprecedented size and durability of the clinical benefit provided by blinatumomab when used early in the treatment pathway for patients in CR with MRD. **3. The uncertainties in the economic evaluation have been fully explored by conducting a range of analyses in line with the Committee's request. All analyses demonstrate that blinatumomab is highly likely to be cost effective when used earlier in the treatment pathway in patients in CR with MRD.** **Our original partitioned survival model:** The Committee raised concerns that our original model and base case analyses did not reflect the current treatment pathway following relapse. At the time of our submission (October 2017), blinatumomab had only recently received its positive recommendation for use in the relapsed/refractory setting, and inotuzumab had not been recommended by NICE. We presented an **alternative base case analysis** in our submission, which included blinatumomab as salvage therapy in patients who relapse following treatment with SOC and so reflected the existing treatment pathway at the time. However, this alternative base case was not reported in the ACD. It should be noted that, compared with our original submitted base case ICER of £28,524/QALY, the incorporation of salvage therapy significantly reduced the ICER to £17,420/QALY. This demonstrates that the ICERs in our original base case analysis were highly conservative, as were the results of all sensitivity and scenario analyses that were conducted by Amgen and the ERG.

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	The ACD also highlighted specific concerns regarding our modelling of cure points and the link between HSCT and outcomes. Whilst accepting there is inevitable uncertainty in some elements of our modelling, we note the ERG analyses demonstrated the ICER estimates were reassuringly close to our base case model estimates when alternative assumptions on cure points and HSCT outcomes were explored. These uncertainties therefore relate to the *precision* of the ICER estimates, rather than the *magnitude*. Had these analyses been conducted using the alternative base case model, which incorporated salvage therapy following relapse, all ICERs would have been well within the thresholds of cost effectiveness. **Additional analyses to address the Committee's concerns on the appropriate treatment pathway using our original partitioned survival model:** We acknowledge that the NICE approval of inotuzumab in September 2018 changed the relapsed pathway from that at the time of our submission. To resolve the Committee's concerns that our model did not fully reflect the current treatment pathway following relapse, we have revised the original model to provide a comparison of blinatumomab in the MRD setting followed by inotuzumab salvage therapy, versus SOC chemotherapy in the MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split). This pathway, which was informed by clinical expert opinion and has been validated as relevant to clinical practice, confirms that early use of blinatumomab in MRD remains cost effective with an ICER of £18,818/QALY. Sensitivity and scenario analyses indicate these results are robust, and confirm blinatumomab is highly likely to be cost effective. **A new Markov model structure to address all the Committee's concerns and specific requests regarding the structural elements of our original model**: We have developed a new, combined decision-tree and Markov cohort model which: • reflects the current treatment pathway in relapsed/refractory setting – by including blinatumomab and inotuzumab as salvage therapy; • provides the link between MRD status, HSCT and survival – using data from re-analysis of BLAST and the historical comparator trial; • models a specific cure point of 5 years – which given the availability of trial data with almost 5 years of follow-up requires little survival curve extrapolation; • includes the different positions in the treatment pathway at which HSCT might be given – as it explicitly models time to transplant in remission and post-relapse states, and • reflects the latest data cut from the BLAST trial – data from the latest BLAST data cut with a median follow-up of 53.1 months has been used to estimate parameters. In the new model, early use of blinatumomab in ALL patients in CR1 with MRD remains highly cost effective with a base case ICER of £25,645/QALY compared with current SOC. This supports the conclusion that, although there are uncertainties in the *precision* of the ICER estimate, the *magnitude* of the ICER is highly likely to be within the thresholds of cost effectiveness. It is important to note that to address the Committee's specific requests on structural relationships between MRD, HSCT and outcomes, post hoc analyses of small subgroups of the clinical trials are necessary; therefore, some uncertainty in the estimation of the required parameters is expected. As a result, our original partitioned survival model structure may better reflect the observed clinical trial data as parameters are estimated based on larger sample sizes and event rates. Collectively, the range of analyses conducted to address the Committee's concerns all point to the same conclusion: **blinatumomab is highly likely to be cost effective when used earlier in the treatment pathway in patients in CR with MRD.**

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	4. Blinatumomab in the treatment of patients in CR with MRD clearly fulfils the criteria for consideration under NICE's end-of-life policy based on compelling clinical data and expert opinion. Blinatumomab clearly fulfils the criteria for consideration under NICE's end-of-life policy based on compelling OS data from the clinical trials and expert opinion. SOC chemotherapy in the historical comparator study had a median OS of [redacted] months, and the clinical expert quoted in the ACD suggested survival at 2 years would be around 20%, clearly fulfilling the short life expectancy criterion. Mature BLAST OS data show a median OS of 36.5 months with blinatumomab, clearly indicating an OS gain of over 3 months. We note the ERG rejected our conclusions that blinatumomab meets the end-of-life criteria due to the use of median rather than mean estimates of OS. However, given the compelling median OS gain of >20 months for blinatumomab versus the historical control in our robust indirect comparison, we believe there is little doubt that patients with MRD treated with SOC chemotherapy have a short life expectancy less than 24 months, and that blinatumomab provides a substantial gain in OS that is highly likely to be in excess of 3 months. We refer the Committee to the pragmatic approach taken in previous appraisals, in which treatments were accepted for consideration under NICE's end-of life policy using median OS data to demonstrate fulfilment of the criteria (e.g. TA366 and TA396). We suggest that a similar pragmatic approach is warranted for blinatumomab in the treatment of people with MRD, not least to avoid the introduction of inconsistencies that would inappropriately penalise the considerations of blinatumomab's cost effectiveness when used earlier in the treatment pathway compared with the later use of blinatumomab or inotuzumab as salvage therapy, which were accepted as cost effective with higher ICERs under NICE's end of life policy. **Conclusion** • ALL patients in CR with MRD remain at very high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to use of blinatumomab earlier in the treatment pathway in these patients, to reduce their risk of relapse and optimise outcomes, rather than treating later (i.e. requiring these patients to first experience unnecessary frank relapse before accessing blinatumomab as salvage therapy.) • We have comprehensively addressed the Committee's requests for additional data and modelling analyses. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, we have demonstrated that there is a high degree of certainty around the unprecedented clinical benefit that blinatumomab brings over SOC chemotherapy when used earlier in the treatment pathway. Importantly we have demonstrated, using different modelling approaches, that earlier use of blinatumomab in patients in CR with MRD remains highly cost effective compared with treating later. Further, compelling survival data and clinical expert opinion support the case that blinatumomab for the treatment of MRD fulfils the end-of-life criteria, which bolsters the conclusion that blinatumomab in this setting provides strong value for money. • Based on this body of compelling evidence of clinical effectiveness and robust additional analyses demonstrating consistently cost-effective ICERs, we propose that blinatumomab is recommended within its full licensed indication for use earlier in the treatment pathway in patients in CR with MRD, to reduce their risk of relapse and optimise outcomes.

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Section 1. There are robust clinical, ethical and economic arguments to use blinatumomab earlier in the treatment pathway in ALL patients in CR with MRD	**1. The relevant comparator for blinatumomab is continued treatment with chemotherapy. HSCT is not a relevant comparator** The ACD states that *'...the position of blinatumomab in the treatment pathway is more complex than is implied by a comparison with …chemotherapy because some patients may have HSCT*' (ACD section 3.5). ALL treatment protocols are complex and variable across countries, but patients typically receive induction chemotherapy with the aim of achieving a complete response (CR), after which they may be eligible for haematopoietic stem cell transplantation (HSCT), with or without intensification chemotherapy. Patients ineligible for transplant may receive consolidation treatment, which aims to ensure the clearance of leukemic cells from sanctuary sites such as the central nervous system (CNS), followed by maintenance therapy[1]. Patients who achieve CR but have MRD are at increased risk of relapse and have poorer survival than those without MRD, as acknowledged in the ACD. Blinatumomab has demonstrated unprecedent response rates in patients with MRD (see section 2 below) and is the only therapy approved for the treatment of patients with MRD. In the absence of blinatumomab, the only other options for patients with MRD are to proceed to HSCT (if well enough and a donor is available), despite the known risks of suboptimal outcomes, or continued treatment with poorly effective chemotherapy. However, if blinatumomab is made available, HSCT would *not* be replaced by blinatumomab; in those able and willing to undergo the procedure, HSCT would still occur *after* treatment with blinatumomab. Therefore, as agreed at the scoping stage and as reflected in the final scope for this appraisal, HSCT is not a comparator for blinatumomab. In contrast, in those awaiting or unable to undergo HSCT, blinatumomab would replace continued chemotherapy. Therefore, the only relevant comparator is continued treatment with chemotherapy, as indicated in our submission. **2. The ACD misrepresents the treatment pathway: salvage chemotherapy is not a comparator for blinatumomab in the treatment of MRD** Throughout the ACD reference is made to "salvage chemotherapy" as the comparator for blinatumomab. This is incorrect – only patients who relapse after achieving CR receive salvage chemotherapy. As the indication under appraisal is for the use of blinatumomab in patients who are in complete remission with MRD, salvage chemotherapy is not relevant. We therefore request that the inappropriate term "salvage chemotherapy" is replaced in the FAD with "continued chemotherapy" as the standard of care comparator. **3. Chemotherapy has poor efficacy in MRD. It is clinically, ethically and economically appropriate to use blinatumomab earlier in the treatment pathway to avoid exposing patients to unnecessary relapses and poorer outcomes** As acknowledged in the ACD (ACD section 3.2), MRD is a marker of chemotherapy resistance and is therefore a predictor of poor response to subsequent chemotherapy. Blinatumomab is currently recommended as a treatment option in relapsed/refractory ALL patients (TA450). However, patients who experience relapse experience poorer outcomes and a reduced likelihood of success with subsequent treatment.[2, 3] We demonstrate in sections 2 and 3 of this response that there is a high degree of certainty that blinatumomab is clinically effective and cost effective when used earlier in patients in CR with MRD compared with its later use in patients who have relapsed. There are therefore robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients with MRD to reduce their risk of relapse, rather than requiring these patients to first experience frank relapse before accessing blinatumomab (or inotuzumab) as salvage therapy. **<u>Conclusion</u>** • **Our comparisons against continued chemotherapy are relevant and appropriate to address the decision problem. HSCT and salvage chemotherapy are not relevant comparators for blinatumomab in the MRD setting.** • **There are robust clinical and ethical arguments to use blinatumomab earlier in the treatment pathway in patients in CR with MRD to reduce their risk of relapse, rather than**

	requiring these patients to first experience frank relapse before accessing this therapy. • **As demonstrated in sections 2 and 3 of this response, there is a high degree of certainty that blinatumomab is clinically effective and cost effective when used earlier in patients in CR with MRD compared with its later use in patients who have relapsed.** • **Permitting patient and clinician access to blinatumomab earlier in the treatment pathway is therefore clinically and ethically appropriate.**

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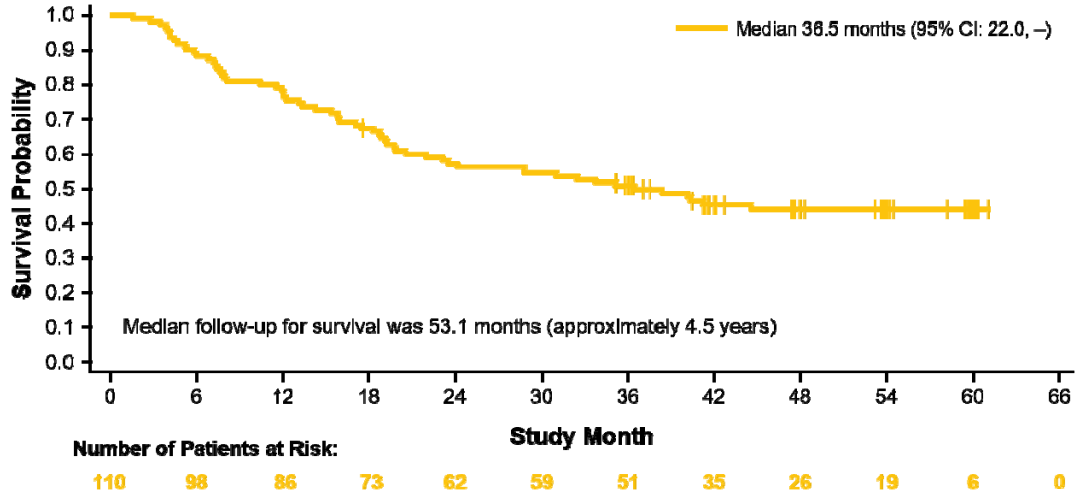
Section 2 The clinical benefit of blinatumomab in patients in CR with MRD is unprecedented and has been clearly and robustly established	The ACD makes several references to uncertainty in the size of the clinical benefit with blinatumomab due to a lack of direct comparative data and long-term survival data, and uncertainty in the methods of the indirect treatment comparison. It also notes that the population in the BLAST trial is wider than the licensed indication and the population in the indirect treatment comparison is narrower than the licensed indication. We address these issues below and demonstrate that the uncertainty in the clinical evidence implied in the ACD is somewhat overstated. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, there is a high degree of certainty in the magnitude and durability of the clinical effects of blinatumomab relative to chemotherapy as presented in our submission. The latest data cut from the BLAST trial, requested by the Committee, further confirms the long-term effectiveness of blinatumomab. **1. The MT103-202 pilot study and the BLAST trial clearly demonstrate the unprecedented, durable clinical efficacy of blinatumomab** The ACD states "*there are no data directly comparing blinatumomab with … chemotherapy … This means that the exact size of the benefit of blinatumomab is unknown*" (ACD section 1.2). It further notes "*The MT103-202 study had a follow-up of about 4 years, but included only 20 patients and did not record overall survival*"; "*The Committee concluded that blinatumomab is clinically effective, but immature survival data and the lack of direct comparative data means the size of this benefit is unclear*" (ACD section 3.7) , and "*The study population in BLAST was wider than the population outlined in the marketing authorisation*". ALL is an ultra-orphan disease, with an incidence in the UK of around 1.2 per 100,000,[4] and MRD is even more rare; only 36% of ALL patients have MRD after induction therapy.[5] With no approved treatments specifically for people with MRD, blinatumomab is a highly innovative treatment in an area of great unmet need. MRD is itself a marker of resistance to chemotherapy, as acknowledged by the Committee, and as continued treatment with chemotherapy is the only relevant comparator for blinatumomab (see section 1) there are substantial ethical and logistical challenges in conducting large randomised clinical trials within this patient population. Given these challenges, and the highly innovative nature of blinatumomab in this indication, the single-arm design of the MT103-202 pilot study and the BLAST trial was appropriate and was agreed with the regulator (European Medicines Agency) during development. Uncertainty is an inherent feature of single-arm trials; however, the collective, consistent evidence of unprecedented response rates with blinatumomab in this population, from the pilot study and the BLAST trial, gives confidence that blinatumomab is a highly effective treatment for patients in CR with MRD. *MT103-202 pilot study* The pilot study demonstrated that blinatumomab induced a complete MRD response in 80% of patients within one cycle. Overall survival (OS) was not specified as an endpoint, as noted by the Committee; however, **median haematological relapse-free survival (RFS) had not been reached after more than 4 years of treatment, and the final RFS estimate was 53% after 5.9 years.** Considering that the adjusted median RFS with SOC chemotherapy in the historical comparator study was only 6.5 months, and median OS was only 19.6 months, the comment by the Committee regarding the lack of formal OS data collection in the pilot blinatumomab study seems unwarranted; the RFS data from the pilot study are in themselves a strong and clear indication of the prolonged OS benefit achievable with blinatumomab in the long-term in this patient population. *BLAST trial* In our submission we presented analyses of the BLAST trial from the most recent data cut that was available at the time (after the last Ph-negative patient completed an 18-month follow-up period - 5th August 2015). Blinatumomab induced a complete MRD response in 78% of patients within the first

cycle of treatment, and in 80% within 2 cycles of treatment, which confirmed the unprecedented high response rates observed in the pilot study. Median haematological RFS had not been reached after more than 40 months and median OS was 36.5 months (95% CI: 19.8 to not estimable), which far exceed the survival estimates for SOC chemotherapy in the historical comparator study.

The latest BLAST data cut was taken on 1st June 2017, and analyses were presented at the American Society of Hematology 60th Annual Meeting, December 1–4 2018. OS was evaluated for the 110 patients with Philadelphia chromosome-negative (Ph−) BCP-ALL and less than 5% blasts at enrolment (i.e. aligned with the licensed indication for blinatumomab), including 74 who received HSCT while in continuous complete remission (CCR) after blinatumomab. Over a median follow-up of 53.1 months, median OS was 36.5 months (95% CI: 22.0 to not estimable) (Figure 1). [6]

These mature OS data are highly consistent with and confirm the OS data that were presented in our submission. Furthermore, these findings, including the plateau observed in the Kaplan-Meier curve post 42 months, support the survival curve extrapolations used in our original company model and submission. There is therefore a high degree of certainty in the long-term efficacy of blinatumomab in this patient population; blinatumomab is a highly effective treatment that clearly improves overall survival substantially in the long-term in patients who are, by virtue of their MRD positive status, resistant to chemotherapy.

Figure 1. Median overall survival after 53.1 months in Ph- patients with BCP-ALL and MRD



Includes patients analyzed for overall survival (N = 110). BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CI, confidence interval. Goekbuget N, et al. Slides presented at: 60th ASH Annual Meeting & Exposition of the American Society of Hematology; December 1-4, 2018; San Diego, CA.[6]

The BLAST trial was designed and initiated before blinatumomab was granted its licensed indication in patients in CR with MRD. Patients in first or second CR (CR1 and CR2) account for 98% of the BLAST population, with only 2 patients in their third CR (CR3). [7] As such the licensed indication excluded patients in CR3 on the basis of limited data. In addition, more than 95% of patients in BLAST were Philadelphia-chromosome-negative (Ph−), and so Philadelphia-chromosome-positive (Ph+) patients were excluded from the licensed indication. Whilst the Committee is correct that the BLAST population was wider than the subsequent licensed population, given the very small number of patients not meeting the subsequent licensed indication it is highly unlikely that the full BLAST trial data are positively biased. Indeed, it is more likely that the full BLAST data provide a conservative estimate of effectiveness of blinatumomab within the licensed population. There are therefore no material uncertainties in the generalisability of the data from the full BLAST trial population to the licensed indication.

2. The indirect comparison against SOC chemotherapy is robust and generalisable to the expected use of blinatumomab in clinical practice

The methods employed for the indirect comparison are robust and results are reliable; contrary reference in the ACD should be removed

The Committee accepted that the indirect comparison of blinatumomab against SOC chemotherapy presented in our submission was appropriate in the absence of randomised controlled trial data, but concluded the methods were subject to uncertainty: "*The ERG noted that there were inconsistencies in efficacy data presented by the company and the data used to inform the economic model. The Committee noted that it would have been helpful to see the range of weights used in the model, as an indicator of the model reliability and the appropriateness of using stabilised weights.*" (ACD section 3.10).

Although the data presented in the clinical and economic sections differed in our original submission, due to an editorial oversight, we addressed this issue in our response to the ERG clarification questions and provided an addendum which clearly demonstrated there was no material difference in the results when the stabilised or unstabilised weights were used. It is clearly stated in the ACD that the ERG noted the method of applying weights to balance the datasets was appropriate (ACD section 3.10, p11). As such, the methods used in the indirect comparison have been shown to be appropriate and robust, and are not a material source of uncertainty. We therefore request that reference to this point is removed from the FAD.

The indirect comparison provides robust comparative data that are highly generalisable to the anticipated use of blinatumomab in clinical practice and underscore that blinatumomab is recommended within its full licensed indication

The Committee concluded the results of the indirect comparison were not generalisable to the full licensed indication: "*…the population in the indirect comparison was narrower than the marketing authorisation and excluded the following groups: patients who could not have HSCT or tolerate chemotherapy; patients whose disease is in second complete remission*" (ACD section 3.9).

The indirect comparison focused on the CR1 subgroup because these data were available in the historical comparator dataset, and were within the licensed indication. Confining the indirect comparison to data from patients in BLAST in CR1 provided a more robust comparison than would have been achieved if data from the (minority) of CR2 patients in BLAST had also been included. Given that blinatumomab is expected to be used in MRD as early in the treatment pathway as possible (i.e. in patients in CR1 with MRD), the indirect comparison provides comparative data specifically in the most relevant patient population in clinical practice. Patients in CR2 are expected to be a small and declining proportion of eligible patients as blinatumomab becomes more established as the standard of care in the CR1 MRD setting; given the positive NICE recommendation for blinatumomab (and inotuzumab) in the relapsed setting, patients who have not received blinatumomab in CR1 would be expected to receive blinatumomab (or inotuzumab) at relapse following CR1 rather than waiting further until a hoped-for CR2 occurs in order to receive blinatumomab under its MRD indication. The exclusion of CR2 patients from the indirect comparison reflects blinatumomab's anticipated use in practice and *reduces* the uncertainty regarding the effectiveness of blinatumomab in its anticipated use in practice. **However, on equity grounds, the prevalent population of patients in CR2 with MRD who have not previously received blinatumomab should be afforded the opportunity to benefit from this highly effective treatment.**

Regarding the exclusion from the indirect comparison of patients who are ineligible for HSCT, it should be noted that HSCT eligibility was not restricted in the protocol for the BLAST study – eligibility for and receipt of HSCT is multi-factorial, and as HSCT is the main route to cure for patients with ALL, it would have been unethical to determine enrolment in BLAST on the basis of HSCT eligibility. The indirect comparison therefore does potentially exclude patients who are ineligible for HSCT. However, as noted

in the ACD, even patients with known suboptimal characteristics for HSCT are offered HSCT in practice where possible (ACD section 3.2). Therefore, patients who are ineligible for HSCT represent a small minority sub-population of patients within this ultra-orphan disease. Pre-specified analyses of the BLAST trial, in which data were censored at HSCT, indicate that blinatumomab improves survival outcomes irrespective of receipt of HSCT (see section B.2.6 of our submission). Therefore, it is likely that the very small number of patients who are ineligible for HSCT would benefit from blinatumomab therapy. The exclusion of this subgroup of patients from the BLAST trial and the indirect comparison does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication. **And on equity grounds, patients who have the misfortune to be ineligible for potentially lifesaving HSCT should not also be denied the opportunity to benefit from the only effective non-transplant therapy**.

Regarding the exclusion from the indirect comparison of patients who are intolerant of chemotherapy, as the aim of the historical comparator study was to provide a SOC chemotherapy arm against which to compare blinatumomab, patients enrolled were, by definition, eligible for chemotherapy. The indirect comparison is therefore not able to provide specific comparative data on the use of blinatumomab in patients who are intolerant of chemotherapy which, according to clinical experts, is only likely to represent a very minor sub-population of patients within this ultra-orphan disease given the substantial risk of relapse with MRD and the resulting need to not withhold active treatment.

Nevertheless, the results of the single-arm BLAST trial would likely be more indicative of blinatumomab's efficacy in these patients, and use of the indirect comparative data to represent the relative treatment effects of blinatumomab in this population would be conservative, rather than biased in favour of blinatumomab. The lack of data specifically in patients who are intolerant of chemotherapy does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication. **And on equity grounds, patients who have the misfortune to be intolerant of chemotherapy should not also be denied the opportunity to benefit from the only effective non-transplant therapy.**

3. **Results of the indirect comparison clearly demonstrate the substantial clinical benefit of blinatumomab compared with SOC chemotherapy in patients in CR with MRD**

Given the appropriate methodology and generalisability of the data to the patients expected to be eligible for blinatumomab in clinical practice, the results of the indirect treatment comparison are robust and reliable. The median RFS was [redacted] with blinatumomab compared with SoC chemotherapy ([redacted]; HR [redacted]), and median OS with blinatumomab was [redacted] after more than 40 months of follow-up, compared to a median OS of [redacted] for SOC chemotherapy, suggesting at least [redacted] of the median OS with blinatumomab. There is therefore little uncertainty in the unprecedented clinical benefit provided by blinatumomab relative to SOC chemotherapy when used early in the treatment pathway for patients in CR with MRD.

Conclusion: There is a high degree of certainty in the size and durability of clinical benefit with blinatumomab when used early in the treatment pathway in patients in CR with MRD

- The single-arm design of the BLAST trial and pilot study is entirely appropriate given the rarity of the condition, lack of standard, effective treatments and the highly innovative nature of blinatumomab.
- The very small number of patients in the BLAST trial not meeting the subsequent licensed indication for blinatumomab is highly unlikely to have positively biased the estimated efficacy of blinatumomab. Results are therefore generalisable to patients meeting the licensed indication.
- The pilot study and BLAST trial both demonstrate high MRD response rates of around 80% with blinatumomab, which is unprecedented in this condition. The pilot study provides RFS data out to almost 6 years, and the latest data cut from the BLAST trial provides OS data from patients followed-up for a median of 4.5 years, confirming the median OS with blinatumomab that was presented in our submission. There is therefore a high degree of certainty in the size

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	and durability of the clinical benefit of blinatumomab. • The ERG confirmed that the methods of our indirect treatment comparison were appropriate. The results of this indirect comparison are robust and reliable, and clearly demonstrate the significant magnitude of the RFS and OS benefit blinatumomab provides compared with SOC chemotherapy. Despite the lack of direct comparative data, there is therefore little uncertainty in the size of the clinical benefit provided by blinatumomab. • The indirect comparison provides comparative effectiveness data specifically in those patients anticipated to use blinatumomab in clinical practice. The exclusion of small subgroups of patients from the analysis does not introduce uncertainty that would preclude a recommendation for appropriate use of blinatumomab within its licensed indication.

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Section 3 Blinatumomab is highly likely to be cost effective when used early in the treatment pathway in patients in CR with MRD	The ACD makes references to what the Committee perceive to be several sources of uncertainty in our original economic model and the estimated cost effectiveness of blinatumomab. We address these issues below and demonstrate that, whilst there may be some uncertainty in the *precision* of the ICER estimates from our original economic model, there is a high degree of certainty in the *magnitude* of the ICER estimates, which are within the usual thresholds for cost effectiveness. To address the Committee's specific concerns regarding the appropriate modelling of the relapsed/refractory treatment pathway, we have provided revised analyses incorporating salvage therapy with blinatumomab and inotuzumab in our original partitioned survival model. We have also provided a new decision tree/Markov cohort model to address the Committee's concerns regarding the structural elements of our original model. **1. Our original economic model and the alternative base case analysis reflected the anticipated use of blinatumomab in clinical practice at that time** The ACD states: *"Clinical experts highlighted that this model is not reflective of current practice or the treatment pathway. They clarified that the treatment pathway has recently changed and now includes inotuzumab ozogamicin or blinatumomab for treating relapses."* (ACD section 3.10); and: *"The population in the cost-effectiveness model cannot be generalised to the full population in the marketing authorisation."* (ACD section 3.12) Our original model reflected the appropriate and anticipated use of blinatumomab early in the treatment pathway in ALL patients in CR with MRD. The robust comparative effectiveness data for blinatumomab versus continued chemotherapy (the relevant comparator) described in section 2 above are congruent with this positioning of blinatumomab in the treatment pathway. The exclusion of CR2 patients from the analysis, and patients ineligible for HSCT or intolerant of chemotherapy, would not introduce uncertainty regarding the clinical or cost effectiveness of blinatumomab in its anticipated use in practice, and on grounds of equity, should not preclude a recommendation for this use. At the time of our submission (October 2017), blinatumomab had only recently received its positive recommendation for use in the relapsed/refractory setting, and inotuzumab had not been recommended by NICE. Our base case analysis therefore represented the clinical pathway at the time of development of our submission and, although completely omitted from the ACD, we presented an alternative base case analysis that incorporated blinatumomab as salvage therapy in the SOC chemotherapy arm, which represented the direction of movement in the clinical pathway given the advent of blinatumomab as an alternative to chemotherapy in the relapsed/refractory setting. As blinatumomab became established as standard of care in the relapsed setting our alternative base case analysis presented in our submission was more reflective of the clinical pathway than our original base case analysis. Compared with our original base case ICER of £28,524/QALY, the incorporation of blinatumomab as salvage therapy significantly reduced the ICER to £17,420/QALY. Although the ERG notes some limitations with this approach (i.e. cost and benefits are not structurally linked within the partition survival model), this nevertheless demonstrates that the ICER in the original base case analysis was highly conservative and therefore so were the results of all sensitivity and scenario analyses that were conducted by Amgen and the ERG. Inotuzumab is now also recommended as an option alongside blinatumomab in relapsed/refractory patients (TA541, Sep 2018). We therefore acknowledge that inotuzumab should be incorporated appropriately in our modelling to reflect the current clinical pathway following relapse. To address this, we have provided revised analyses incorporating blinatumomab and inotuzumab as salvage therapy. These analyses are discussed in detail in sections below.

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	2. Our original modelling approach is appropriate to address the decision-problem The ACD states: "*The company's model is not acceptable for decision-making*", noting particular issues with the modelling of the cure point, and the link between HSCT and outcomes. However, the impact of the uncertainty in these elements of our modelling approach relates to the *precision* of the ICER estimates and not the *magnitude*, which is highly likely to be within the thresholds of cost effectiveness. Our original modelling approach was and remains appropriate and sufficiently reliable to inform decision-making. *Uncertainty in the modelled cure point relates to the precision of the ICER estimates, not the magnitude* The Committee rejected our approach to modelling the cure point on the basis that this resulted in different cure points between the RFS and OS extrapolation. The ACD notes that the assumptions around the cure fraction and cure point were a key driver in the cost effectiveness analysis and an explicitly modelled cure point was required (ACD section 3.13). The ERG provided analyses assuming a 5-year cure point in line with clinical expert opinion. While this introduced bias in favour of the SOC chemotherapy arm and against blinatumomab, the ICER increased from £27,700 to only £30,200 per QALY. These ICERs are compatible with our original base case ICER estimate (£28,524/QALY), and do not incorporate salvage therapy in the clinical pathway, which would significantly reduce these ICERs to well below £30,000/QALY (see section above). The ERG also provided analyses exploring cure fractions for SOC chemotherapy in the range 25-35%.[8] No basis is provided for this range of cure fractions, which increases the proportion of patients achieving a cure whist on SOC chemotherapy by up to 67% compared with the ERG's preferred base case. Given that MRD is acknowledged in the ACD as an indicator of resistance to chemotherapy, and given that patients with MRD are at increased risk of relapse and have poorer survival compared with those without MRD, we feel these analyses are unjustified. Clinical expert opinion sought during the development of our original submission consistently verified that the survival analyses presented in the base case model were reasonable and indeed this was reiterated during the 1st Appraisal Committee Meeting. The ERG also conducted an independent validation exercise on the survival extrapolations – the ERG's clinical advisors' preferred OS models resulted in ICERs in the range £25,810 per QALY gained to £34,904 per QALY gained, without incorporating the impact of salvage therapy in the clinical pathway. These results confirm the appropriateness of the original assumptions and underline that the modelled cure point is unlikely to meaningfully impact on the magnitude of ICERs presented. *Uncertainty in the modelling of HSCT relates to the precision of the ICER estimates, not the magnitude* ALL is an ultra-orphan disease, and whilst the magnitude of the clinical benefit of blinatumomab is clearly and robustly established from the BLAST and historical control trial data, these trials were not sufficiently powered or designed to provide complete analyses of the incidence of HSCT both pre- or post-relapse, or by MRD status. Our approach to modelling HSCT reflected these data limitations. The ERG performed exploratory analysis using alternative HSCT survival probabilities, which increased the ICER from its preferred base case of £30,200/QALY to only £32,667/QALY.[8] Whilst we acknowledge these analyses were conducted within the constraints of our model structure, the fact the increase in the ICERs is marginal suggests the uncertainty in the approach to modelling HSCT outcomes is of limited impact. These ICERs are reassuringly similar to our original base case ICER estimate (£28,524/QALY), and do not incorporate salvage therapy in the clinical pathway, which would significantly reduce these ICERs to well below £30,000/QALY (see section above). Any uncertainty in the modelling of HSCT outcomes may therefore lead to uncertainty in the *precision* of the ICER estimate, but not the *magnitude* of the ICER estimate, which is highly likely to be within the thresholds of cost effectiveness.

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3. Revised analyses reflecting the relapsed treatment pathway in our original model confirm the cost effectiveness of early use of blinatumomab in patients in CR with MRD

Given the above, which leads to the conclusion our original modelling approach was sufficient to address the decision problem at the time of our submission, we have used our original partitioned survival model to address the Committee's concerns on the appropriate treatment pathway following relapse. We have therefore provided revised analyses for comparison of:

- blinatumomab in the MRD setting followed by inotuzumab salvage therapy, versus
- SOC chemotherapy in the MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split).

This comparison has been validated by clinical experts as reflective of the current clinical pathway. Further details of this revised partitioned survival model are provided in **Appendix 1**.

In this setting, the early use of blinatumomab in MRD was shown to be highly cost effective with an ICER of £18,818/QALY (Table 1).

Table 1: Revised Partitioned Survival Model – Base Case Analysis

Treatment	Total Cost, (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£)
Blinatumomab	[redacted]	7.79	39,720	2.11	**18,818**
SOC	[redacted]	5.68			

Consistent with clinical expert opinion as to the importance of achieving MRD-negativity, the use of blinatumomab earlier in the treatment pathway results in a substantial increase in the proportion of patients remaining relapse free at 5-years (42.7% vs.17.5% for blinatumomab and SOC, respectively). The highly cost effective ICER is also driven by the ability of blinatumomab to reduce the need for subsequent salvage treatment, realising a reduction in post-relapse costs of [redacted] in the base case analysis.

One-way deterministic sensitivity analyses and scenario analyses are presented in **Appendix 1** and indicate that the base case results are robust when considering parameter uncertainty. Of note, when implementing the Committee's preferred fixed cure-point at 5-years, the ICER only marginally increases to £21,340/QALY and remains well within standard cost effectiveness thresholds. Probabilistic sensitivity analysis generated a mean ICER of £20,024/QALY with a 71.9% and 85.5% probability of being cost-effective at willingness-to-pay thresholds of £30k- and £50k/QALY, respectively.

These analyses therefore confirm that early use of blinatumomab in the treatment pathway in patients in CR with MRD is highly likely to be cost effective compared with later use of blinatumomab (or inotuzumab) as salvage therapy following relapse.

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4. New Markov modelling approach as requested by the Committee confirms that early use of blinatumomab in patients in CR with MRD is highly likely to be cost effective

To further address the Committee's concerns regarding the structural elements of our original partitioned survival model we have developed a new, combined decision-tree and Markov cohort model, which incorporates the Committee's specific requests:[1]

- it reflects the current treatment pathway in relapsed/refractory setting – by including blinatumomab and inotuzumab as salvage therapy as per clinical expert guidance;
- it provides the link between MRD status, HSCT and survival – using data from re-analysis of BLAST and the historical comparator trial;
- it models a specific cure point of 5 years – which given the availability of trial data with almost 5 years of follow-up requires little survival curve extrapolation;
- it includes the different positions in the treatment pathway at which HSCT might be given – as it explicitly models time to transplant in remission and post-relapse states, and
- it reflects the latest data cut from the BLAST trial – data from the latest BLAST data cut with a median follow-up of 53.1 months has been used to estimate parameters (see section 2).

In addition to the above, the new Markov modelling approach addresses the limitation of the partitioned survival model by providing a structural link between costs and QALYs generated when incorporating blinatumomab or inotuzumab as salvage therapies.
The ERG acknowledged that a revised model structure using the available data to populate specific transitions would be limited by very small sample sizes, may be subject to selection bias, and would be associated with considerable uncertainty.[8] It was for these reasons that we adopted a partitioned survival modelling approach in our original submission, and we maintain that the revised partitioned survival model incorporating blinatumomab and inotuzumab salvage therapy discussed above (section 3 above) better reflects the observed data from the clinical trials.

The combined decision-tree and Markov cohort model was informed by previous modelling approaches in this disease area.[8-10] However, building on these approaches, it was deemed necessary to implement a Markov structure to fully address the Committee requests around a causal link between MRD status, HSCT and survival, in addition to reflecting the current treatment pathway. It is important to note that *post hoc* analyses of small subgroups of the clinical trials are necessary in this model structure, therefore, some uncertainty in the estimation of the required parameters is expected. Full details of the new model structure and parameter estimation are provided in Appendix 2, along with the results of scenario analyses and one-way deterministic sensitivity analyses. Probabilistic sensitivity analyses (PSA) are not yet implemented at the time of submission but will be provided in full for consideration by the Committee.

Base Case Results

The base case ICER of £25,645/QALY (Table 2) supports the conclusion of the revised partitioned survival model in that blinatumomab is highly likely to be cost-effective when used in the MRD setting.

Table 2: New Modelling Approach – Base Case Results

Treatment	Total Cost, (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£)
Blinatumomab	[redacted]	6.56	54,264	2.12	**25,645**
SOC	[redacted]	4.44			

[1] The ACD also referred to the latest available evidence on survival outcomes after HSCT. These data, highlighted by the clinical expert at the Committee meeting, are unpublished

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The main clinical outcomes generated by the model are RFS and OS which are causally linked to MRD status and receipt of HSCT, as requested by the Committee. Survival projections from the model are compared with the Kaplan-Meier estimates from BLAST and the historical control data in Figure 2 and Figure **3**, below.

Figure 2: Relapse Free Survival

Figure 3: Overall Survival

Based on visual inspection of the RFS plot compared to the Kaplan-Meier data, both projections are highly consistent with observed data and demonstrate an excellent fit. The proportion of patients estimated to be relapse-free at 5-years (Committee preferred cure time point) was 40% and 18.1% for blinatumomab and SOC, respectively. Because fewer patients receiving blinatumomab are projected to relapse, salvage therapy costs were notably higher in the SOC arm than with blinatumomab [redacted], as were post-relapse HSCT and hospitalisation costs ([redacted]). Therefore, in total, the early use of blinatumomab in the MRD setting resulted in a reduction in post-relapse costs of [redacted] when compared with SOC in the base case analysis.

Similarly, visual inspection of the OS plot suggests a slight underestimation of long-term survival in the blinatumomab arm and overestimation of long-term survival in the SOC arm. The fact that the modelled OS projections are higher than the KM data in the SOC arms is to be expected given the Markov model incorporates blinatumomab/inotuzumab as salvage treatment, with greater efficacy than SOC chemotherapy received on trial. This effect points to a conservative estimate of the magnitude of survival benefit with blinatumomab and its ICER compared with SOC chemotherapy.

Key Scenario Analyses

The results of scenario analyses and one-way deterministic sensitivity analyses are presented in full in Appendix 2 and underline that blinatumomab is highly likely to be cost-effective even when considering the inherent uncertainty in this modelling approach.

Key scenario analyses exploring limitations in parameter estimation, internal consistency of the MRD-response based modelling approach, the impact of varying HSCT rate and the robustness of the base case model results to the cure time point, are presented in Table 3. These results demonstrate that the ICER remains reasonably stable with respect to changes in key parameters and robust to alternative data sources informing transitions.

Table 3: Key Scenario Analyses

Scenario	Rationale	ICER
SOC survival curves to inform survival in MRD+ patients receiving blinatumomab	**Given the low number of MRD non-responders in BLAST, parameters estimated from the historical cohort were used to inform MRD+ transitions in the blinatumomab arm**	**24,852**
Blinatumomab MRD Response		
74.17% MRD response rate (lower CI)	**Explore sensitivity to MRD response rate for blinatumomab**	**31,210**
91.17 MRD response rate (upper CI)		**22,457**
SOC estimated based on BLAST data:		
8% MRD response rate	**Consistency of MRD-response based modelling approach utilising BLAST data (with varying MRD response rates) to model SOC arm**	**26,829**
15% MRD response rate		**29,515**
0% response rate		**24,311**
Impact of varying HSCT rate:		
HSCT rate for MRD+ based on SOC (historical control) data	**Exploration of impact of HSCT rates by setting all arms to use the time to HSCT survival distributions**	**11,695**
HSCT rate based on SOC (historical control) for all		**31,851**
HSCT based on MRD-(BLAST) for all		**25,936**
Impact of Cure Timepoint:		
Cure time point 3 years	**Exploration of the cure time point on modelled results, based on assumptions in other models in this disease area (e.g. inotuzumab in TA541)**	**25,551**
Cure time point 4 years		**25,479**

In conclusion, the combined decision-tree and Markov cohort model, developed specifically to address the Committee's concerns around the structural limitations of the original partitioned survival model, produces ICER estimates that are broadly consistent with the original modelling approach when the current clinical pathway is reflected. This supports the conclusion that blinatumomab is highly likely to be cost-effective when used earlier in the treatment pathway. Scenario and sensitivity analyses demonstrate that the ICERs in both models are reasonably stable to alternative assumptions for key parameters. In particular, the new Markov model is shown to be robust when implementing the Committee's preferred fixed cure point and assessing the impact of varying the timepoint at which this

occurs. Taken together, these results support the conclusion that, although there are uncertainties in the *precision* of the ICER estimate, the *magnitude* of the ICER is highly likely to be within the thresholds of cost effectiveness.

5. Blinatumomab clearly meets the criteria for consideration under NICE's end-of-life policy based on expert opinion and compelling survival data

The ACD states*: "Blinatumomab does not meet the criteria to be considered a life-extending treatment at the end of life"; "It concluded that it was plausible that blinatumomab offered more than 3-months' additional survival but they could not be certain because of flaws in the modelling."* (ACD section 3.18)

The clinical experts quoted in the ACD "*suggested that for patients with MRD, survival at 2 years would be around 20%,"* clearly indicating that the short life expectancy criterion was met. While we acknowledge the perspective of the Committee with regards to the results of the model, consideration of the clinical data alone provides compelling evidence that SOC chemotherapy is associated with a short life expectancy of less than 24 months, and that blinatumomab provides an OS gain that is substantially greater than 3 months. Mature data from the BLAST trial confirms a median OS of 36.5 months, and our robust indirect treatment comparison in patients in CR1 (discussed in our submission and above in section 2) demonstrates that the median OS in patients treated with blinatumomab had not been reached after more than 40 months of follow up, in comparison to [redacted] months with standard of care chemotherapy (i.e. at least a doubling of OS with blinatumomab, and a life expectancy with SOC therapy less than 24 months).

In addition to these compelling trial data, emerging real-world evidence confirms the substantial survival gains in clinical practice associated with achieving MRD negative status compared with MRD positive status, after front-line treatment. Results from a chart review in Belgium, Greece and Switzerland demonstrate that in patients who achieve MRD negativity (n=50), the median OS was [redacted] after a median follow-up of [redacted] compared to [redacted] months ([redacted]) after a median follow-up of [redacted] in MRD positive patients (n=17).[11] These real-world data confirm and support our trial-based estimates of short life expectancy for patients who do not achieve MRD-negativity and the substantial increase in survival for those who do.

We note the ERG rejected our conclusions that blinatumomab meets the end-of-life criteria due to the use of median rather than mean estimates of OS.[8] Given the compelling median OS data above we feel there is little doubt that patients with MRD treated with SOC chemotherapy have a short life expectancy less than 24 months, and it is not only plausible that blinatumomab provides a substantial gain in OS in excess of 3 months compared with SOC chemotherapy, it is highly likely. We refer the Committee to the pragmatic approach taken in the appraisals of blinatumomab (TA450)[8] and inotuzumab (TA541)[10] in the relapsed/refractory setting, both of which were accepted for consideration under NICE's end-of life policy using trial-based median OS data to demonstrate fulfilment of the criteria. This approach has also been adopted in NICE technology appraisals in other cancer types, where the specific issue of long tails in the survival curve that skews the mean OS estimates have been recognised and median OS estimates accepted (e.g. TA366[12] and TA396[13]). We suggest that a similar pragmatic approach is warranted for blinatumomab in the treatment of people with MRD, not least to avoid the introduction of inconsistencies that would inappropriately penalise the considerations of blinatumomab's cost effectiveness when used earlier in the treatment pathway compared with the later use of blinatumomab or inotuzumab as salvage therapy, which were accepted as cost effective with higher ICERs under NICE's end of life policy.

Conclusion: All evidence indicates blinatumomab is highly likely to be cost effective when used early in the treatment pathway in patients in CR with MRD

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	• Although the Committee had highlighted specific uncertainties relating to our original modelling approach, the impact of the uncertainty in these elements related to the precision of the ICER estimates and not the magnitude. • We have demonstrated using our original model, revised to reflect the current treatment pathway in relapsed/refractory patients, and the new model, requested by the Committee to address the structural relationships between MRD, HSCT and survival outcomes, that the ICER estimates are highly likely to be within the thresholds for cost effectiveness. • Our models, driven by compelling clinical data, clearly demonstrate that early use of blinatumomab in these patients leads to higher response rates, fewer relapses requiring salvage therapy and improved survival compared with SOC chemotherapy, which translates into a high likelihood of blinatumomab being cost effective. • Given that blinatumomab clearly fulfils the criteria for consideration under NICE's end-of-life policy, and should therefore be assessed against a higher threshold of cost effectiveness, there is little doubt that the early use of blinatumomab in the treatment pathway for patients in CR with MRD is cost effective compared with the later use of blinatumomab (or inotuzumab) as salvage therapy in the relapsed setting.

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Section 4 Conclusion	ALL patients in CR with MRD remain at very high risk of relapse and have very poor survival outcomes. With no other approved, effective treatments available, there are robust clinical and ethical arguments to use of blinatumomab earlier in the treatment pathway in these patients, to reduce their risk of relapse and optimise outcomes, rather than treating later (*i.e. requiring these patients to first experience unnecessary frank relapse before accessing blinatumomab as salvage therapy*.) We have addressed the Committee's requests for additional data and analyses and believe we have resolved all areas of uncertainty highlighted in the ACD. Despite the many challenges presented by the rarity of the condition and the lack of effective standardised treatments, we have demonstrated that there is a high degree of certainty around the unprecedented clinical benefit that blinatumomab brings over SOC chemotherapy when used earlier in the treatment pathway. Importantly, we demonstrate using different modelling approaches which address the specific concerns and requests of the Committee in the ACD, that the earlier use of blinatumomab in patients in CR with MRD remains highly cost effective compared with treating later. Further, compelling survival data and clinical expert opinion support the case that blinatumomab for the treatment of MRD fulfils the end-of-life criteria, which bolsters the conclusion that blinatumomab in this setting provides strong value for money. **Based on this body of compelling evidence of clinical effectiveness and comprehensive additional analyses of cost effectiveness demonstrating highly cost-effective ICERs, we propose that blinatumomab is recommended within its full licensed indication for use earlier in the treatment pathway in patients in CR with MRD, to reduce their risk of relapse and optimise outcomes.**
Section 5 Additional Comments	In addition to the responses above, we request that the following points of clarification should be noted and considered for the FAD: **i. Throughout** Throughout the ACD reference is made to salvage chemotherapy as a comparator to blinatumomab. This is incorrect, as discussed in section 1 of our response. Amgen requests this is corrected within the FAD **i. Section 1.1, page 3** *Context: "The Committee was minded not to recommend blinatumomab as an option for treating acute lymphoblastic leukaemia in adults with Philadelphia-chromosome-negative CD19-positive B-precursor whose disease is in first or second complete remission with minimal residual disease (MRD) of at least 0.1%."* The indication provided is worded unusually; Amgen requests that the full approved indication is given, and the section updated as follows: "as an option for treating 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. Section 1.2, page 4** *Context: "Evidence from 2 studies suggests that blinatumomab may help people have longer without their disease relapsing. Also, their disease responds well to treatment."* Amgen requests that for clarity, this statement is reworded as follows: "Evidence from two studies suggests that blinatumomab may provide a longer period of disease remission, and may lead to a greater number of patients achieving a cure."

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v. Section 3.1, pages 5–6

Context: "About 44% of adults have acute lymphoblastic leukaemia that is expected to relapse."

Amgen believes that this statement is ambiguous and suggests that it be reworded for clarity, as follows: "Although more than 80% of patients achieve complete remission, up to 44% of patients will ultimately relapse.[14]"

v. Section 3.2, page 6

Context: "Once patients have had induction, consolidation and maintenance therapy and their disease is in complete remission, they will be monitored for the presence of MRD."

Amgen does not believe that this statement aligns with the current treatment pathway for ALL; ESMO guidelines for the treatment of ALL recommend MRD testing immediately following achievement of a CR after induction therapy, and subsequently in the post-induction phase, and every 3 months in the follow-up of asymptomatic patients.[1] Indeed, in a survey of MRD testing patterns in the UK, 79% of clinicians performed an initial MRD test 4–8 weeks after commencing induction therapy when CR is first observed; it is not current practice to wait until after consolidation and maintenance therapy.[15] Amgen therefore suggests rewording as follows: "In the NHS, patients are routinely monitored for the presence of MRD 4–8 weeks after beginning induction when complete remission is first observed."

i. Section 3.7, page 9

Table 1 (Clinical effectiveness results for blinatumomab) refers to progression-free survival; Amgen suggests that this be reworded to "relapse-free survival", in order to align with the terminology used in the rest of the ACD. In addition, the final row of Table 1 ("Progression-free survival"), for consistency the cell in the BLAST column should be updated to "53.0% (95% CI 44 to 62) at 18 months", in line with the cell in the MT103-202 column.

i. Section 3.15, page 14

Context: "The company's post-relapse utility value is too high"

The ACD includes this unqualified bold heading; however, it is clearly noted that the ERG ran exploratory analyses using a wide range of alternative values, which clearly demonstrate that the model is insensitive to this parameter and the committee concluded this was not a key driver of the model results. We further note that, despite a high utility value, based on clinical expert opinion sought by the ERG, our base case may nevertheless be conservative. The prominence of this section of the ACD, including the unqualified bold heading, implies a level of uncertainty that is not warranted.

NICE National Institute for Health and Care Excellence

Blinatumomab for treating minimal residual B-precursor acute lymphoblastic leukaemia in remission [ID1036]

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Section 6 References	1. Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(suppl 5):v69-v82. 2. Gökbuget N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012;120(9):1868-76. 3. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA oncology. 2017:e170580. 4. Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence statistics 2016. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero. 5. Amgen Inc. ALL epidemiology estimates. 2017. 6. Goekbuget N, Dombret H, Zugmaier G, Bonifacio M, Graux C, Faul C, et al. Blinatumomab for Minimal Residual Disease (MRD) in Adults With B-Cell Precursor Acute Lymphoblastic Leukemia: Median Overall Survival Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months. American Society of Hematology Annual Meeting 20182018. 7. Gokbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood. 2018;131(14):1522-31. 8. National Institute for Health and Care Excellence. Blinatumomab for treating Philadelphia-chromosome-negative relapsed or refractory acute lymphoblastic leukaemia [ID804] - Committee papers. 2017. 9. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health technology assessment. 2017:1-204. 10. National Institute for Health and Care Excellence. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (TA451). 2018. 11. Pharmerit International. Disease Management and Outcomes in B-Precursor ALL Patients: Greece, Belgium, Switzerland. 2019. 12. National Institute for Health and Care Excellence. Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366]. 2015. 13. National Institute for Health and Care Excellence. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma [TA396]. 2016. 14. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944-50. 15. Amgen I. Data on File: Minimal residual disease testing patterns and healthcare utilization for adults with B-precursor acute lymphoblastic leukemia - results of a physician survey in the UK. 2017.

Insert extra rows as needed

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Blinatumomab for treating minimal residual B-precursor acute lymphoblastic leukaemia in remission [ID1036]

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Appendix 1

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity [ID1036]

Amgen Limited

Date 16th April 2019

Contains confidential information

LIST OF TABLES

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1 METHODS

1.1 Overview

We acknowledge that the NICE approval of inotuzumab in September 2018 changed the relapsed pathway from that at the time of our submission. To resolve the Committee's concerns that our model did not fully reflect the current treatment pathway following relapse, we have revised the original model to provide a comparison of blinatumomab in the MRD setting followed by inotuzumab salvage therapy, versus SOC chemotherapy in the MRD setting followed by salvage therapy with either blinatumomab or inotuzumab (50:50 split). This pathway was informed by clinical expert opinion and has been validated as relevant to clinical practice.

1.2 Model Description

As per our original submission, the model is implemented as a Microsoft Excel workbook and uses a PartSA approach with states defined based on relapse and death. PartSA is a transparent, intuitive approach which yields estimates of survival that correspond closely to survival observed during the study that are the basis for the evaluation.[1] The PartSA approach has been used in numerous prior economic analyses of treatments for oncology therapies including haematologic malignancies,[1] and in the recent manufacturer's submission in response to the STA of blinatumomab in R/R B-precursor ALL.[2]

In our original submission, we presented an Alternative Base Case where patients who relapse on SOC would receive blinatumomab in the salvage setting to reflect established clinical practice at the time. Here, we expand on this analysis to reflect the recent reimbursement of inotuzumab in the salvage setting.

The assumed proportions of relapsing patients who would receive salvage therapy with blinatumomab, inotuzumab or other therapy were estimated based on clinical expert opinion.

Table 1. Assumed distributions of first salvage treatment by initial treatment received

	Treatment	
First Salvage Therapy	**Blinatumomab**	**SOC**
Blinatumomab	0%	50%
Inotuzumab	100%	50%
SOC	0%	0%
Total	100%	100%

1.3 Model Estimation

1.3.1 Salvage Therapy

The analysis was implemented using the incremental LYs and QALYs of blinatumomab versus SOC salvage treatment from the company evidence submission in response to the recent NICE STA of blinatumomab with R/R B-precursor ALL. Specifically, the estimated discounted incremental life-year gain (2.40 LYs) and QALY gained (1.98 QALYs) were assigned at the time of relapse as a one off for patients expected to receive blinatumomab and inotuzumab salvage treatment upon relapse. For simplicity the analysis thus assumes that the benefit for patients receiving inotuzumab and blinatumomab salvage therapy is the same.

The cost of blinatumomab salvage therapy was taken from the manufacturer's submission for the NICE STA of blinatumomab for R/R Ph- ALL patients based on the TOWER trial, and included the cost of blinatumomab medication ([redacted]), and administration (£10,641)[3]. A [redacted] discount was applied to the medication cost of blinatumomab salvage therapy consistent with that assumed for initial therapy. The total cost of blinatumomab salvage was therefore estimated to be [redacted]. The cost of inotuzumab salvage therapy was estimated to be £85,417, based on the inotuzumab estimate used in the manufacturer's submission for the NICE STA of inotuzumab for R/R ALL patients in their first or second line of salvage therapy based on the INO-VATE-ALL trial. Medication costs for inotuzumab was estimated to be £76,376, which was calculated by multiplying the price per vial of inotuzumab (£8,048) by the average number of vials received in the INO-VATE-ALL trial (9.49). Administration costs for inotuzumab were estimated by multiplying the NICE recommended number of inpatient days for administration of inotuzumab (11.23) by the average NHS reference costs for ALL-related

hospitalization (£805) [4]. The cost of medication and administration of multi-agent chemotherapy was estimated to be £16,176 based on the estimated medication and administration cost of FLAG-IDA in the manufacturers' submission to NICE for blinatumomab for R/R Ph- ALL [3].

1.3.2 Other Parameter Estimates

All other parameters were taken from the partitioned survival model used in the original submission.

2 RESULTS

2.1 Base Case Results

Base-case results for the cost effectiveness of blinatumomab versus SOC in adult patients with Ph- B-precursor ALL in the MRD setting are reported in Table 2. Blinatumomab was projected to yield 2.47 more discounted life-years (LYs) and 2.11 more discounted QALYs than SoC. Total costs were estimated to be £39,720 higher with blinatumomab than with SoC. The ICER for blinatumomab versus SoC was therefore estimated to be £18,818 per QALY gained.

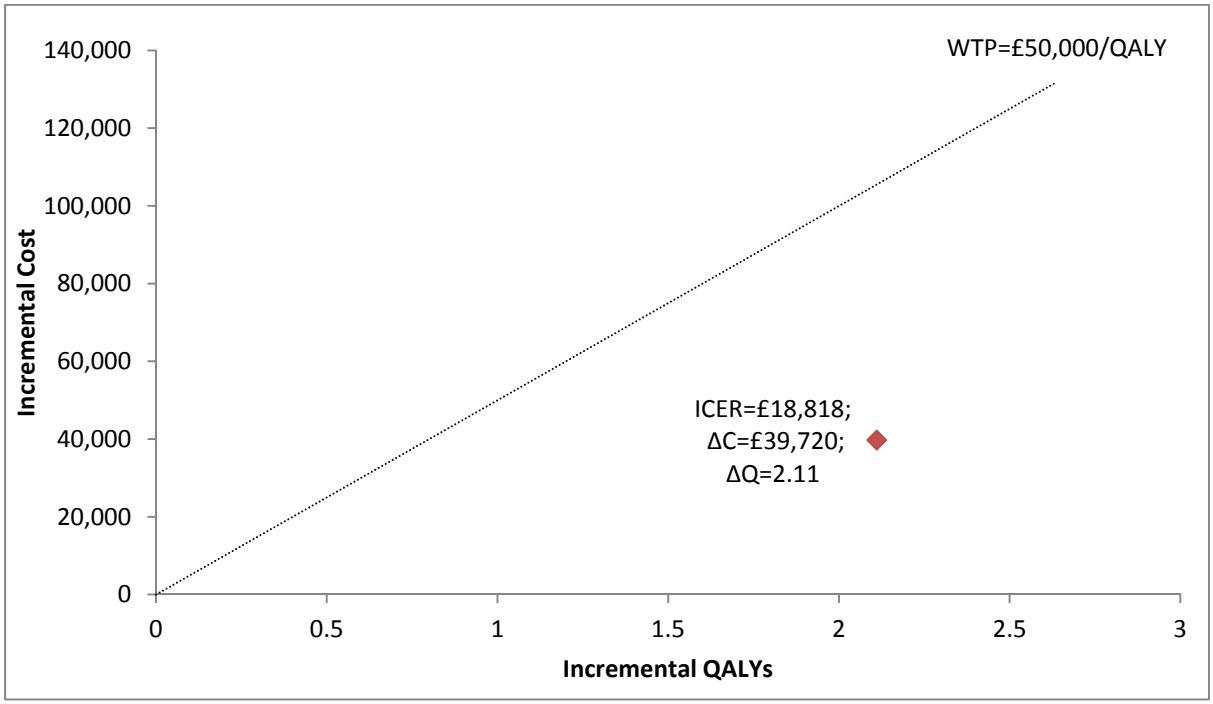
Table 2: Base-case results

Treatment	Total Cost (£)	Total LYs (Discounted)	Total QALYs (Discounted)	Incremental Costs (£)	Incremental LYs (Discounted)	Incremental QALYs (Discounted)	ICER (Cost per QALY Gained) (£)
Blinatumomab	[redacted]	9.76	7.79	39,720	2.47	2.11	**18,818**
SOC	[redacted]	7.29	5.68				

Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years; SoC: standard of care.

Incremental costs and QALYs with blinatumomab versus SoC are plotted on the cost-effectiveness plane in Figure 1. Also shown on the figure is the line representing a willingness-to-pay (WTP) threshold of £50,000 per QALY gained. The co-ordinates for the base-case estimate of the ICER is below the line suggesting that blinatumomab is a cost-effective use of healthcare resources given this threshold.

Figure 1. Incremental costs and QALYs with blinatumomab versus SoC

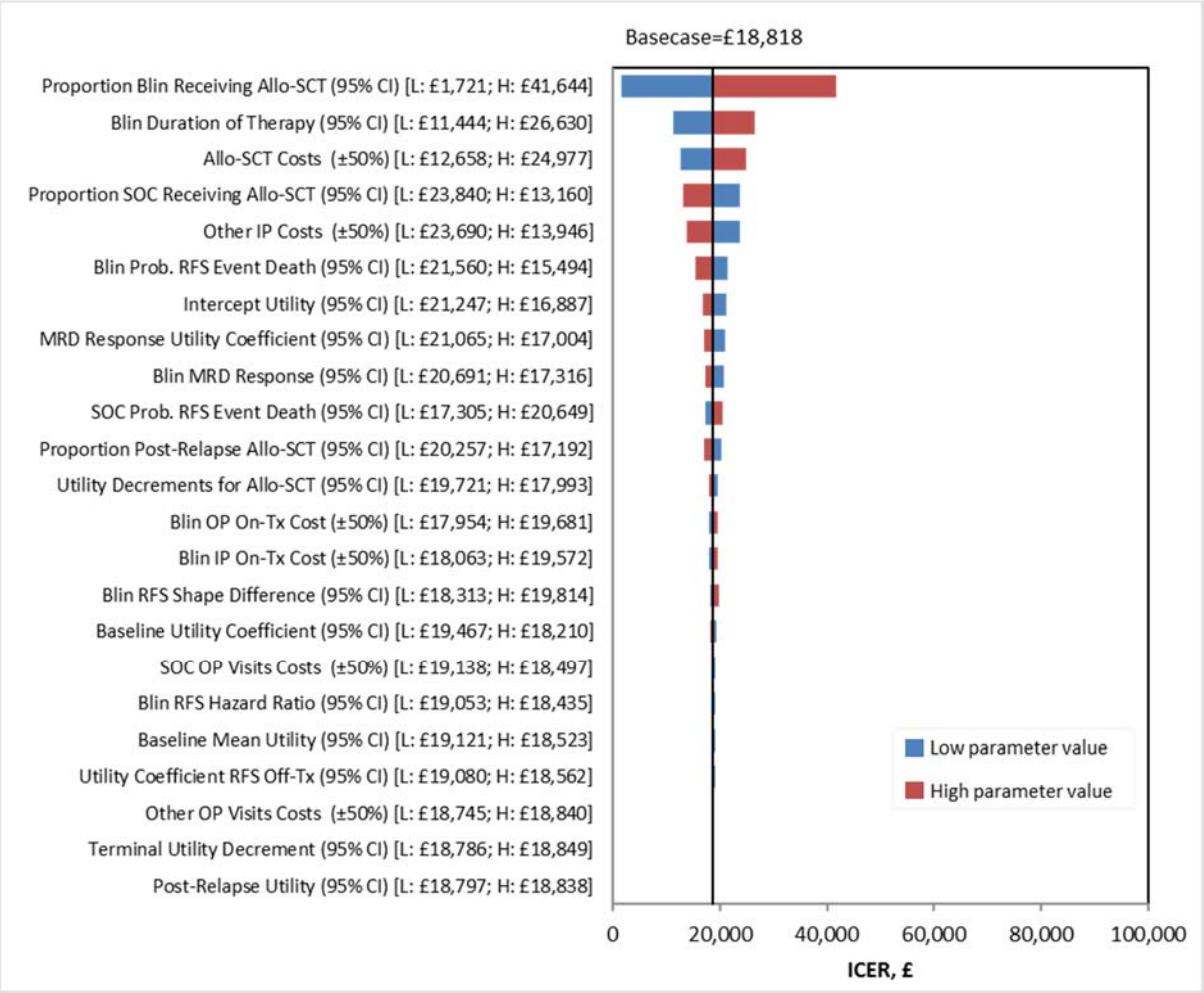


Abbreviations: SoC: standard of care; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-years; WTP: willingness to pay.

2.2 Deterministic Sensitivity Analyses

A tornado chart for the ICER for blinatumomab vs. SoC is shown in Figure 2. Changes in the proportion of blinatumomab patients receiving HSCT had a relatively large effect on the ICER, which varies from £1,721 to £41,644 per QALY gained as this parameter is varied across its 95% CI. The model was also relatively sensitive to the parameters relating to the duration of treatment with blinatumomab, as seen by varying the proportion starting and completing treatment, with the ICER varying from £11,444 to £26,630 per QALY gained as these parameters were varied simultaneously across their 95% CIs.

Figure 2. Tornado diagram of ICER of blinatumomab versus SoC



Abbreviations: ICER: incremental cost-effectiveness ratio; SoC: standard of care; OS: overall survival; Allo-SCT: allogeneic stem cell transplantation; IP: inpatient; MRD: minimal residual disease' RFS: relapse-free survival; OP: outpatient; Tx: treatment.

2.3 Scenario Analyses

A description of the various scenario analyses is provided in Table 3.

Table 3. Description of scenario analyses

No.	Description	Base-case setting	Scenario setting	Justification
1	ATE weights	ATT weights	Utilities, MRD response rates, age, proportion male, duration of therapy, RFS distribution, OS distribution, probability RFS event is death, all with ATE rather than ATT weights.	Alternative methodology as per NICE DSU TSD 17 using ATE weights explored
2	Alternative Extrapolation Methods	RFS Gompertz (U), OS Lognormal Mix (Cure)	RFS and OS distributions changed to restricted Gompertz and unrestricted Weibull non-mixture cure, respectively.	Restricted Gompertz was the best-fitting RFS distribution based on the fit criteria used for distribution selection. The unrestricted Weibull non-mixture cure distribution was the best-fitting OS distribution that was compatible with the restricted Gompertz, i.e. RFS never exceeded OS. This combination presents a more favourable scenario.
3		RFS Gompertz (U), OS Lognormal Mix (Cure)	RFS and OS distributions changed to restricted RCS log-logistic and restricted RCS Weibull, respectively.	The RCS log-logistic was the third-best fitting distribution for RFS (the second was used for the base-case) based on the fit criteria used for distribution selection. The restricted RCS Weibull distribution was the best fitting OS distribution that was compatible with the selected RFS distribution, i.e. RFS never exceeded OS, and the second-best OS distribution overall. This combination presents a less favourable scenario.
4	2-fold increase in long-term excess mortality	4-fold increase in long-term excess mortality	Long-term excess mortality set to 2 (scenario 4) and 6 (scenario 5).	The base-case assumed a minimum of a 4-fold increase in mortality versus general population based on an analysis of the long-term consequences of allogeneic HSCT conducted by Martin et al.[5] We evaluated the sensitivity of the model to this assumption by increasing and decreasing this estimate by 50%.
5	6-fold increase in long-term excess mortality			
6	Duration of benefits = 60 months	In the base-case, RFS and OS were modelled based on parametric survival distributions fit to survival data from BLAST and the historical control, combined with age- and sex-matched general population mortality adjusted for excess risk of death	Duration of benefits set to 60 months.	While the base-case assumption implicitly limits the duration of benefits of blinatumomab on survival, this scenario was generated to investigate the impact of explicitly limiting the duration of benefit to 60 months. 60 months was chosen as the point when patients are considered “cured” and

No.	Description	Base-case setting	Scenario setting	Justification
		due to exposure to radiotherapy, chemotherapy, and HSCT. This approach was assumed to accurately represent the long-term benefits of blinatumomab on survival. Based on this approach, the HR for OS for blinatumomab versus SoC reached a nadir of approximately 0.37 at 8 years and was equal to approximately 1.0 by 11 years. Hence this approach implicitly limits the duration of benefit on OS to 11 years.		therefore no longer under the influence of blinatumomab.
7	Inpatient costs with on-treatment inpatient days from BLAST	4 inpatient days cycle 1, 2 inpatient days cycle 2, 0 inpatient days thereafter, based on the NICE guidance TA450 for R/R Ph-B-cell precursor ALL[2]	8.8 inpatient days' cycle 1, 5.4 inpatient days' cycle 2, 4.2 inpatient days' cycle 3, 3.8 inpatient days' cycle 4.	The base-case uses the number of inpatient days outlined in the NICE guidance TA450 for blinatumomab for R/R ALL.[2] For sensitivity, we generated results first using the number of inpatient days observed in the BLAST trial for the CR1 population and then based on the number of inpatient days in the proposed EMA SmPC for blinatumomab MRD indication.
8	Inpatient costs with on-treatment inpatient days from blinatumomab label		3 inpatient days' cycle 1, 2 inpatient days in each subsequent cycle (cycles 2-4).	
9	Blinatumomab RFS events that are deaths	47.1%	23.55%	Because the relatively high proportion of RFS events that were deaths for blinatumomab may reflect incomplete capture of relapses after transplant in BLAST, a scenario analysis was conducted assuming the proportion of RFS that were deaths was only 23.55% (ie. 50%).
10	HRU data from online survey	In the base-case, HRU data were based on results of face-to-face interviews of two UK clinicians: • Inpatient days MRD+: 1.75 • Inpatient days MRD-: 0.06 • Visits to haematologist, MRD+: 2.00 • Visits to haematologist, MRD-: 1.50 • Visits to radiologist, MRD+: 0.42	In the scenario analysis, HRU was based on results of the online survey of 20 UK clinicians: • Inpatient days MRD+: 3.10 • Inpatient days MRD-: 2.33 • Visits to haematologist, MRD+: 1.17 • Visits to haematologist, MRD-: 0.92 • Visits to radiologist, MRD+: 0.25 • Visits to radiologist, MRD-: 0.08 • Visits to physician, MRD+: 0.83	To investigate the impact of alternative data source for HRU associated with MRD In the base-case, inpatient and outpatient healthcare resource utilisation (HRU) by MRD response was based on results of face-to-face interviews of two UK experts – this approach was considered appropriate given the rare and complex nature of this disease area. Nevertheless, a follow-up, larger multinational online survey that was also

No.	Description	Base-case setting	Scenario setting	Justification
		• Visits to radiologist, MRD-: 0.25 • Visits to physician, MRD+: 0.75 • Visits to physician, MRD-: 0.42 • Other visits, MRD+: 0.50 • Other visits, MRD-: 0.25	• Visits to physician, MRD-: 0.50 • Other visits, MRD+: 0.25 • Other visits, MRD-: 0.25	conducted to gather more information on patterns of testing for MRD response. The results for the online survey were considered only in a scenario analysis as despite the increased sample size, the distribution of results received suggested that many physicians participating in the online survey did not adequately understand the questions, thus this likely reflected a less accurate estimate of the resource impact.
11	Cumulative probability of pre-relapse HSCT identical for blinatumomab as for SoC	The cumulative probability of pre-relapse HSCT for CR1 population of BLAST trial was 72.6%. The six-month probability for months 1–48 was estimated to be 14.15%	The cumulative probability of pre-relapse HSCT for patients in the historical control study was 38.4%. The six-month probability for months 1–48 that yielded this value at 48 months for blinatumomab patients was 7.47%	A high rate of HSCT was observed in the BLAST trial, which might not be accurately reflecting the UK clinical practice, given that a large proportion of the patients in BLAST are from Germany. This scenario was run to investigate results using an HSCT rate equal to that observed in the historical control study.
12	ALL-related costs applied indefinitely	ALL-related costs applied to 60 months	Time when ALL-related costs not applied set to infinity.	To investigate the sensitivity of the model to assumptions regarding ALL-related costs.
13	0% MRD response rate for SoC	8% MRD response rate for SoC	SoC MRD response rate set to 0%.	To investigate other reasonable assumptions about the MRD response rate for SoC.
14	15% MRD response rate for SoC		SoC MRD response rate set to 15%.	
15	No disutility for long-term survivors	0.02 disutility for long-term survivors	Set disutility for long-term survivors to 0.	To investigate other reasonable assumptions regarding disutility for long-term survivors.
16	0.04 disutility for long-term survivors		Set disutility for long-term survivors to 0.04.	
17	SoC RFS utility equal to blinatumomab off-treatment RFS utility	Utility during RFS for patients receiving SoC was estimated to be 0.806 based on the estimated utility value from the GLM/GEE regression analysis of EQ-5D utility values in BLAST for patients who were off treatment, in haematological relapse, and assuming 8% MRD response	Utility during RFS for patients receiving SoC was set to 0.842 based on the estimated utility value from the GLM/GEE regression analysis of EQ-5D utility values in BLAST for patients who were off treatment, in haematological relapse, and assuming the same MRD response as blinatumomab (83.5%)	To address any the impact of base-case assumption that blinatumomab patients having a higher utility during RFS than SoC patients as a consequence of higher rate of MRD response.

No.	Description	Base-case setting	Scenario setting	Justification
18	Use ALL-related utilities and costs only to 36 months	ALL-related utilities and costs used up to 60 months	Set times when pre-relapse other inpatient/outpatient, post-relapse other inpatient/outpatient, salvage, and terminal care costs no longer applied, as well as the time beyond which general population utilities are used and the terminal decrement is no longer applied to 36 and 48 months, respectively.	To investigate the sensitivity of the model to the time when ALL-related costs and utilities are no longer applied, i.e., patients are cured after 36 months or 48 months.
19	Use ALL-related utilities and costs only to 48 months			
20	Model timeframe = 30 years	Model timeframe = 50 years	Model timeframe set to 30 and 60 years, respectively	To investigate the impact on model results of varying the model timeframe.
21	Model timeframe = 60 years			
22	Annual discount rate for costs and QALYs = 1.5%	Discount rates for costs and effectiveness are 3%	Discount rates for costs and effectiveness set to 1.5%.	To investigate the alternative discount rate suggested by the NICE Guide to Technology Appraisal.[6]
23	Exclude costs of cycle 6+ from blinatumomab salvage therapy costs	Patients in the TOWER trial could receive additional cycles of maintenance therapy beyond the marketing authorisation	Excludes Cycle 6+ costs from blinatumomab salvage costs	Explores effect of excluding maintenance cycles, cycles 6+, from the cost of blinatumomab as salvage therapy to better reflect use in clinical practice

Abbreviations: HSCT: haematopoietic stem cell transplant; HSCT: haematologic stem cell transplant; MRD: minimal residual disease; QALY: quality-adjusted life-year; RFS: relapse-free survival; SoC: standard of care; OS: overall survival.

Results of scenario analyses are presented in Table 4.

Table 4. Results of scenario analyses

#	Scenario	Blinatumomab			SoC			Blinatumomab vs. SoC			
		Cost (£)	Life-Years	QALYs	Cost (£)	Life-Years	QALYs	Cost (£)	Life-Years	QALYs	ICER (£)
	Base case	[redacted]	9.76	7.79	[redacted]	7.29	5.68	39,720	2.47	2.11	18,818
1	ATE weights	[redacted]	9.43	7.73	[redacted]	7.65	6.06	42,264	1.78	1.67	25,281
2	Alternative extrapolation methods	[redacted]	10.06	8.04	[redacted]	7.24	5.64	35,704	2.82	2.40	14,893
3	Unfavourable - RFS RCS Log-	[redacted]	9.26	7.39	[redacted]	7.07	5.51	38,754	2.19	1.88	20,644

	Logistic (R), OS RCS Weibull (R)										
4	2-fold increase long-term excess mortality	[redacted]	10.71	8.48	[redacted]	7.71	5.99	39,795	3.00	2.50	15,931
5	6-fold increase long-term excess mortality	[redacted]	9.14	7.32	[redacted]	7.01	5.48	39,672	2.13	1.85	21,454
6	Duration of benefits = 60 months	[redacted]	9.11	7.27	[redacted]	7.29	5.68	39,724	1.82	1.59	25,034
7	IP costs with on-Tx IP days from BLAST	[redacted]	9.76	7.79	[redacted]	7.29	5.68	44,710	2.47	2.11	21,182
8	IP costs with on-Tx IP days from Blincyto® label	[redacted]	9.76	7.79	[redacted]	7.29	5.68	39,868	2.47	2.11	18,888
9	23.55% of blinatumomab RFS events are deaths	[redacted]	10.08	8.05	[redacted]	7.29	5.68	53,498	2.79	2.37	22,607
10	HRU data from online survey	[redacted]	9.76	7.79	[redacted]	7.29	5.68	60,848	2.47	2.11	28,827
11	Cumulative probability of pre-relapse HSCT same for blinatumomab as for SoC	[redacted]	9.76	7.84	[redacted]	7.29	5.68	5,333	2.47	2.15	2,476
12	ALL-related costs applied to end of model time horizon	[redacted]	10.01	7.99	[redacted]	7.46	5.82	36,929	2.55	2.17	17,001
13	0% MRD response rate for SoC	[redacted]	9.76	7.79	[redacted]	7.29	5.68	37,997	2.47	2.12	17,957
14	15% MRD response rate for SoC	[redacted]	9.76	7.79	[redacted]	7.29	5.69	41,227	2.47	2.11	19,574
15	No disutility for long-term survivors	[redacted]	9.76	7.91	[redacted]	7.29	5.74	39,720	2.47	2.17	18,321
16	0.04 disutility for long-term survivors	[redacted]	9.76	7.67	[redacted]	7.29	5.62	39,720	2.47	2.05	19,342

17	SoC RFS utility = blinatumomab off-Tx RFS utility	[redacted]	9.76	7.79	[redacted]	7.29	5.70	39,720	2.47	2.09	19,000
18	ALL-related utilities and costs only to 36 months	[redacted]	9.69	7.77	[redacted]	7.25	5.71	41,837	2.44	2.06	20,342
19	ALL-related utilities and costs only to 48 months	[redacted]	9.74	7.79	[redacted]	7.28	5.70	40,426	2.46	2.09	19,364
20	Model timeframe = 30 y	[redacted]	9.46	7.59	[redacted]	7.14	5.58	39,703	2.33	2.01	19,720
21	Model timeframe = 60 y	[redacted]	9.76	7.79	[redacted]	7.29	5.68	39,720	2.47	2.11	18,818
22	Annual discount rate for costs and QALYs=1.5%	[redacted]	11.94	9.49	[redacted]	8.43	6.57	39,210	3.51	2.92	13,419
23	Exclude costs of cycle 6+ from blinatumomab salvage therapy costs	[redacted]	9.76	7.79	[redacted]	7.29	5.68	45,136	2.47	2.11	21,384

Abbreviations: SoC: standard of care; LY: life years; QALY: quality-adjusted life year; ATE: average treatment effect; RFS: relapse-free survival; R: restricted; OS: overall survival; U: unrestricted; Tx: treatment; HRU: healthcare costs and resource use; HSCT: haematopoietic stem cell transplantation; ALL: acute lymphoblastic leukaemia

The impact of the key scenario analyses are discussed in more detail below.

The first scenario examined the cost-effectiveness of blinatumomab versus SoC using ATE rather than ATT weighting. ATE weights were applied to the RFS and OS survival distributions, utilities, duration of therapy, mean starting age, mean proportion of male patients, and mean body surface area. Cost effectiveness of blinatumomab is somewhat less favourable using the ATE weights, yielding an ICER of £25,281.

As outlined in the curve fitting section of our original submission, the models selected for the base-case were selected based on fit statistics, visual fit, and consistency of RFS and OS projections. Other survival distributions that were not selected but still performed well are presented in scenarios 2 and 3 (see Section B. 3.3 of original submission). Of the parametric cure models, we decided to use the more conservative of the best-fitting options as the base-case. Scenario 2 presents a more favourable selection whereas scenario 4 presents a less favourable approach. ICERs for these scenarios were £14,893 and £20,644 for scenarios 3 and 4, respectively.

The base-case uses estimates of HRU for follow-up and monitoring based on face-to-face interviews of 2 UK clinicians. In Scenario 10 HRU data from the online survey of 20 UK clinicians was used instead. The projected mean number of inpatient days was substantially greater, and the difference in mean inpatient days for MRD+ versus MRD- patients was substantially less, based on the online survey data versus the face-to-face interviews. Use of the online survey data therefore increased the ICER to £28,827 per QALY gained. However, as discussed in Section B.3.5.4 of our original submission, the HRU costs based on in-depth interviews were considered to more accurately reflect the true resource implications despite the smaller sample size.

In the base-case, the probability of allogeneic HSCT pre-relapse was estimated to be greater in patients receiving blinatumomab compared with SoC. In Scenario 12, the probability of allogeneic HSCT with blinatumomab was calibrated so that the cumulative probability of pre-relapse HSCT is the same for blinatumomab as for SoC. Because LYs and QALYs are estimated independently of the rate of HSCT, changes in this parameter only impact the expected costs. Given the high cost of HSCT, setting the cumulative probabilities of HSCT to be the same for blinatumomab and SoC reduced the ICER considerably, to £2,476 per QALY gained.

Finally, a further scenario analysis was conducted to explore the impact of varying blinatumomab costs in the salvage setting to better reflect potential use in clinical practice. In this scenario, the additional costs of the maintenance cycles (Cycles 6+) were excluded, resulting in an increase in the ICER to £21,384 per QALY gained.

2.4 Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses (PSAs) were generated based on 10,000 Monte-Carlo simulations with sampling from the distributions of parameter estimates for which distributional information was available. Parameters of survival distributions were sampled from bootstrap distributions derived from the source data (BLAST and historical control).

Results of PSAs for the comparison of blinatumomab versus SoC are summarised in Table 5.

Table 5. Results of PSA of blinatumomab versus SoC

Outcome	Blinatumomab	SoC	Incremental
Life years (not discounted)			
Mean	13.23	7.76	5.47
SD	2.27	1.27	2.42

Median	13.43	7.85	5.43
95% LCL	7.23	5.19	0.00
95% UCL	16.97	10.08	9.86
QALYs (discounted)			
Mean	7.67	5.67	2.00
SD	1.07	0.68	1.16
Median	7.75	5.69	2.03
95% LCL	5.00	4.30	-0.55
95% UCL	9.47	6.94	4.13
Cost (discounted) (£)			
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
95% LCL	[redacted]	[redacted]	[redacted]
95% UCL	[redacted]	[redacted]	[redacted]

Abbreviations: PSA: probabilistic sensitivity analyses; SoC: standard of care; SD: standard deviation; LCL: lower confidence limit; UCL: upper confidence limit; QALY: quality-adjusted life year.

The results of the PSA with respect to cost-effectiveness are summarised in Table 6. Given an ICER threshold of £50,000/QALY, the mean NMB was £57,855. The mean ICER from the PSA was £29,673.

Table 6. Cost-effectiveness results from probabilistic sensitivity analyses

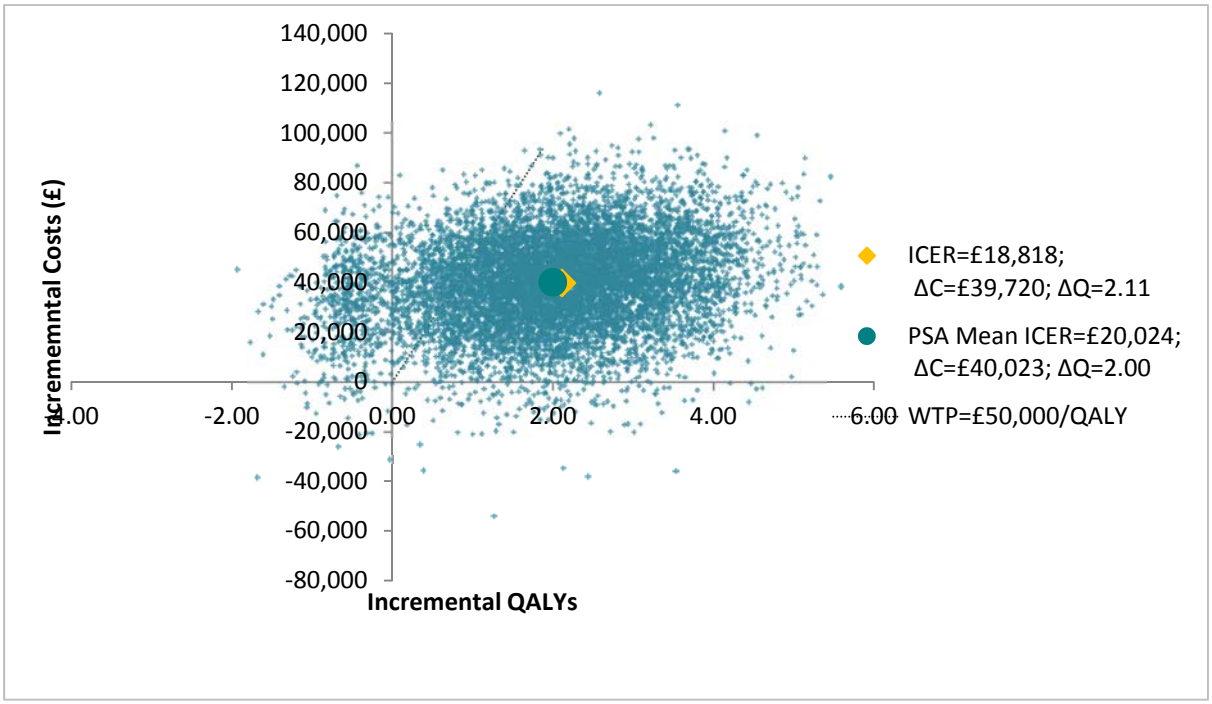
	Value
Percent of simulations in quadrant of CE plane	
Northeast (more costly and more effective)	92.6%
Southeast (dominant)	1.3%
Southwest (less costly and less effective)	0.3%
Northwest (dominated)	5.7%
NMB (WTP = £50,000 per QALY) (£)	
Mean	59,917
SD	56,996
Median	61,094
95% LCL	-62,084
95% UCL	166,623
Probability that therapy is preferred (WTP = £50,000)	
Blinatumomab	85.5%
SoC	14.5%
PSA mean ICER (ratio of mean incremental cost to mean incremental QALYs) (£)	20,024

Abbreviations: CE: cost-effectiveness; NMB: net monetary benefit; WTP: willingness to pay threshold; QALY: quality-adjusted life year; SD: standard deviation; LCL: lower confidence limit; UCL: upper confidence limit; SoC: standard of care; PSA: probabilistic sensitivity analyses; ICER: incremental cost-effectiveness ratio.

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is shown in Figure 3. It should be noted that the correlation of the incremental costs and QALYs is

relatively modest which reflects that the blinatumomab medication and administration costs are modelled independently of clinical outcomes.

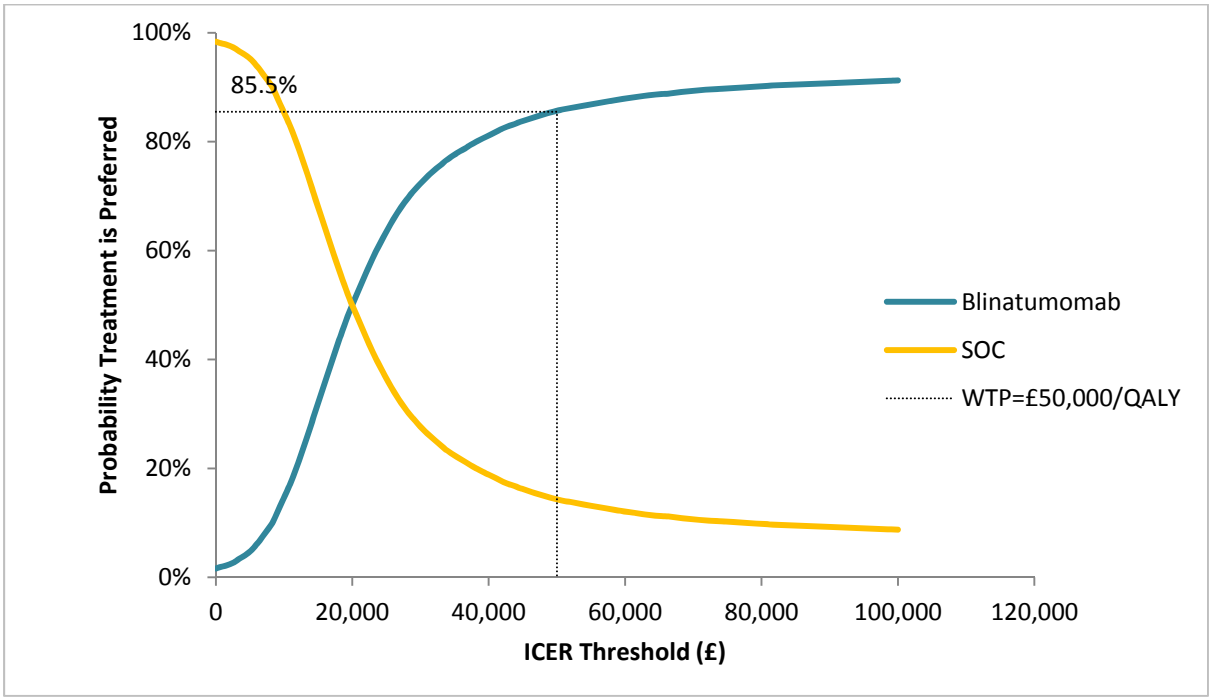
Figure 3. Scatter plot of simulations on cost-effectiveness plane



Abbreviations: ICER: incremental cost-effectiveness ratio; WTP: willingness to pay threshold; QALY: quality-adjusted life year.

Cost-effectiveness acceptability curves for blinatumomab and SoC care shown in Figure 4. The probability that blinatumomab is preferred was estimated to be 85.5% given an ICER threshold of £50,000 per QALY.

Figure 4. Cost-effectiveness acceptability curves for blinatumomab and SoC maintenance therapy



Abbreviations: SoC: standard of care; ICER: incremental cost-effectiveness ratio; WTP: willingness to pay threshold; QALY: quality-adjusted life year.

3 CONCLUSION

In this setting, the early use of blinatumomab in MRD was shown to be highly cost effective with an ICER of £18,818/QALY. Two-way deterministic sensitivity analyses and scenario analyses indicate that the base case results are robust when considering parameter uncertainty. Probabilistic sensitivity analysis generated a mean ICER of £20,024/QALY with a 71.9% and 85.5% probability of being cost-effective at willingness-to-pay thresholds of £30k- and £50k/QALY, respectively.

These analyses therefore confirm that early use of blinatumomab in the treatment pathway in patients in CR with MRD is highly likely to be cost effective compared with later use of blinatumomab (or inotuzumab) as salvage therapy following relapse.

4 REFERENCES

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Appendix 2

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity [ID1036]

Amgen Limited

Date 16th April 2019

Contains confidential information

LIST OF TABLES

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1 METHODS

1.1 Overview

To address the NICE Committee's concerns regarding the structural elements of our original partitioned survival model we have developed a new, combined decision-tree and Markov cohort model, which incorporates the Committee's specific requests:

- It reflects the current treatment pathway in relapsed/refractory setting – by including blinatumomab and inotuzumab as salvage therapy;
- It provides the link between minimal residual disease (MRD) status, hematopoietic stem cell transplant (HSCT) and survival – using data from re-analysis of BLAST and the historical comparator trial;
- It models a specific cure point of 5 years – which given the availability of trial data with almost 5 years of follow-up requires little survival curve extrapolation; and
- It includes the different positions in the treatment pathway at which HSCT might be given – time to transplant in complete response (CR) is explicitly modelled and post-relapse transplant rates, dependent on previous receipt of HSCT, are captured
- It reflects the latest data cut from the BLAST trial – data from the latest data cut of BLAST with a median follow-up of 53.1 months has been used to estimate parameters

1.2 Model Description

The model is an adaptation of the partitioned survival model originally used to evaluate the cost-effectiveness of blinatumomab in patients with Ph-negative MRD-positive B-precursor acute lymphoblastic leukemia (ALL) from a UK healthcare perspective. The population of interest is patients with Ph-negative B-precursor ALL in first complete response (CR1) with MRD. The intervention of interest is blinatumomab as administered in the BLAST trial. The comparator of interest is standard of care (SOC) which is assumed to be conventional maintenance chemotherapy and is represented by the inverse probability of treatment weight (IPTW) matched population of the historical control (HC) study.

A combined decision-tree and Markov cohort model is employed (Figure 1). Patients entering the model may receive blinatumomab or SOC. Patients are then partitioned in the decision tree by MRD response to initial therapy. Patients then enter the Markov model which has the following states:

- First complete hematologic response (CR1)
- Post HSCT
- Post Relapse Receiving Blinatumomab or Inotuzumab Salvage
- Post Relapse Receiving Other Salvage Therapy
- Dead

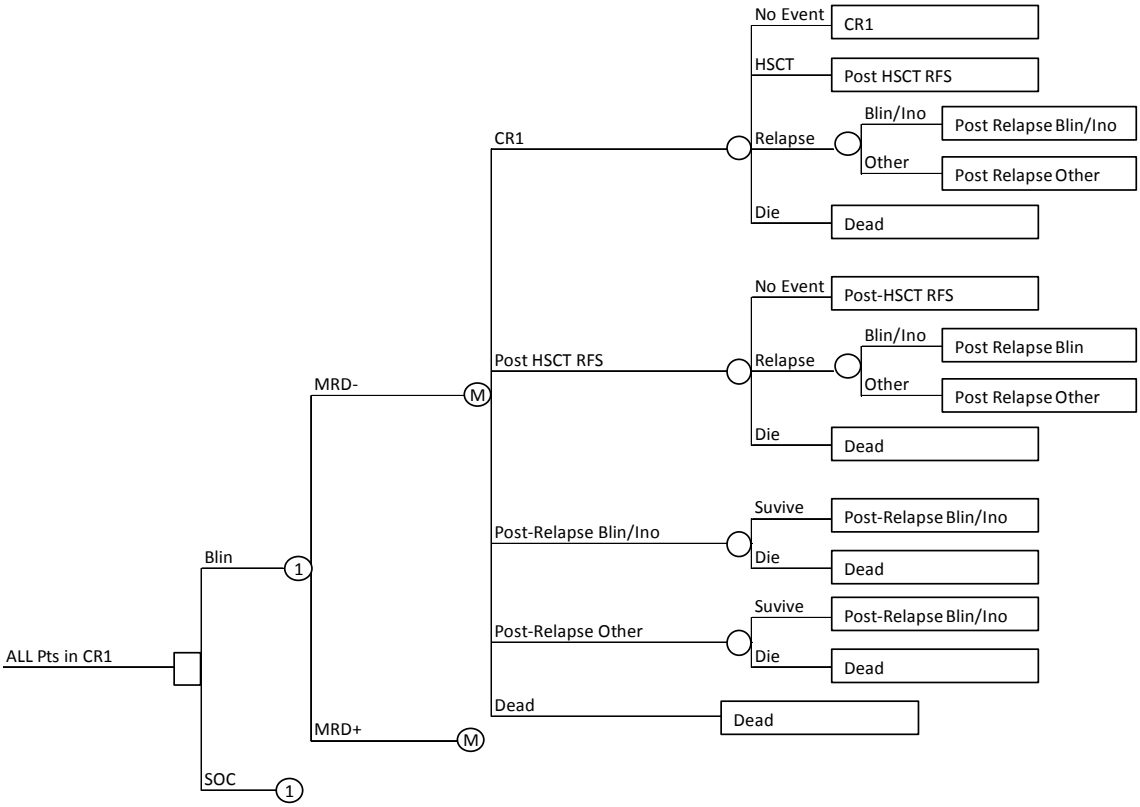
All patients enter the Markov in the CR1 state wherein they are assumed to be at risk of HSCT, relapse or death. Patients who experience relapse may initiate salvage treatment with innovative treatments (assumed to be either blinatumomab or inotuzumab) or other conventional salvage treatment. Patients who undergo HSCT and transit to the HSCT state are at risk of relapse or death. Those in the relapse states are assumed to be at risk of death. Death is an absorbing state.

Although the Markov model does not include an explicit cure state, the model does have the facility to use cure models for the survival distributions for events. It is also possible to assume after a specified duration in each state that patients are only at risk of general population mortality (i.e., "cured"). In the base case, patients are assumed to be cured 5 years after entering a health state. The percentage of patients who are cured is therefore defined implicitly based on the assumed survival distribution(s) for the event(s) and the point at which patients are assumed to be cured.

The periodicity of the model is six weeks, corresponding to the duration of one cycle of treatment with blinatumomab. The time horizon of the model is flexible with a maximum of 50 years (base case = 50 years). Probabilities of MRD response are conditioned on (i.e., may vary by) treatment. Other probabilities are conditioned on MRD response, treatment, time in state, and time since entry into the model. A total of 44 tunnel states corresponding to 5 years are specified for each of the HSCT, Relapsed Blin/Ino, and

Relapsed/Other states to permit transition probabilities, costs, and utility values to vary by time in state for up to five years.

Figure 1. Model schematic



1.3 Model Estimation

1.3.1 Transition Probabilities

Transition probabilities were estimated using data from BLAST and data from the HC study used in the original submission. Patients in BLAST and the HC study were weighted using the same ATT and ATE weights as used in the original submission. For the base case, ATT weights were used. A scenario analysis was conducted in which model inputs were estimated using ATE weights.

The probabilities of MRD response for patients receiving blinatumomab and SOC were the same as were used in the original submission. Probabilities of transition from CR1 to HSCT, Relapse (Blin/Ino or other), or dead, and HSCT to Relapse or dead were estimated using data from BLAST and the HC study. Data from BLAST were from the updated June 1, 2017 data cut-off.

Probabilities of death for patients in the Relapse Blin/Ino or Relapse/ Other states were estimated using data for patients in TOWER receiving blinatumomab or chemotherapy, respectively. Thus, survival for patients receiving inotuzumab salvage therapy was assumed to be the same as that for patients receiving blinatumomab. Patients in TOWER were limited to those in the no prior salvage therapy group who were not primary refractory (to correspond to the relapsing patients in BLAST). These patients were then matched to those in BLAST using ATT IPTW weights with the relapsing patients in BLAST defined as the "treated" population. It should be noted that this population and approach to weighting is the same as that employed for estimating utility values for relapsed patients in the original submission.

Transition probabilities were estimated by fitting parametric survival distributions to the IPD in BLAST, the HC study, and TOWER using FlexSurv. Parametric survival distributions were fit separately to BLAST MRD responder, BLAST MRD non-responders, and patients in the HC study. It was not possible to estimate probabilities conditioned on MRD response for patients receiving SOC as data on MRD response was not available from the historical control study.

Survival distributions considered were the same as those considered in the original submission and mixture cure distributions. Distributions were selected based on visual fit, fit statistics and clinical plausibility. When estimating transition probabilities, a competing risk framework was employed. Accordingly, when estimating the survival distribution for a particular transition, patients who experience other competing risks were censored at the time of the event. For example, when estimating the survival distribution for transitioning from CR1 to HSCT, patients who experienced relapse or death prior to undergoing HSCT were censored. This process was repeated for each potential event for patients in each state. Thus, the following survival distributions were estimated for each of three groups (blinatumomab MRD responders, blinatumomab MRD non-responders, and SOC).

- CR1 to HSCT
- CR1 to Relapsed
- CR1 to Dead
- HSCT to Relapsed
- HSCT to Dead

For the TOWER patients, the following survival distributions were estimated

- Relapsed Blin/Ino to Dead.
- Relapsed Other to Dead.

The table below reports the distribution number of patients at risk, the number of events, and the distribution selected for each of the transition probabilities. A brief description of the rationale for the selection of each distribution is also provided. It is important to note that the numbers of patients at risk and numbers of events for some events were small and it was therefore difficult in some cases to select from among the candidate distributions. Also, for MRD non-responders in BLAST, no patients who underwent HSCT prior to relapse or death experience relapse after HSCT (zero events). Accordingly, in the model, this probability was set to zero.

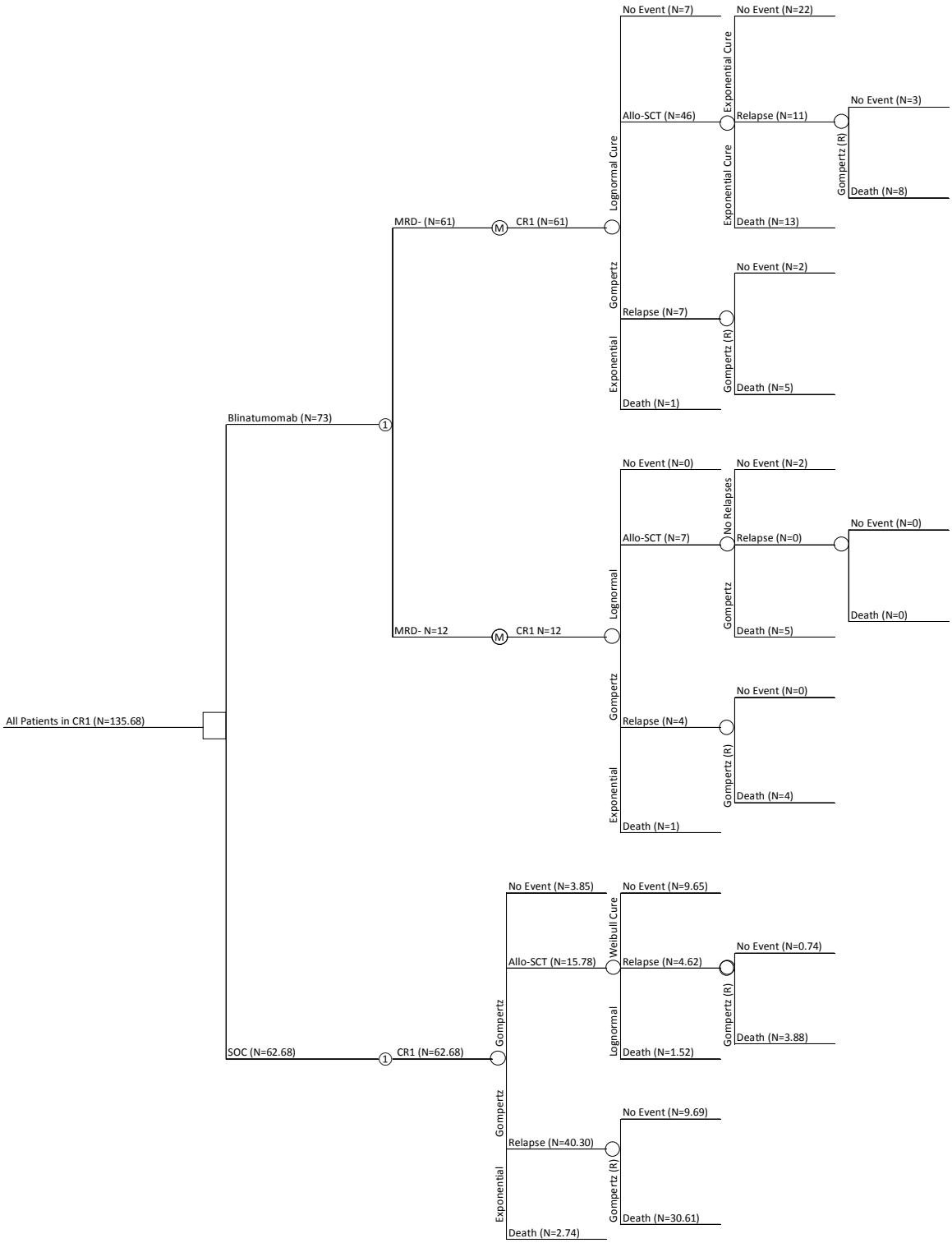
Table 1. Summary of distribution used for transition probabilities

Population	From	To	N at Risk	N Events	N Censored	Distribution	Comment
BLAST MRD Responders	CR1	HSCT	61	46	15	Lognormal Cure	Lowest BIC Excellent visual fit Reasonable to assume no risk after ~6 months
		Relapsed		7	54	Gompertz	Good statistical fit Good visual fit Reasonable to assume cure (w/Gomperts, no explicit but effective cure)
		Dead		1	60	Exponential	Only one event so constant probability assumed
	HSCT	Relapsed	46	11	35	Exponential Cure	Good statistical fit Excellent visual fit Reasonable to assume cure with HSCT
		Dead		13	33	Exponential Cure	Lowest BIC Excellent visual fit Reasonable to assume long-term cure with HSCT
	CR1	HSCT	12	7	5	Lognormal	Lowest BIC Excellent Visual Fit

BLAST MRD Non-Responders							Yields 100% Probability of HSCT at ~12 months
		Relapsed		4	8	Gompertz	Lowest BIC Excellent visual fit Consistent with assumed distribution for SOC
		Dead		1	11	Exponential	Only one event so constant probability assumed
	HSCT	Relapsed	7	0	7	Exponential	Since no events, set to zero by specifying exponential distribution with approximately zero probability of event in model time horizon
		Dead		5	2	Gompertz	Good statistical fit Excellent visual fit Reasonable to assume long-term cure with HSCT
SOC	CR1	HSCT	62.68	15.78	46.89	Gompertz	Best statistical fit Excellent visual fit Reasonable to assume no risk after ~6 months
		Relapsed		40.30	22.38	Gompertz	Best statistical fit Excellent visual fit Reasonable to assume no risk after ~6 months
		Dead		2.74	59.93	Exponential	Curve fitting difficult due to small number of events Constant hazard assumed
	HSCT	Relapsed	15.78	4.62	11.17	Weibull Cure	Good statistical fit Good visual fit Reasonable to assume cure after HSCT
		Dead		1.52	14.26	Lognormal	Good statistical fit Good visual fit Decreasing hazard with lognormal yields long tail approximating cure model which is reasonable post HSCT
TOWER S0 Not Primary Refractory ATT-IPTW	Relapsed Blin/Ino	Dead	13.03	7.43	5.60	Restricted Gompertz	Good statistical fit Excellent visual fit Consistent with approach employed in Mfg. submission
	Relapsed Other	Dead	12.89	9.37	3.53	Restricted Gompertz	

The numbers of patients at risk, numbers of events, and distribution used are displayed in the form of a tree diagram below

Table 2 Numbers of patients at risk, numbers of events, and distribution used for estimation of Markov model, ATT weights for SOC



Note: Allo-SCT in the above diagram is equivalent to HSCT

1.3.2 Distribution of Salvage Therapies for Patients who Relapse

The assumed proportions of relapsing patients who would receive salvage therapy with blinatumomab, inotuzumab or other therapy were estimated based on clinical expert opinion.

Table 3. Assumed distributions of first salvage treatment by initial treatment received

	Treatment	
First Salvage Therapy	**Blinatumomab**	**SOC**
Blinatumomab	0%	50%
Inotuzumab	100%	50%
SOC	0%	0%
Total	100%	100%

1.3.3 Costs of Salvage Therapy

The cost of blinatumomab salvage therapy was taken from the manufacturer's submission for the NICE STA of blinatumomab for R/R Ph- ALL patients based on the TOWER trial, and included the cost of blinatumomab medication ([redacted]), and administration (£10,641)[1]. A [redacted] discount was applied to the medication cost of blinatumomab salvage therapy consistent with that assumed for initial therapy. The total cost of blinatumomab salvage was therefore estimated to be [redacted]. The cost of inotuzumab salvage therapy was estimated to be £85,417, based on the inotuzumab estimate used in the manufacturer's submission for the NICE STA of inotuzumab for R/R ALL patients in their first or second line of salvage therapy based on the INO-VATE-ALL trial. Medication costs for inotuzumab was estimated to be £76,376, which was calculated by multiplying the price per vial of inotuzumab (£8,048) by the average number of vials received in the INO-VATE-ALL trial (9.49). Administration costs for inotuzumab were estimated by multiplying the NICE recommended number of inpatient days for administration of inotuzumab (11.23) by the average NHS reference costs for ALL-related hospitalization (£805) [2]. The cost of medication and administration of multi-agent chemotherapy was estimated to be £16,176 based on the estimated medication and administration cost of FLAG-IDA in the manufacturers' submission to NICE for blinatumomab for R/R Ph- ALL [1].

1.3.4 Costs of HSCT

As in the original submission, for costing purposes, it is assumed (a) that patients may undergo HSCT after relapse, (b) the costs of post-relapse HSCT are assigned at entry to the relapse states, and (c) the probability of post-relapse HSCT depend on whether the patient had received HSCT previously. The proportion of patients entering the relapse states from the CR1 vs. the HSCT state as calculated in the model. While the percent entering the relapse states from the CR1 vs HSCT states vary over time, the proportion over the entire modelling time horizon was used for simplicity.

1.3.5 Other Parameter Estimates

All other parameters were taken from the partitioned survival model used in the original submission.

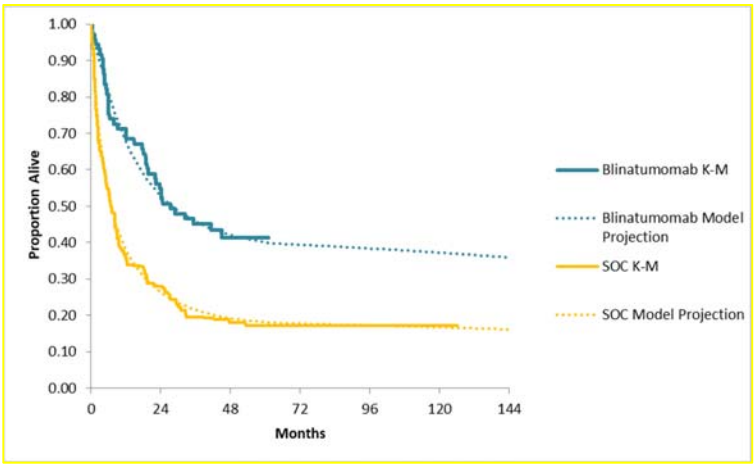
2 RESULTS

2.1 Base Case Results

The main clinical outcomes generated by the model are RFS and OS. Estimates of RFS and OS from the model are compared with Kaplan-Meier estimates of RFS and OS from BLAST and the historical control in Figure 2 and
Table 4. The survival curves projected by the model fit both the BLAST and historical control data very well.

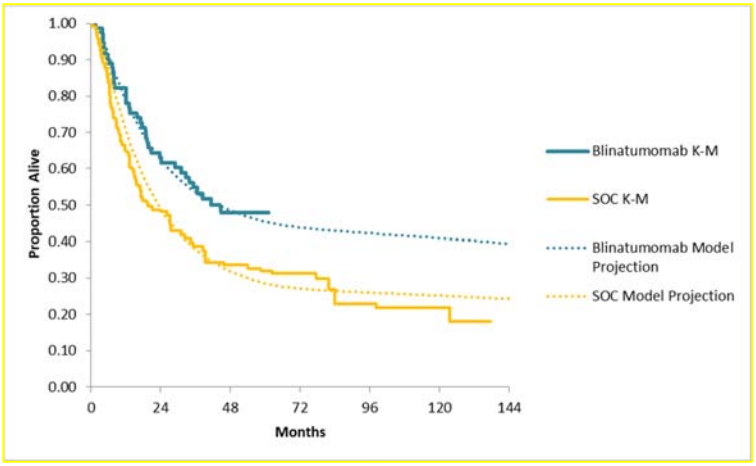
Figure 2. RFS and OS in the model

A. Relapse free survival



K-M: Kaplan-Meier; SOC: standard of care.

B. Overall survival



K-M: Kaplan-Meier; SOC: standard of care.

Table 4. Comparison of probabilities of survival in the model and in BLAST at selected landmarks

Month	Relapse Free Survival				Overall Survival			
	Blinatumomab		Standard of Care		Blinatumomab		Standard of Care	
	BLAST	Model	Historical Control	Model	BLAST	Model	Historical Control	Model
6	[redacted]							
12	[redacted]							

24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The percentage of patients achieving a cure as predicted by the model are presented **Error! Not a valid bookmark self-reference.**.

Table 5. Cure fraction

	Blinatumomab	Standard of Care
Cure among patients in CR	8.82%	4.35%
Cure among patients who receive HSCT	30.92%	13.49%
Cure among patients who relapse	3.85%	8.93%
TOTAL	43.59%	26.78%

Expected life years (LYs) and quality-adjusted life years (QALYs) by health state for blinatumomab and SOC maintenance therapy are shown in Table 6. Blinatumomab is expected to yield 2.58 more discounted LYs and 2.12 more discounted QALYs than SOC.

Table 6. Base-case effectiveness results

Effectiveness	Blinatumomab	SOC	Incremental	Absolute Incremental	Absolute Incremental %
Undiscounted					
LYs					
Complete response	2.67	1.67	1.00	1.00	13.6
HSCT	8.26	3.56	4.70	4.70	64.1
Post-relapse	1.22	2.86	-1.64	1.64	22.3
Total	12.14	8.08	4.06	7.34	100.00
QALYs					
Complete response	2.16	1.36	0.80	0.80	13.9
HSCT	6.53	2.82	3.71	3.71	64.5
Post-relapse	0.91	2.15	-1.24	1.24	21.5
Total	9.60	6.32	3.28	5.75	100.00
Discounted					
LYs					
Complete response	1.88	1.28	0.61	0.61	12.3
HSCT	5.51	2.36	3.15	3.15	63.9
Post-relapse	0.86	2.04	-1.18	1.18	23.9
Total	8.26	5.68	2.58	4.94	100.00
QALYs					
Complete response	1.54	1.05	0.49	0.49	12.8
HSCT	4.38	1.88	2.50	2.50	64.5
Post-relapse	0.63	1.51	-0.88	0.88	22.7
Total	6.56	4.44	2.12	3.87	100.00

SOC: Standard of care; LYs: life years; QALYs: quality adjusted life years; HSCT: allogeneic hematopoietic stem cell transplant.

Expected discounted costs by health state and category of service for blinatumomab and SOC are shown in Table 7. Medication costs were estimated to be [redacted] higher with blinatumomab versus SOC. Total treatment costs, including medication, hospitalization, outpatient visits, and infusion pump costs were

estimated to be [redacted] higher with blinatumomab. Costs of pre-relapse HSCT were [redacted] higher with blinatumomab than SOC. Other pre-relapse inpatient costs were estimated to be [redacted] lower with blinatumomab versus SOC, whereas other pre-relapse outpatient costs were [redacted] higher with blinatumomab versus SOC.

Because fewer patients receiving blinatumomab are projected to relapse, salvage therapy costs were [redacted] higher with SOC than with blinatumomab. Post-relapse HSCT costs were [redacted] higher with SOC than with blinatumomab. Because post-relapse LYs were projected to be greater with SOC with blinatumomab, other PR inpatient costs were [redacted] higher with SOC than with blinatumomab. Similarly, other PR outpatient costs were [redacted] higher with SOC than with blinatumomab. Total post-relapse costs were [redacted] higher with SOC than blinatumomab. Because fewer blinatumomab are projected to die within five years, terminal care costs were [redacted] higher for SOC than for blinatumomab. Total incremental costs were [redacted] higher with blinatumomab versus SOC. A diagram of incremental costs with blinatumomab versus SOC is shown in

Figure 3.

Table 7. Base case expected costs results

Cost Category	Blinatumomab (£)	SOC (£)	Incremental (£)
Pre-relapse			
Blinatumomab and SOC maintenance treatment			
Medication	[redacted]	[redacted]	[redacted]
Administration			
Hospitalization	[redacted]	[redacted]	[redacted]
Outpatient visits	[redacted]	[redacted]	[redacted]
Infusion pump	[redacted]	[redacted]	[redacted]
Total medication and administration	[redacted]	[redacted]	[redacted]
HSCT	[redacted]	[redacted]	[redacted]
Other inpatient	[redacted]	[redacted]	[redacted]
Other outpatient pre-relapse	[redacted]	[redacted]	[redacted]
Total pre-relapse	[redacted]	[redacted]	[redacted]
Post-relapse			
Salvage therapy	[redacted]	[redacted]	[redacted]
HSCT	[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]	54,264

SOC: Standard of care; HSCT: allogeneic hematopoietic stem cell transplant.

Figure 3. Waterfall diagram of incremental costs with blinatumomab versus SOC

Admin.: administration; HSCT: allogeneic hematopoietic stem cell transplant; IP: inpatient; OP: outpatient.
Base case results for the cost-effectiveness of blinatumomab versus SOC in adult patients with Ph- B-precursor ALL are reported in Table 8. Blinatumomab was projected to 2.12 more discounted QALYs than SOC at an incremental cost of £54,264. The ICER for blinatumomab versus SOC was therefore estimated to be £25,645 per QALY gained.

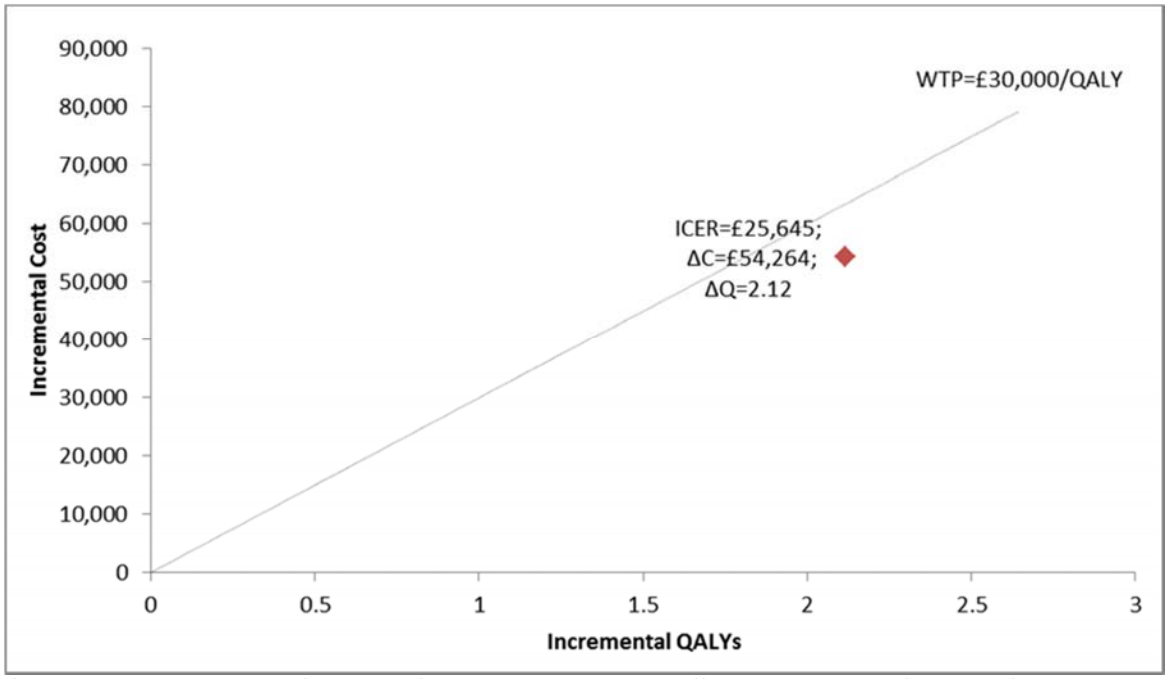
Table 8. Base case cost-effectiveness results

Technologies	Total costs (£)	Total LY gain	Total QALYs	Incremental costs (£)	Incremental LY gain	Incremental QALYs	ICER (£/QALY)
Blinatumomab	[redacted]	8.26	6.56	54,264	2.58	2.12	**25,645**
SOC	[redacted]	5.68	4.44				

LY: life year; QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; SOC: standard of care.

Incremental costs and QALYs with blinatumomab versus SOC are plotted on the cost-effectiveness plane in Figure 4. The line in the figure represents the willingness-to-pay (WTP) threshold of £30,000 per QALY gained.

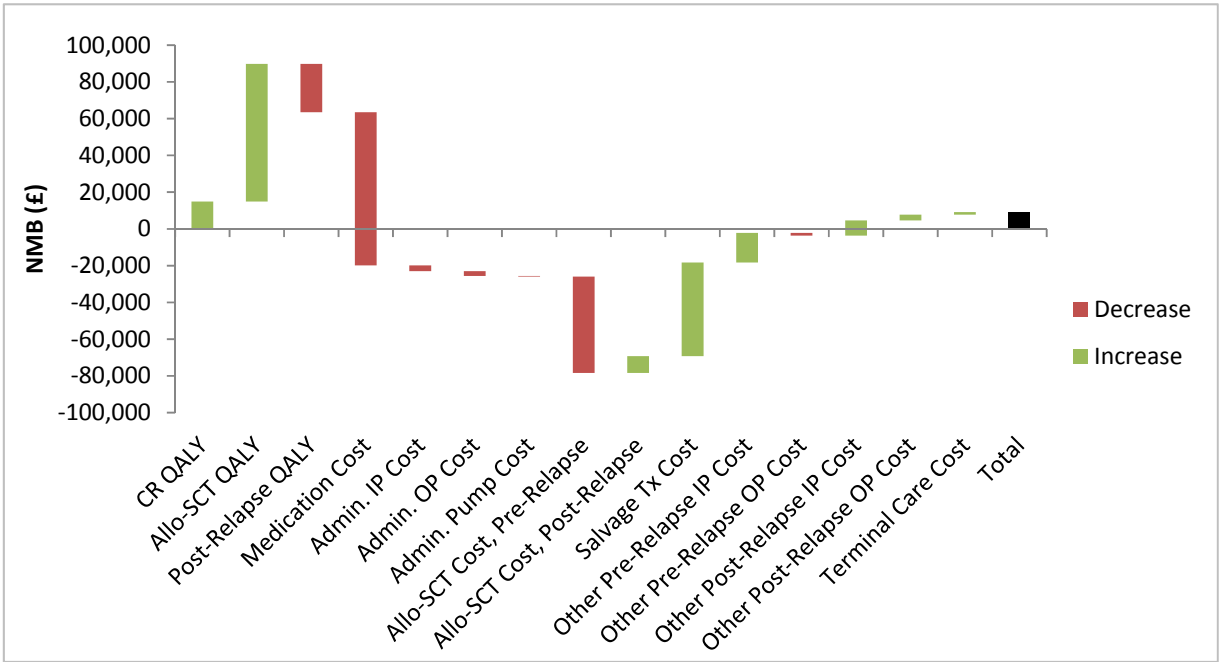
Figure 4. Incremental costs and QALYs with Blinatumomab versus SOC



QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; C: costs; Q: quality-adjusted life years; WTP: willingness-to-pay threshold

The contributions of various components of incremental costs and QALYs to net monetary benefit (NMB) given an assumed willingness to pay (WTP) threshold of £30,000 per QALY gained are displayed in Figure 5. The largest positive contributor to NMB is the gain in HSCT QALYs, followed by incremental salvage treatment costs. The largest negative contributor is the acquisition cost of blinatumomab, followed by the incremental costs of HSCT. Other factors have relatively small individual contributions to NMB.

Figure 5. Incremental costs and QALY contribution to NMB given ICER threshold of £30,000 per QALY

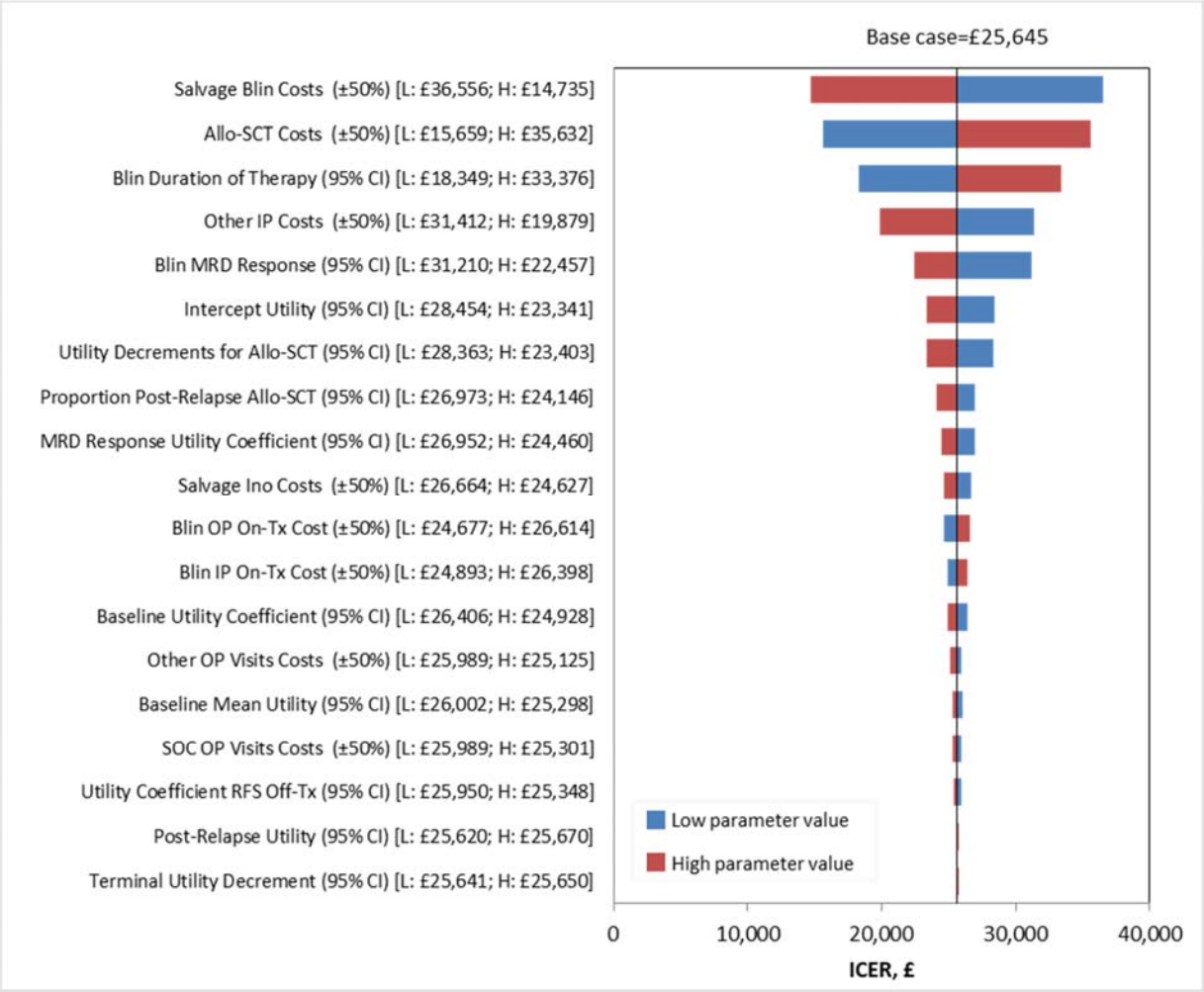


CR: complete response; QALY: quality-adjusted life year; HSCT: allogeneic hematopoietic stem cell transplant; admin.: administration; IP: inpatient; OP: outpatient; tx: treatment.

2.2 Deterministic Sensitivity Analyses

A tornado chart for the ICER for blinatumomab versus SOC is shown in Figure 6. The most important parameter examined, measured in terms of the range of ICER values across the range of input values, is the cost of blinatumomab as salvage therapy. The estimated ICER ranges from £14,735 to £36,556 as this parameter is by ±50%. The model also was sensitive to the costs of HSCT, with the ICER ranging from £15,659 to £35,632 as these costs were varied by ±50%, and the duration of blinatumomab therapy, with the ICER ranging from £18,349 to £33,376 as these costs were varied by ±50%.

Figure 6. Tornado diagram of ICER of blinatumomab versus SOC



Blin: blinatumomab; HSCT: allogeneic hematopoietic stem cell transplant; IP: inpatient; OP: outpatient; MRD: minimum residual disease; ino: inotuzumab; tx: treatment; SOC: standard of care; RFS: relapse-free survival

2.3 Scenario Analyses

Results of scenario analyses are presented in Table 9.

Table 9. Results of scenario analyses

#	Scenario	Blinatumomab			SOC			Blinatumomab vs. SOC			
		Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	Cost (£)	LYs	QALYs	ICER (£)
	Base case	[redacted]	8.26	6.56	[redacted]	5.68	4.44	54,264	2.58	2.12	**25,645**
1	ATE weights	[redacted]	10.72	8.74	[redacted]	8.82	7.12	56,573	1.90	1.62	**35,014**
2	100% of patients receive salvage treatment with multi-agent chemotherapy upon relapse	[redacted]	7.71	6.14	[redacted]	4.38	3.45	104,196	3.33	2.69	**38,753**
3	Exclude costs of cycle 6+ from Blincyto salvage	[redacted]	8.26	6.56	[redacted]	5.68	4.44	59,800	2.58	2.12	**28,262**
4	Use SOC survival curves to inform survival in	[redacted]	8.53	6.77	[redacted]	5.68	4.44	57,979	2.86	2.33	**24,852**
5	SOC estimated based on BLAST data (0%	[redacted]	8.26	6.56	[redacted]	4.00	3.11	83,698	4.25	3.44	**24,311**
6	SOC estimated based on BLAST data (8%	[redacted]	8.26	6.56	[redacted]	4.41	3.45	83,481	3.84	3.11	**26,829**
7	SOC estimated based on BLAST data (15%	[redacted]	8.26	6.56	[redacted]	4.77	3.74	83,292	3.49	2.82	**29,515**
8	Time to death given HSCT and time to relapse given HSCT based on MRD- data for all	[redacted]	8.58	6.81	[redacted]	5.36	4.19	65,062	3.22	2.62	**24,825**
9	Time to death given HSCT and time to relapse given HSCT based on SOC data for all	[redacted]	9.44	7.49	[redacted]	5.68	4.44	72,646	3.76	3.05	**23,813**
10	Time to death given HSCT and time to relapse given HSCT for MRD+ patients same as for SOC	[redacted]	8.68	6.89	[redacted]	5.68	4.44	60,528	3.01	2.45	**24,679**
11	Time to HSCT based on SOC for all	[redacted]	8.53	6.82	[redacted]	5.68	4.44	27,848	2.85	2.38	**11,695**
12	Time to HSCT based on MRD- for all	[redacted]	8.23	6.54	[redacted]	7.01	5.50	32,948	1.22	1.03	**31,851**
13	Time to HSCT based for MRD+ based on SOC data	[redacted]	8.13	6.46	[redacted]	5.68	4.44	52,307	2.45	2.02	**25,936**
14	2-fold increase in long-term mortality	[redacted]	9.21	7.26	[redacted]	6.26	4.87	54,428	2.95	2.39	**22,793**
15	6-fold increase in long-term mortality	[redacted]	7.65	6.10	[redacted]	5.30	4.16	54,167	2.35	1.94	**27,906**
16	0% MRD response rate for SOC	[redacted]	8.26	6.56	[redacted]	5.68	4.44	52,413	2.58	2.12	**24,751**
17	15% MRD response rate for SOC	[redacted]	8.26	6.56	[redacted]	5.68	4.44	55,883	2.58	2.11	**26,426**
18	Utility value post-relapse 0.5	[redacted]	8.26	6.48	[redacted]	5.68	4.26	54,264	2.58	2.23	**24,381**
19	Utility value post-relapse 0.25	[redacted]	8.26	6.39	[redacted]	5.68	4.02	54,264	2.58	2.37	**22,908**
20	30-year model timeframe	[redacted]	8.00	6.39	[redacted]	5.52	4.34	54,221	2.48	2.05	**26,450**
21	Annual discount rate for costs and QALYs=1.5%	[redacted]	10.14	8.04	[redacted]	6.85	5.36	53,840	3.30	2.68	**20,075**
22	Cure time point 3 years	[redacted]	8.84	7.04	[redacted]	6.29	4.97	59,024	2.55	2.07	**28,492**
23	Cure time point 4 years	[redacted]	8.46	6.73	[redacted]	5.89	4.63	56,262	2.58	2.11	**26,718**

ATE: average treatment effect weights; SOC: standard of care; HSCT: allogeneic hematopoietic stem cell transplant; MRD: minimum residual disease; QALYs: quality-adjusted life years.

The first scenario examined the cost-effectiveness of blinatumomab versus SOC using ATE rather than ATT weighting. ATE weights were applied to the time-to-event survival distributions, utilities, duration of therapy, mean starting age, mean proportion of male patients, and mean BSA. Cost effectiveness of blinatumomab is somewhat less favourable using the ATE weights, yielding an ICER of £35,014.

Although clinicians advise that upon relapse patients should be treated with innovative therapies, blinatumomab and/or inotuzumab, rather than standard chemotherapy, a scenario was run where it was assumed that all patients would receive salvage multi-agent chemotherapy upon relapse. Costs and survival for patients receiving multi-agent chemotherapy upon relapse were taken from the SOC arm of the no prior salvage subgroup of patients in the TOWER trial of R/R Ph- ALL patients. The resulting ICER is £38,753 but is highly unlikely to reflect clinical practice in the UK.

Patients in the TOWER trial could receive additional cycles of maintenance therapy with blinatumomab. Scenario 3 looks at the effect of excluding these maintenance cycles (ie. Cycle 6+), from the cost of blinatumomab as salvage therapy, which may better reflect UK clinical practice. The resulting ICER is £28,262.

In scenario 4, SOC time-to-event survival curves were used to inform survival for MRD+ patients in BLAST. The resulting ICER of £24,852 is more favourable for blinatumomab than the base case.

Scenarios 5 to 7 examine the outcome of using BLAST data to model MRD responders and non-responders, because MRD response was not measured in the historical control study, while testing different SOC MRD response rates. The ICERs are similar to the base case ICER, attesting to the robustness of the base case modelling method.

Because HSCT is an important driver for costs and outcomes, scenarios 11 to 13 tested different assumptions on time to HSCT, by setting all arms to use the same time to HSCT survival distributions. The ICERs for these scenarios ranged from £11,695 to £31,851.

The model incorporates general population mortality at five years when patients are considered “cured” from ALL disease. We assume that due to complications of radiotherapy, chemotherapy, and HSCT, patients will never reach general population mortality levels, and apply a relative increment of four times general population mortality, based off of evidence by Martin et al, tracking long-term survival after five years of receipt of HSCT [3]. In scenario 14, we assumed a more favourable two-fold mortality increase in mortality, which we believe relevant because Martin et al. tracked R/R patients, while the BLAST population does not include R/R patients and is therefore healthier. The ICER in Scenario 14 was £22,793 per QALY. In scenario 15 a less favourable six-fold long-term increase in excess mortality was assumed, resulting in an ICER of £27,906, still cost-effective at a £30,000/QALY WTP threshold.

In the base case, an estimated 8% of SOC patients were assumed to achieve MRD response, according to clinical expert opinion. To assess the impact of this assumption on model results, Scenario 16 assumes no MRD response in SOC patients, which reduced the ICER to £24,751. In Scenario 17, it was assumed that MRD response in patients receiving SOC would be 15%, based on the implied value in results from the meta-analysis by Berry et al. [4]). The use of this assumption resulted in a modest increase in the ICER to £26,426.

In the base case, a post-relapse utility of 0.692 was estimated using the no prior salvage therapy subgroup among patients in TOWER matched to BLAST patients. While we feel that this value most accurately reflects the utility among blinatumomab patients upon relapse, scenarios 18 and 19 examine alternative post-relapse utility values of 0.5 and 0.25, respectively. Because more SOC patients relapse than blinatumomab patients, the resulting ICERs are more favourable for blinatumomab, £24,381 for scenario 18 and £22,908 for scenario 19.

Scenario 20 examined the impact of changing the modelling time horizon on the ICER (50 years in the base case). The ICER was £26,450 per QALY gained with a model time horizon of 30 years. Note that this scenario may be biased however, as approximately 15% of patients in the blinatumomab group and 9% of those in the SOC maintenance therapy group are projected to remain alive after 30 years.

Scenario 21 used an annual discount rate of 1.5% for costs and QALYs consistent with the NICE guidance for sensitivity analyses on the discount rates [5]. The ICER for blinatumomab versus SOC maintenance therapy was more favourable using the lower discount rate (£20,075 per QALY gained).

In the base case, it was assumed that patients will stop incurring ALL-related costs, and switch over to general population mortality and utility after five years, when they are considered “cured.” In scenarios 22 and 23, we examined changing the cure assumption to three and four years, respectively. The resulting ICERs, £28,492 and £26,718 respectively, were slightly less favourable for blinatumomab.

2.4 Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses (PSAs) were generated based on 10,000 Monte-Carlo simulations with sampling from the distributions of parameter estimates for which distributional information was available. Transition probabilities derived from BLAST and the HC studies were sampled bootstrap distributions consisting of 9949 bootstrap replicates derived from the IPD (fifty-one of 1,000 bootstrap

replicates yielded errors for one or more time-to-event distributions and were dropped from the bootstrap distributions). Results of PSAs for the comparison of blinatumomab versus SOC are summarized in Table 10.

Table 10. Results of PSA of blinatumomab versus SOC

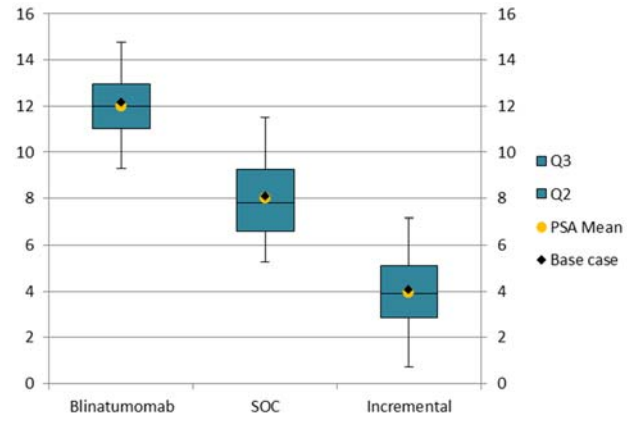
Outcome	Blinatumomab	SOC	Incremental
Life years (not discounted)			
Mean	11.98	8.00	3.98
SD	1.41	1.73	-0.32
Median	11.98	7.81	4.17
95% LCL	9.30	5.29	4.01
95% UCL	14.76	11.51	3.24
QALYs (discounted)			
Mean	6.48	4.40	2.08
SD	0.72	0.85	-0.14
Median	6.48	4.31	2.16
95% LCL	5.12	3.03	2.09
95% UCL	7.88	6.13	1.75
Cost (discounted) (£)			
Mean	[redacted]	[redacted]	56,619
SD	[redacted]	[redacted]	2,466
Median	[redacted]	[redacted]	55,805
95% LCL	[redacted]	[redacted]	54,230
95% UCL	[redacted]	[redacted]	64,075

SOC: standard of care; SD: standard deviation; LCL: lower confidence level; UCL: upper confidence level.

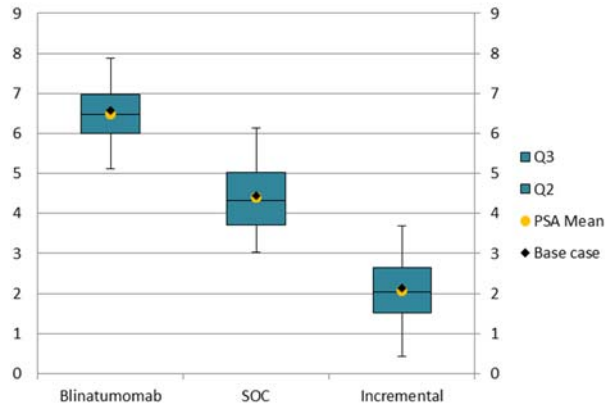
Box and whisker plots of the PSA results for undiscounted life-years, QALYs, and costs are shown in Figure 7. Probabilistic mean LYs, QALYs, and costs are similar to deterministic estimates.

Figure 7. Box and whisker plots for distributions of life years, QALYs and costs from PSA

A. Life Years



B. QALYs



C. Costs

QALYs: quality adjusted life years; SOC: standard of care; Q2: quartile 2 (median); Q3: quartile 3.

The results of the PSA with respect to cost-effectiveness are summarized in Table 11. Given an ICER threshold of £30,000/QALY, the mean NMB was £5,669. The mean ICER from the PSA (calculated as the ratio of the mean incremental costs to the mean incremental QALYs) is £27,257.

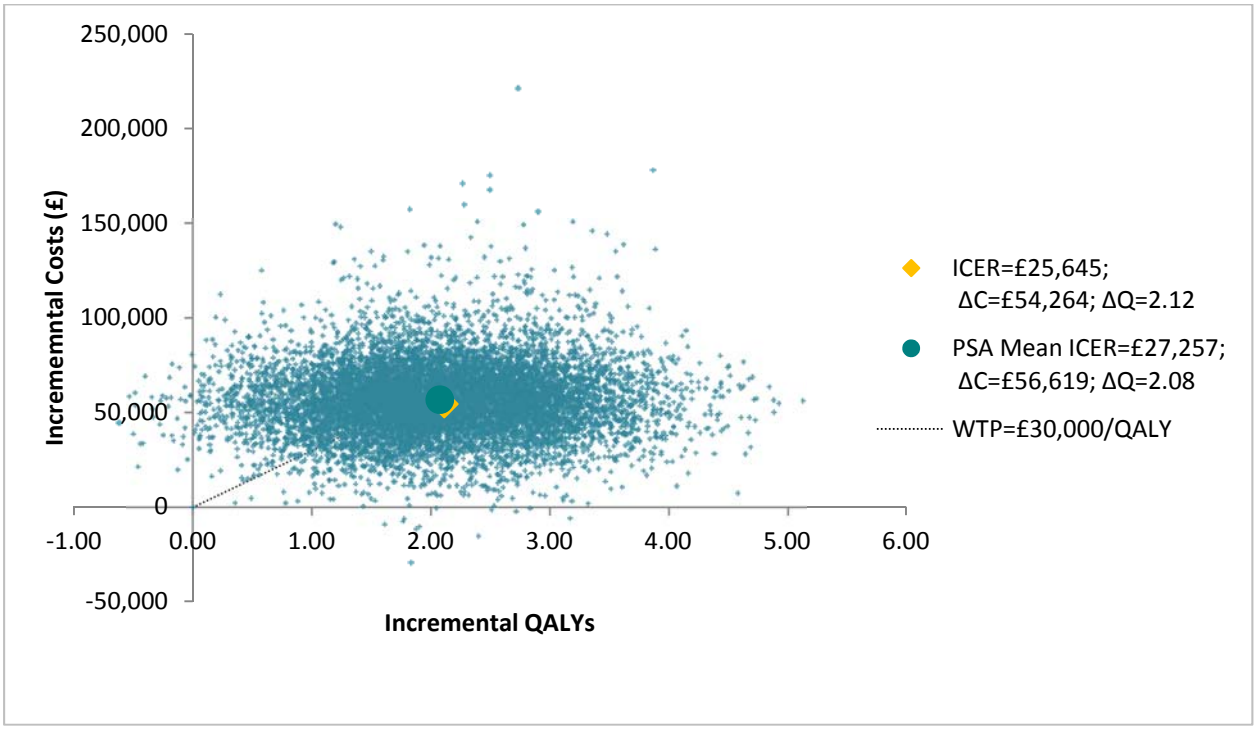
Table 11. Cost-effectiveness results from PSA

Percent of Simulations in Quadrant of CE Plane	**Value**
Northeast (more costly and more effective)	99.0%
Southeast (dominant)	0.1%
Southwest (less costly and less effective)	0.0%
Northwest (dominated)	0.4%
NMB (WTP=£30,000 per QALY) (£)	
Mean	5,669
SD	30,001
Median	5,206
95% LCL	-52,370
95% UCL	66,049
Probability that therapy is preferred (WTP=£30,000)	
Blinatumomab	57.1%
SOC	42.9%
Ratio of Mean Incremental Cost to Mean Incremental QALYs (£)	
PSA Mean ICER	27,257

CE: cost effectiveness; NMB: net monetary benefit; QALYs: quality adjusted life years; WTP: willingness to pay; LCL: lower confidence level; UCL: upper confidence level; SOC: standard of care; PSA: probabilistic sensitivity analysis; ICER: incremental cost-effectiveness ratio.

A scatter plot of the joint distribution of incremental costs and incremental QALYs from the PSA is shown in Figure 8. There is relatively little correlation of incremental costs and incremental QALYs in the PSA.

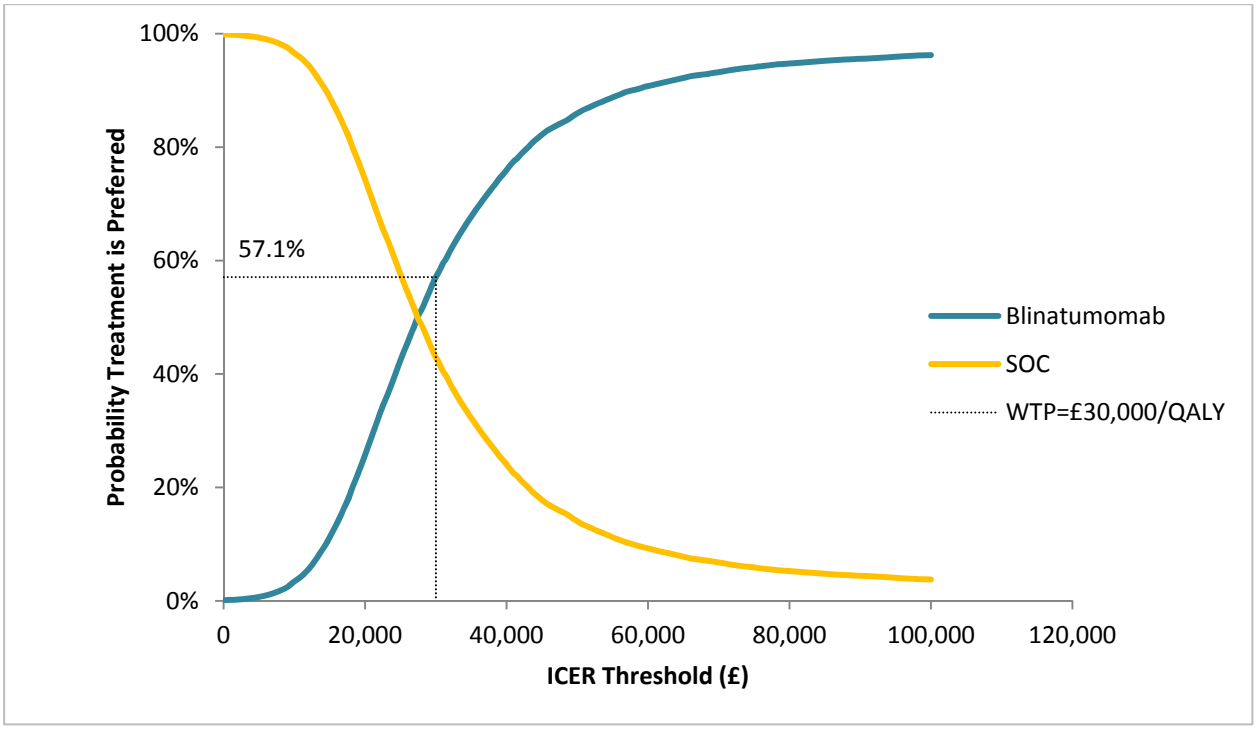
Figure 8. Scatter plot of simulations on cost-effectiveness plane



ICER: incremental cost-effectiveness ratio; QALYs: quality adjusted life years; WTP: willingness to pay; PSA: probabilistic sensitivity analysis; ΔC: incremental costs; ΔQ: incremental quality-adjusted life years.

Cost-effectiveness acceptability curves for blinatumomab and SOC are shown in Figure 9. The probability that blinatumomab is preferred was estimated to be 57.1% given an ICER threshold of £30,000 per QALY.

Figure 9. Cost-effectiveness acceptability curves for blinatumomab and SOC maintenance therapy



ICER: incremental cost-effectiveness ratio; WTP: willingness to pay; SOC: standard of care.

3 CONCLUSION

This analysis, which used a de novo combined decision tree based on MRD response and Markov cohort model with states defined on HSCT, relapse , and salvage treatment, the cost-effectiveness of blinatumomab versus SOC for patients with MRD+ Ph- B-precursor ALL was be £25,645 per QALY gained. The robustness of this analysis should also be noted – in particular, model projections of RFS and OS were very similar to Kaplan Meier estimates throughout the duration of the BLAST trial and results of the model were relatively insensitive to changes in model parameters and assumptions. Of particular significance, model results were similar to the base case when outcomes for patients receiving SOC were estimated based on data from BLAST stratified on MRD response.

In conclusion, the combined decision-tree and Markov cohort model, developed specifically to address the Committee's concerns around the structural limitations of the original partitioned survival model, produces ICER estimates that are broadly consistent with the original modelling approach when the current clinical pathway is reflected. This supports the conclusion that blinatumomab is highly likely to be cost-effective when used earlier in the treatment pathway. Scenario and sensitivity analyses demonstrate that the ICERs in both models are reasonably stable to alternative assumptions for key parameters. In particular, the new Markov model is shown to be robust when implementing the Committee's preferred fixed cure point and assessing the impact of varying the timepoint at which this occurs. Taken together, these results support the conclusion that, although there are uncertainties in the precision of the ICER estimate, the magnitude of the ICER is highly likely to be within the thresholds of cost effectiveness.

4 REFERENCES

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3. Martin PJ, Counts GW, Jr., Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol. 2010;28(6):1011-6.
4. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA oncology. 2017:e170580.
5. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 (PMG9). Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed: 4 August 2017.

1 APPENDICES

1.1 BLAST MRD Responders

Figure 10. Fit Statistics for Survival Distributions for Time to HSCT from CR1, BLAST MRD Responders

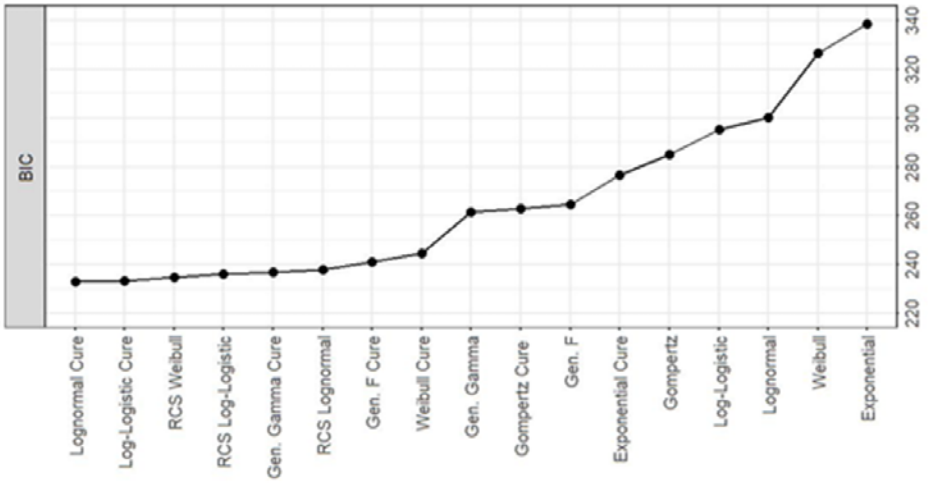

Figure 11. Best Fitting Survival Distributions for Time to HSCT from CR1, BLAST MRD Responders

Figure 12. Fit Statistics for Survival Distributions for Time to Relapse from CR1, BLAST MRD Responders

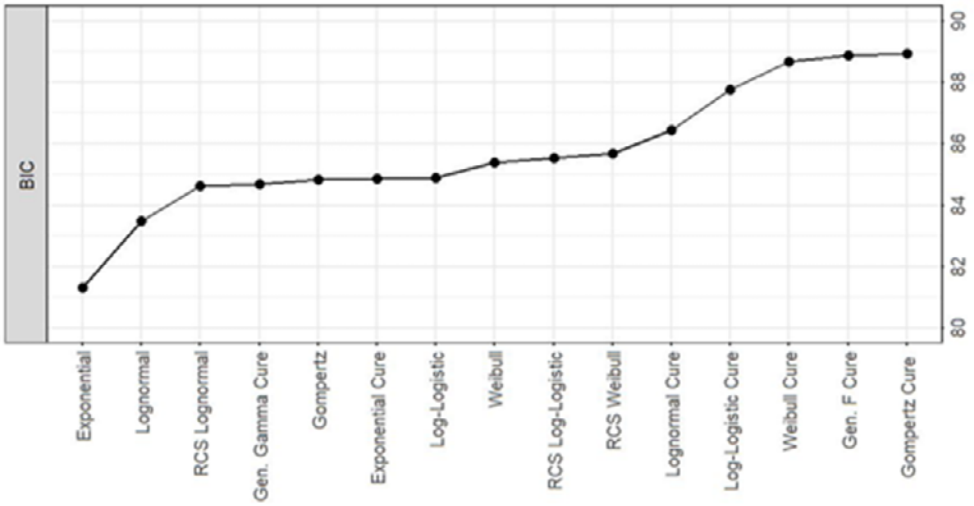

Figure 13. Best Fitting Survival Distributions for Time to Relapse from CR1, BLAST MRD Responders

Figure 14. Fit Statistics for Survival Distributions for Time to Death from CR1, BLAST MRD Responders

Only one event.

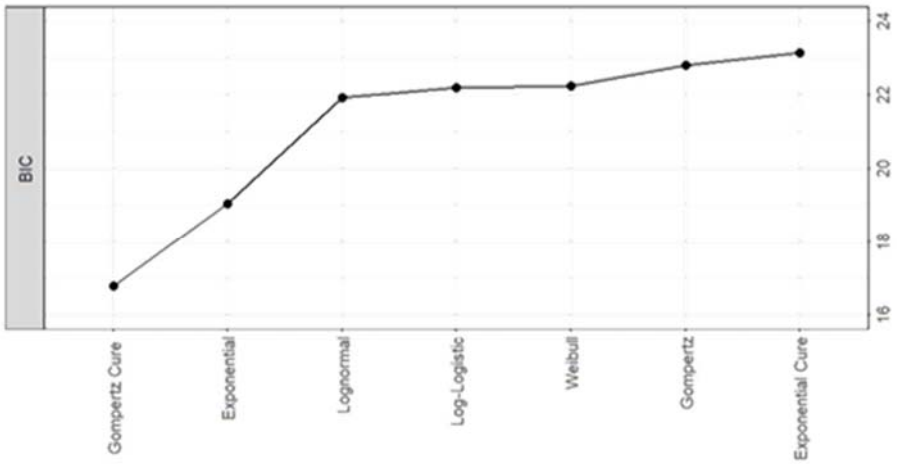

Figure 15. Best Fitting Survival Distributions for Time to Death from CR1, BLAST MRD Responders

Only one event.

[redacted]

m HSCT, BLAST MRD

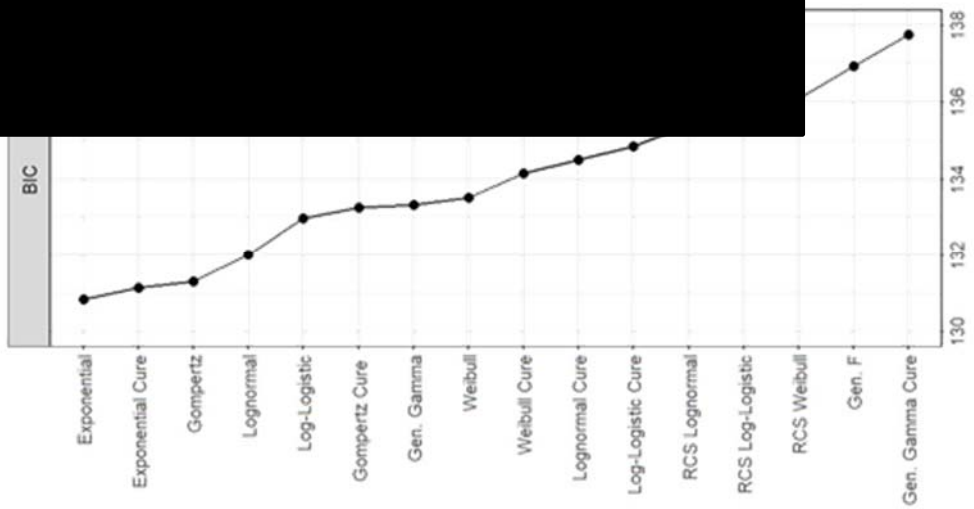

Figure 17. Best Fitting Survival Distributions for Time to Relapse from HSCT, BLAST MRD Responders

[redacted]

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Figure 18. Fit Statistics for Survival Distributions for Time to Death from HSCT, BLAST MRD Responders

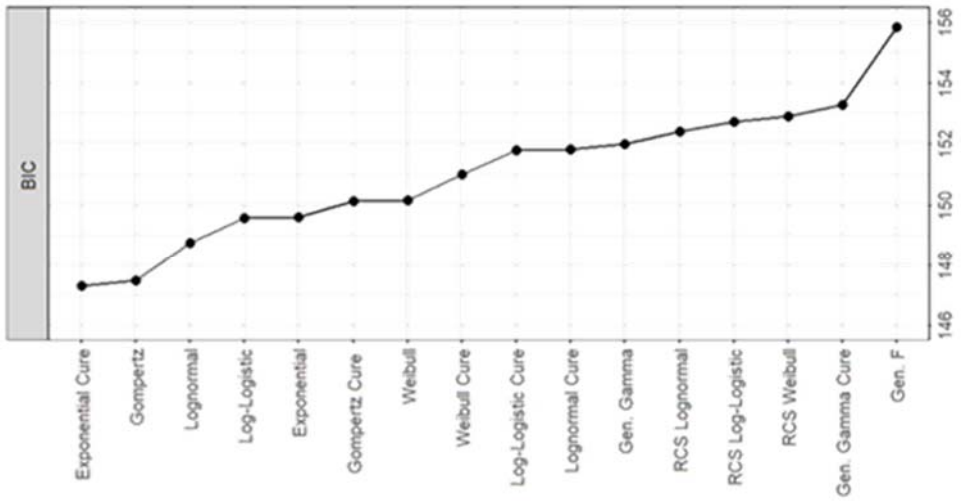


Figure 19. Best Fitting Survival Distributions for Time to Death from HSCT, BLAST MRD Responders

[redacted]

1.2 BLAST MRD Non-Responders

Figure 20. Fit Statistics for Survival Distributions for Time to HSCT from CR1, BLAST MRD Non-Responders

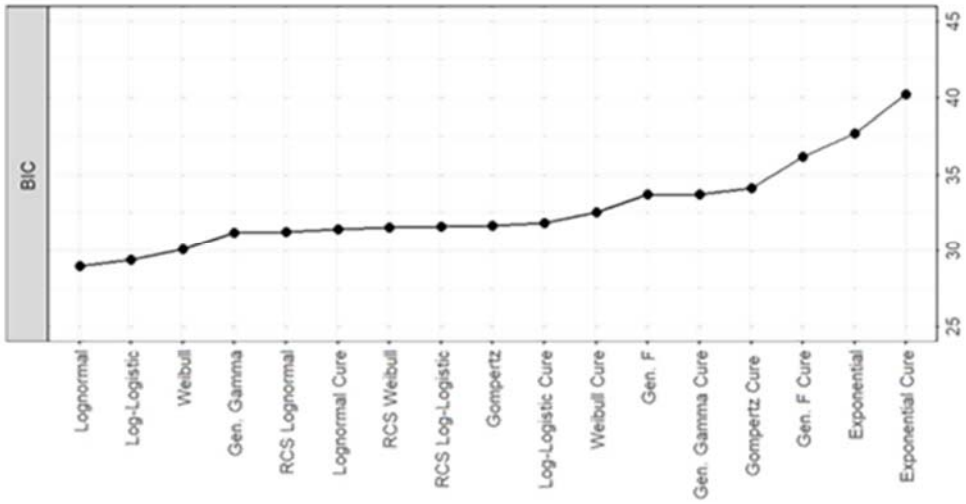


Figure 21. Best Fitting Survival Distributions for Time to HSCT from CR1, BLAST MRD Non-Responders

[redacted]

om CR1, BLAST MRD

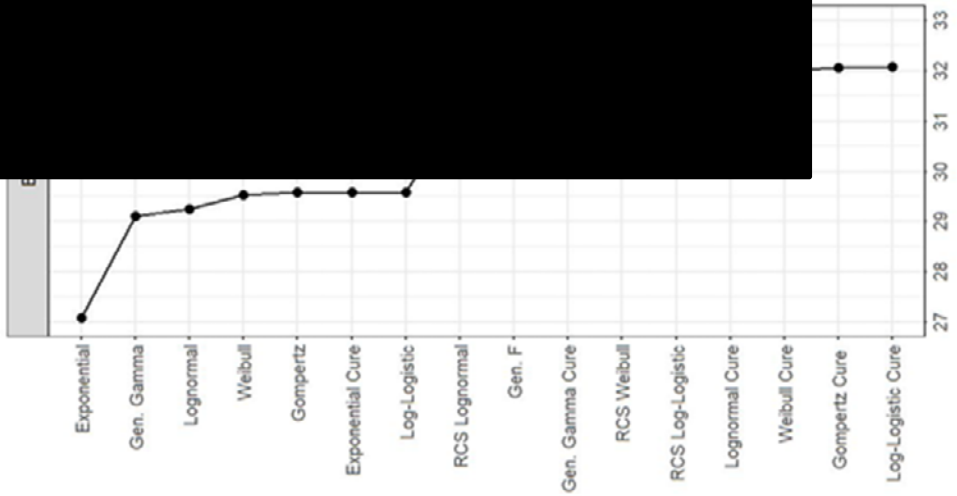


Figure 23. Best Fitting Survival Distributions for Time to Relapse from CR1, BLAST MRD Non-Responders

[redacted]

036]

Figure 24. Fit Statistics for Survival Distributions for Time to Death from CR1, BLAST MRD Non-Responders

Only one event.

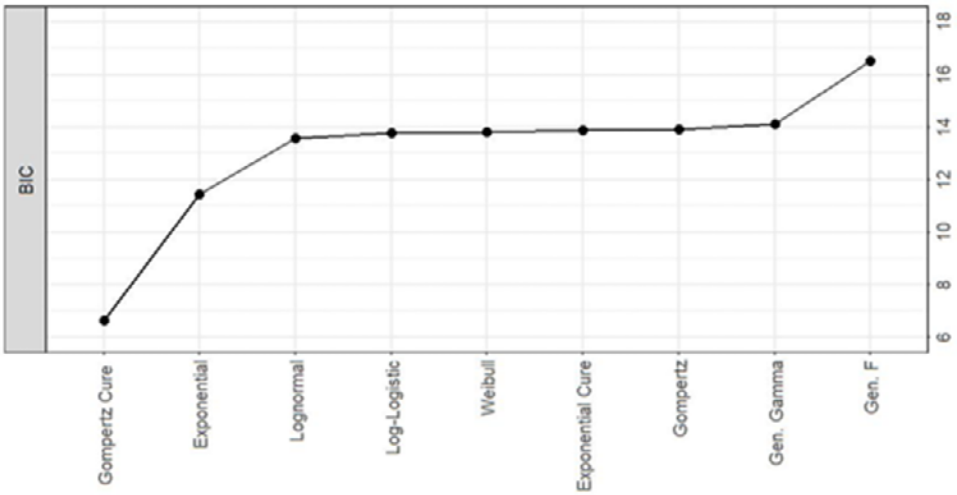


Figure 25. Best Fitting Survival Distributions for Time to Death from CR1, BLAST MRD Non-Responders

Only one event.

[redacted]036]

Figure 26. Fit Statistics for Survival Distributions for Time to Relapse from HSCT, BLAST MRD Non-Responders

No events.

Figure 27. Best Fitting Survival Distributions for Time to Relapse from HSCT, BLAST MRD Non-Responders

No events.

Figure 28. Best Fitting Survival Distributions for Time to Death from HSCT, BLAST MRD Non-Responders

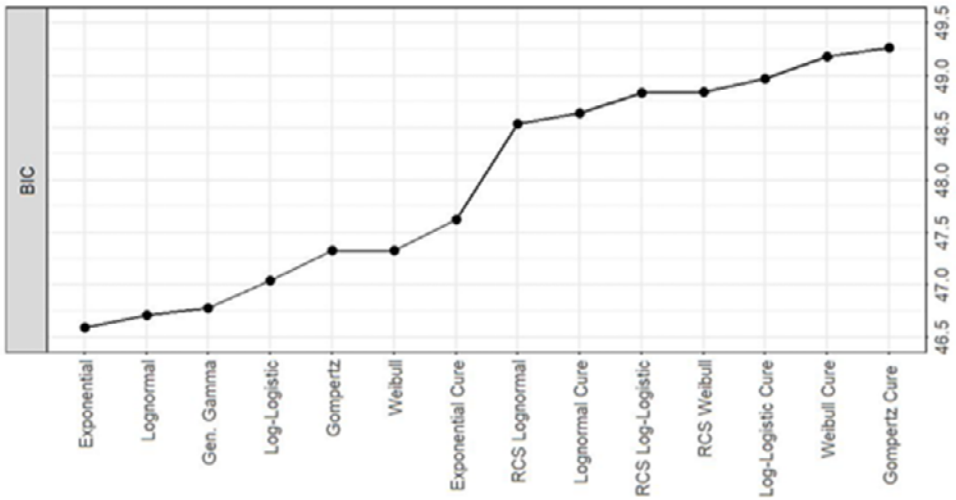


Figure 29. Fit Statistics for Survival Distributions for Time to Death from HSCT, BLAST MRD Non-Responders

[redacted]036]

Figure 30. Fit Statistics for Survival Distributions for Time to HSCT from CR1, Historical Control/SOC

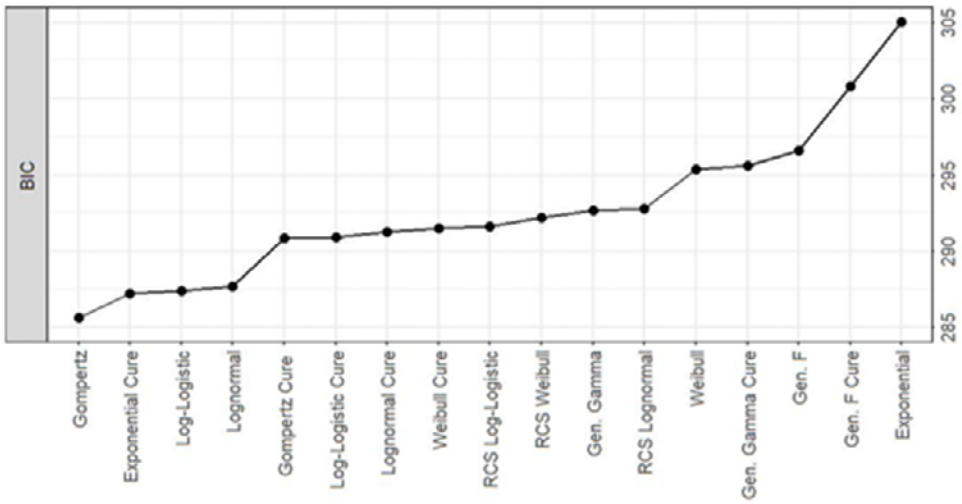


Figure 31. Best Fitting Survival Distributions for Time to HSCT from CR1, Historical Control/SOC

[redacted]

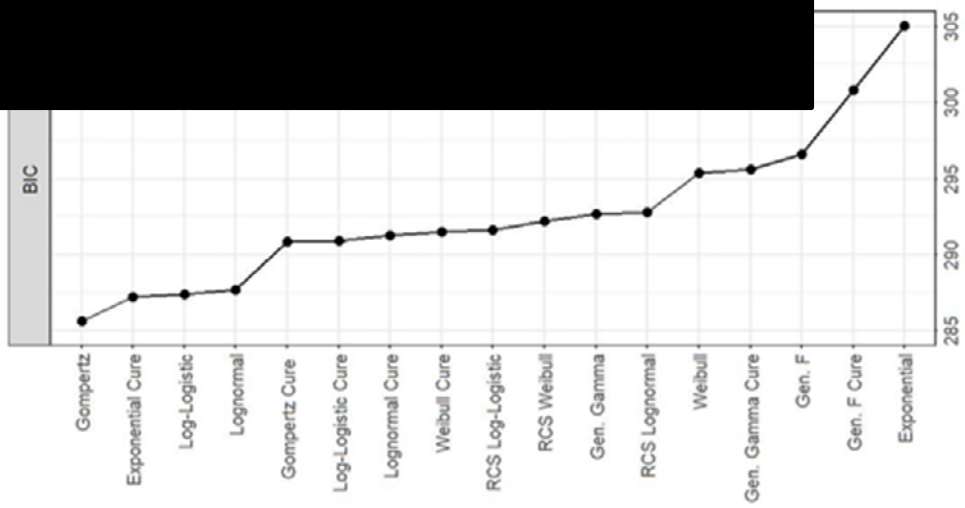


Figure 25. Best Fitting Survival Distributions for Time to Relapse from CR1, Historical Control/SOC

[redacted]

from CR1, Historical

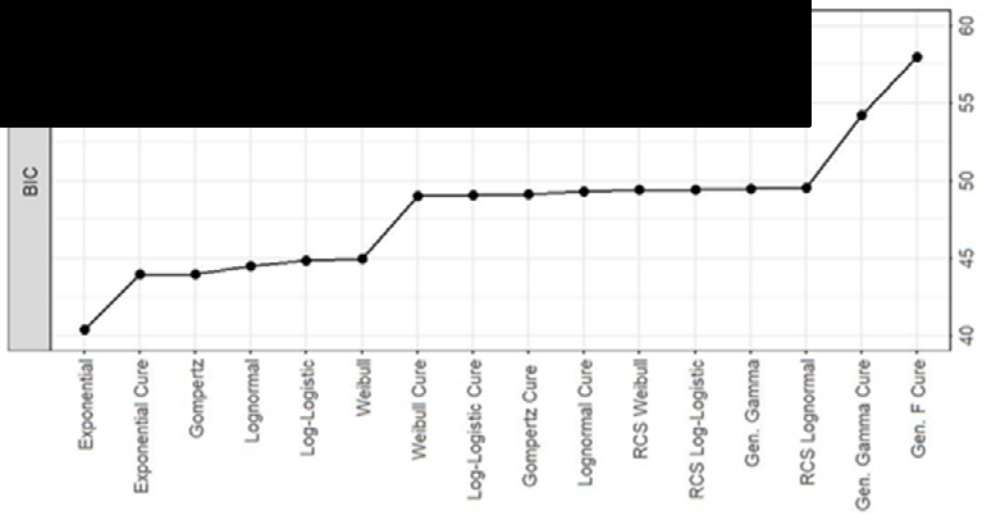


Figure 27. Best Fitting Survival Distributions for Time to Death from CR1, Historical Control/SOC

[redacted]

Figure 28. Fit Statistics for Survival Distributions for Time to Relapse from HSCT, Historical Control/SOC

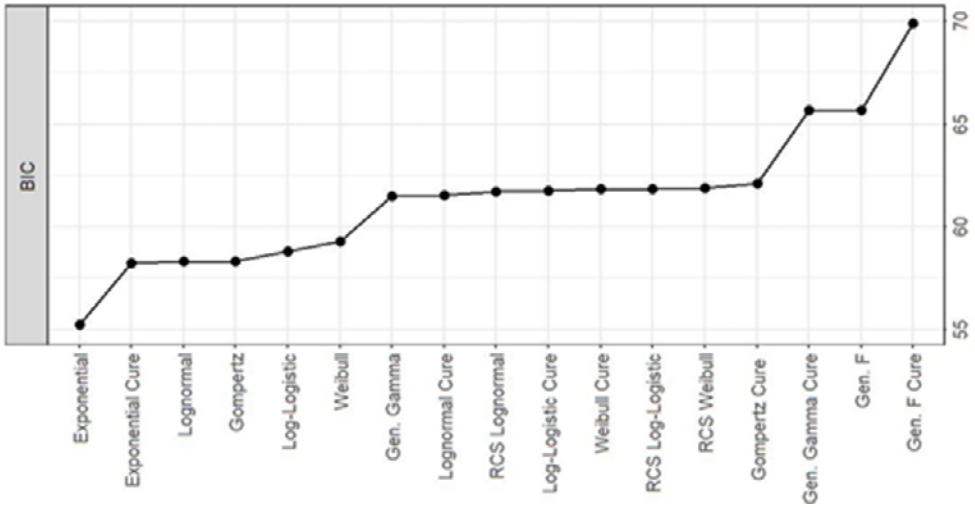


Figure 29. Best Fitting Survival Distributions for Time to Relapse from HSCT, Historical Control/SOC

[redacted]

rom HSCT, Historical

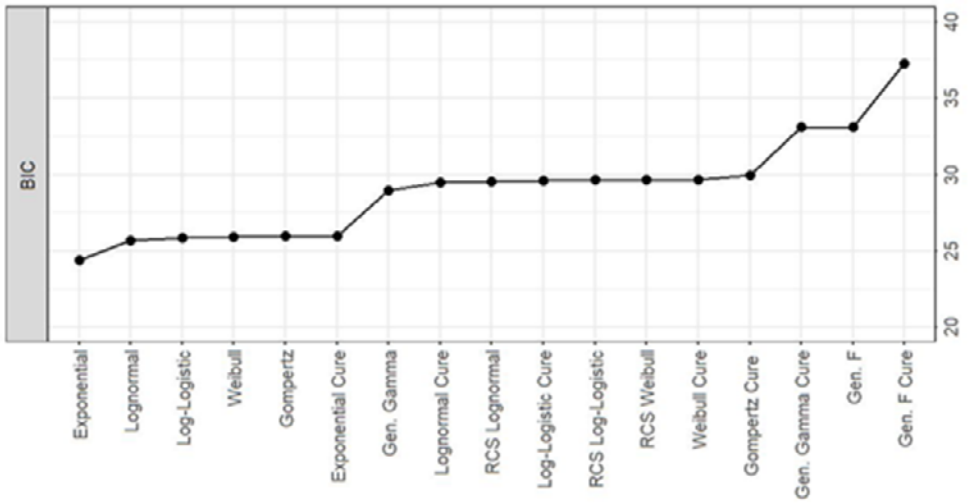


Figure 31. Best Fitting Survival Distributions for Time to Death from HSCT, Historical Control/SOC

[redacted]

036]

1.4 TOWER / Relapsed Patients

Figure 30. Fit Statistics for Survival Distributions for Time to Relapse from Death using matched TOWER data

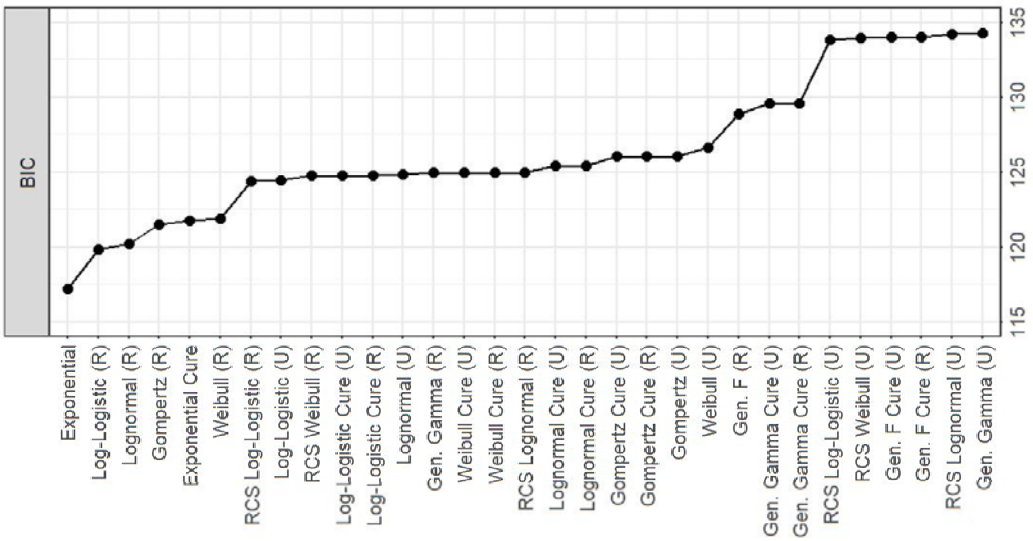


Figure 31. Best fitting Statistics for Survival Distributions for Time to Relapse from Death using matched TOWER data

Additional Clarification Questions

1. **Where have the costs of blinatumomab/IO for relapse been taken from. Please could you provide details about which documents these are sourced from (including page numbers)?**

Inotuzumab

Parameter	Input(s)	Total Cost	Description/Source
Drug costs	9.49 vials £8,048	76,376	An average of 9.49 vials were administered over the course of inotuzumab therapy in INO-VATE. *NICE STA Committee Papers. Inotuzomab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]. June 13, 2017* [**Page 36 of Manufacturer Submission**]
Inpatient costs	[redacted] days *805.10 per day	9,041	Inpatient Stay During Inotuzumab appraisal clinical experts provided the committee with real-life data from Bristol and UCLH showing the combined effect of the 3 factors described above on duration of in-patient stay. The mean days for in-patient stay for inotuzumab was [redacted] cycles delivered as an out-patient). This assumption formed the basis of the Committee preferred base case. Data was originally presented in the Committee Papers but has subsequently been redacted as AIC. Inpatient Cost Weighted averaged of NHS reference costs for elective inpatient stays for the following HRG codes: • SA24G - Acute Lymphoblastic Leukaemia with CC Score 5+; • SA24H- Acute Lymphoblastic Leukaemia with CC Score 2-4; and

			• SA24J-Acute Lymphoblastic Leukaemia with CC Score 0-1.
Total		**85,417**	

Blinatumomab

The cost of blinatumomab salvage therapy was taken from the manufacturer's submission for the NICE STA of blinatumomab for R/R Ph- ALL patients based on the TOWER trial, and included the cost of blinatumomab medication ([redacted]), and administration ([redacted]).

Specifically, this was reported in Table 5-29 of Manufacturer Submission, page 200 (shown below).

Table Error! No text of specified style in document.**-1. Summary of predicted resource use by category of cost, patients with no prior salvage therapy**

	Blinatumomab (£)	**FLAG-IDA (£)**	**Incremental (£)**	**Absolute incremental (£)**	**Absolute Incremental %**
Salvage therapy					
Medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Administration					
Inpatient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pump	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total salvage therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
allo-SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent salvage therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	**127,315**	**147,850**	**100.0**
allo-SCT, allogenic stem cell transplant; FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin.					

2. What is the date of the last data cut used in the updated models (both BLAST & TOWER)?

- Partitioned Survival Model: Data Cut – As per original submission, 5th August 2015
- Updated Markov Model: Using the latest BLAST data cut taken on 1st June 2017 andpresented at the American Society of Hematology 60th Annual Meeting, December 1–4 2018

Not on HSCT post-relapse costs

HSCT is currently included before and after relapse and the cost of HSCT after relapse is presented in Table 6 of the report (see below). The costs of HSCT post relapse amounted to [redacted] for the blinatumomab strategy and [redacted] for SOC strategy. The difference in costs is explained by the longer time spent in the post relapse state for patients receiving initial SOC treatment (0.86 vs 2.04 discounted life years).

Table 1. Base case expected costs results

Cost Category	Blinatumomab (£)	SOC (£)	Incremental (£)
Pre-relapse			
Blinatumomab and SOC maintenance treatment			
Medication	[redacted]	[redacted]	[redacted]
Administration			
Hospitalization	[redacted]	[redacted]	[redacted]
Outpatient visits	[redacted]	[redacted]	[redacted]
Infusion pump	[redacted]	[redacted]	[redacted]
Total medication and administration	[redacted]	[redacted]	[redacted]
Allo-SCT	[redacted]	[redacted]	[redacted]
Other inpatient	[redacted]	[redacted]	[redacted]
Other outpatient pre-relapse	[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]	54,264

The post relapse cost calculation can be detailed as followed.

<u>Post relapse HSCT proportion</u>

The post relapse HSCT proportion is estimated considering the probability of receiving HSCT conditional on prior HSCT based on historical control study (Protocol 20120310; Clinicaltrials.gov:

NCT02003612). The probability of receiving HSCT post relapse is then calculated accounting for the proportion of relapse from CR and from HSCT respectively over the full model. This proportion of HSCT among relapse patient is assumed to be constant across the cycles. In the base case, the proportion of patient receiving HSCT post relapse is estimated to be:

- 18% for Blin MRD-
- 20% for Blin MRD+
- 19% for SOC

Post relapse HSCT costs

The cost of HSCT is then calculated as the sum of the initial costs and the per cycle costs. The initial costs are applied as the product of the proportion of relapse in the first cycle of HSCT, the post relapse HSCT proportion and the initial cost of HSCT. The per cycle HSCT follow-up costs are applied as the product of the proportion of relapse in each cycle, the post-relapse HSCT proportion and the follow-up cost of HSCT per cycle. These costs are then summed to calculate the total cost of HSCT post-relapse. Alternatively, the model has the option to calculate HSCT costs using the pre-relapse HSCT costs. If this option is selected, the post-relapse HSCT costs are calculated by multiplying the proportion of patients who relapsed and the post-relapse HSCT proportion by the expected pre-relapse cost of HSCT per patient. The model does not differentiate between survival for patients who did or did not receive HSCT after relapse.

Post-Relapse Survival Estimation Using TOWER Data

Of the 73 BLAST CR1 patients, 22 patients relapsed before death. Among the 22 patients 13 had remission duration less than 12 months and 9 patients had a remission duration more than 12 months. Since TOWER inclusion criteria specify that patients with no prior salvage therapy must have relapsed within 12 months of remission, these 9 BLAST patients are not represented in TOWER study and were excluded from the matching exercise.

From TOWER, 78 BLIN patients and 39 SOC patients in S0 cohort were matched with 13 BLAST patients based on age and their receipt of HSCT (at baseline among TOWER patients and prior to relapse among BLAST patients). BLAST patients were weighted to achieve balance with the historical cohort study patients with stabilized ATE weights.

Table 1. Characteristics of BLAST patients who relapsed before death vs TOWER patients (unweighted)

	Relapsed BLAST patients N (%)		TOWER BLIN patients N (%)		TOWER SOC patients N (%)	
N	13	(100)	78	(100)	39	(100)
Age						
≥ 18 and < 35 years	3	(23.1)	23	(29.5)	14	(35.9)
≥ 35 and < 55 years	4	(30.8)	26	(33.3)	12	(30.8)
≥ 55 and < 65 years	4	(30.8)	11	(14.1)	8	(20.5)
≥ 65 years	2	(15.4)	18	(23.1)	5	(12.8)
With HSCT	4	(30.8)	33	(42.3)	17	(43.6)

Logistic regression models were estimated among the above 13 BLAST and either 78 TOWER BLIN or 39 TOWER SOC patients. Using the estimated predicted probability of being in BLAST (vs TOWER BLIN or SOC), ATT weights were calculated for 78 TOWER BLIN patients and 39 TOWER SOC patients, and Kaplan-Meier estimates for survival were calculated among TOWER BLIN and SOC patients with ATT weights.

Unweighted and weighted Kaplan-Meier estimates for survival are shown in the figured below.

Figure 1. TOWER Unweighted Kaplan-Meier estimates of time to event

Figure 2.TOWER Weighted Kaplan-Meier estimates of time to event

Figure ATT_HSCT
Kaplan-Meier estimates of time to event

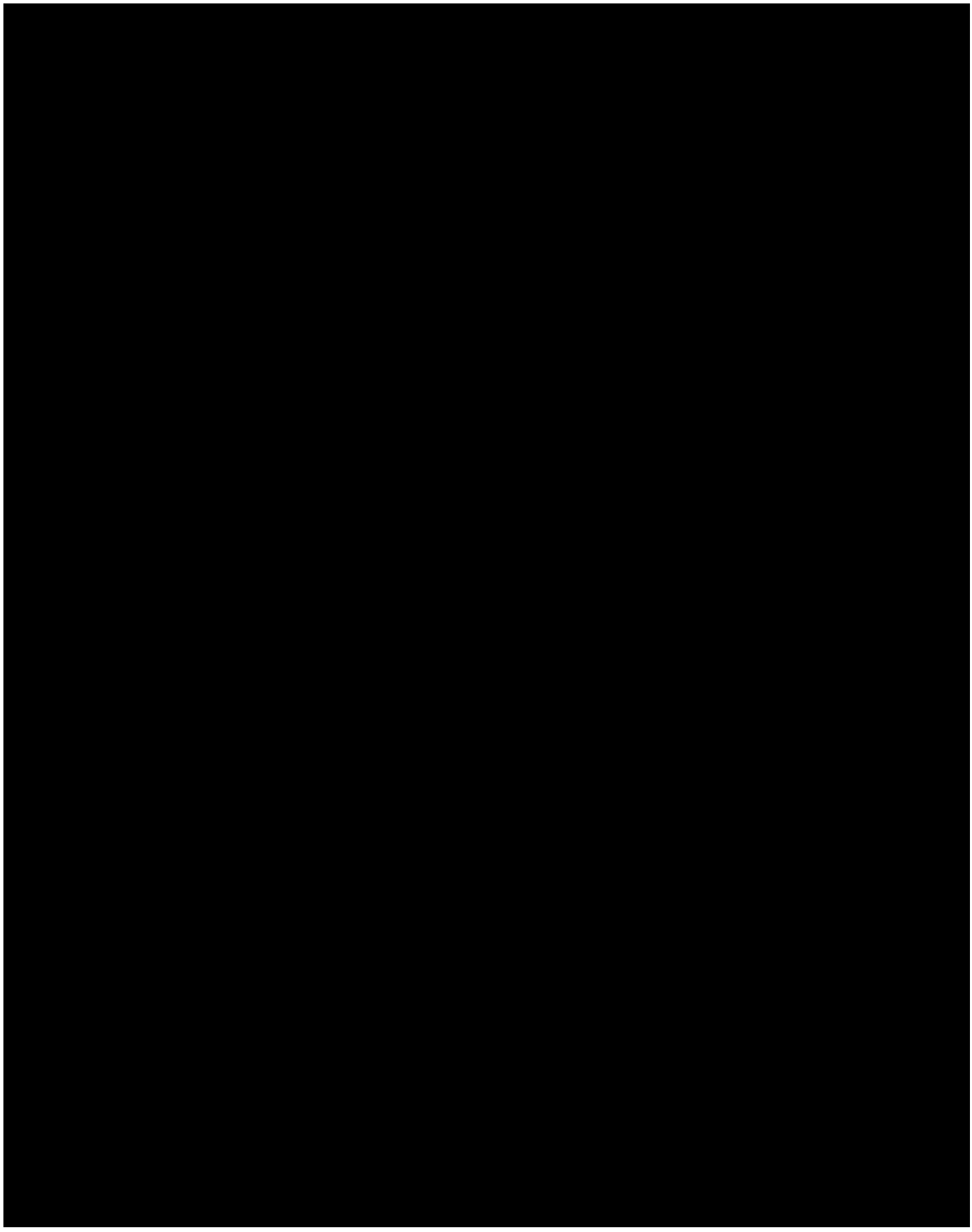


Figure ATT_RLPS
Kaplan-Meier estimates of time to event

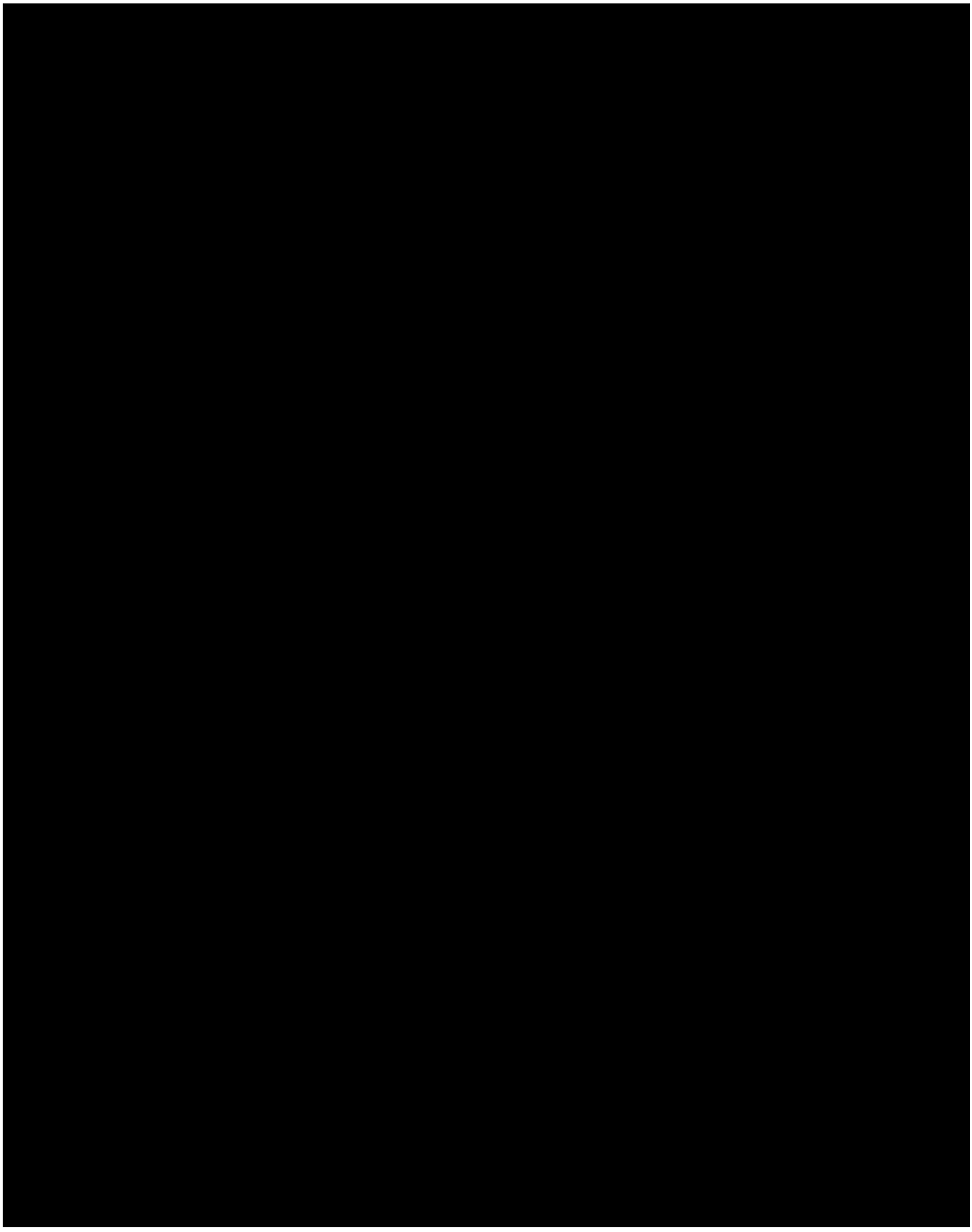


Figure ATT_DTH
Kaplan-Meier estimates of time to event

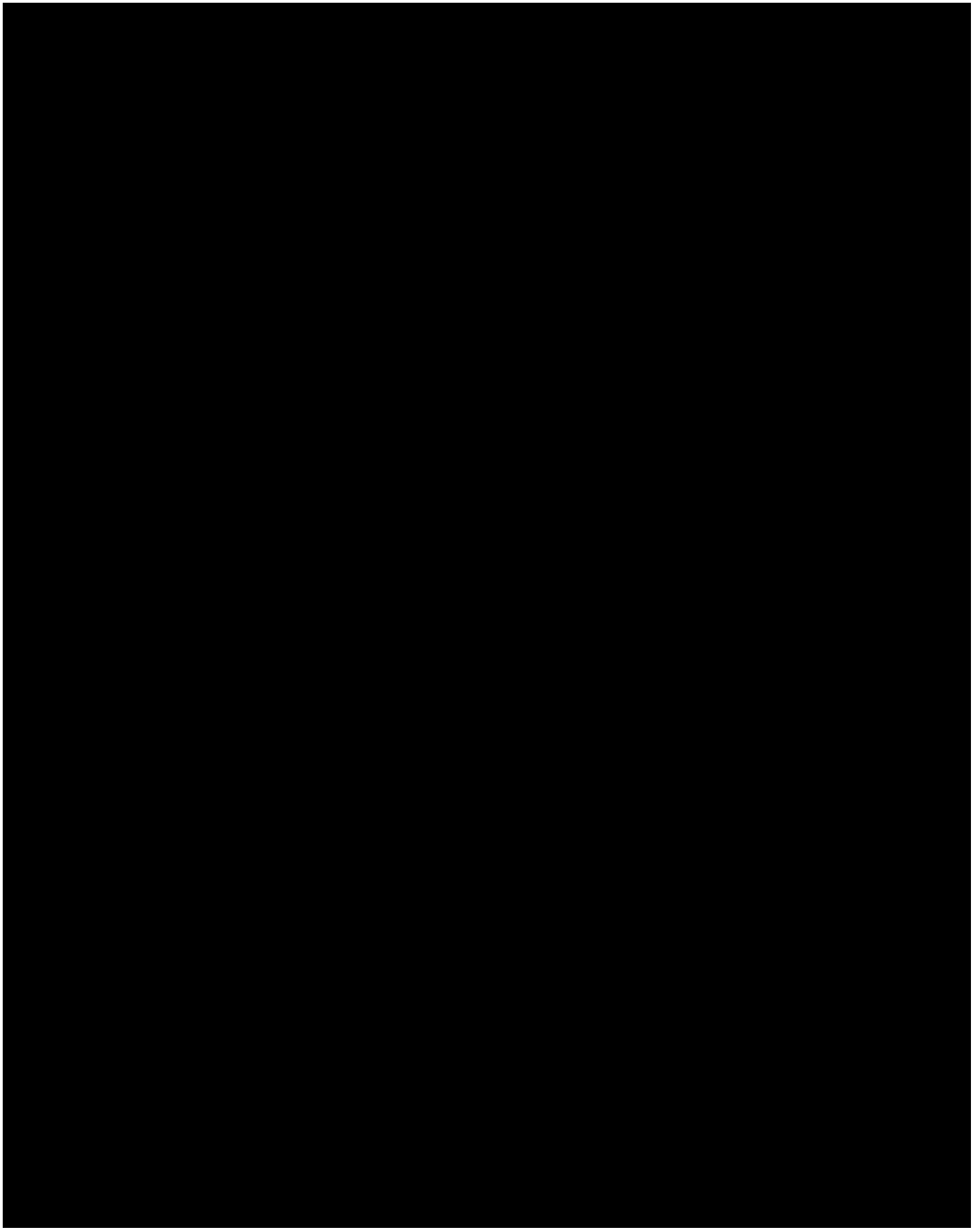


Figure ATT_RLPS Post HSCT
Kaplan-Meier estimates of time to event

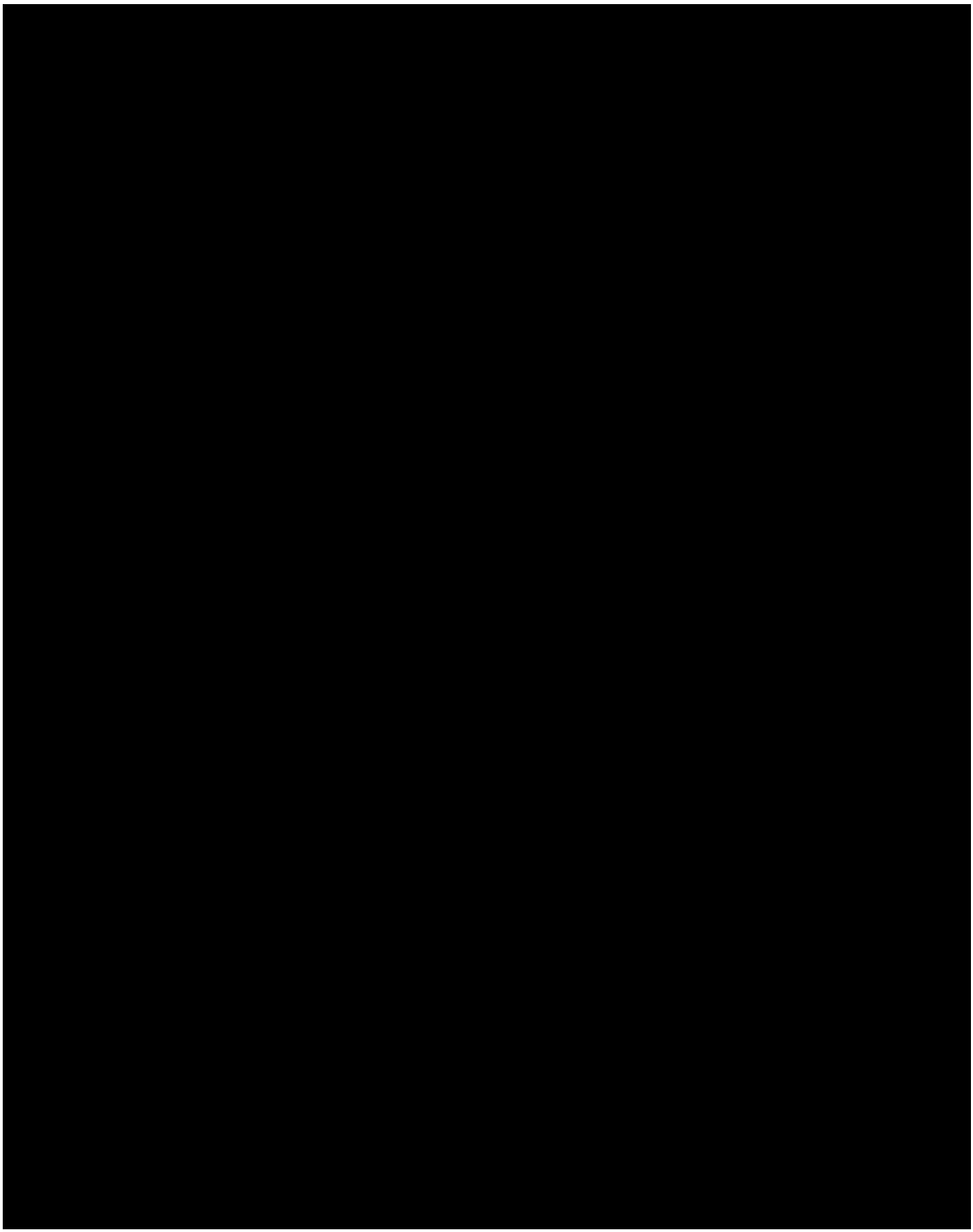


Figure ATT_DTH Post HSCT
Kaplan-Meier estimates of time to event

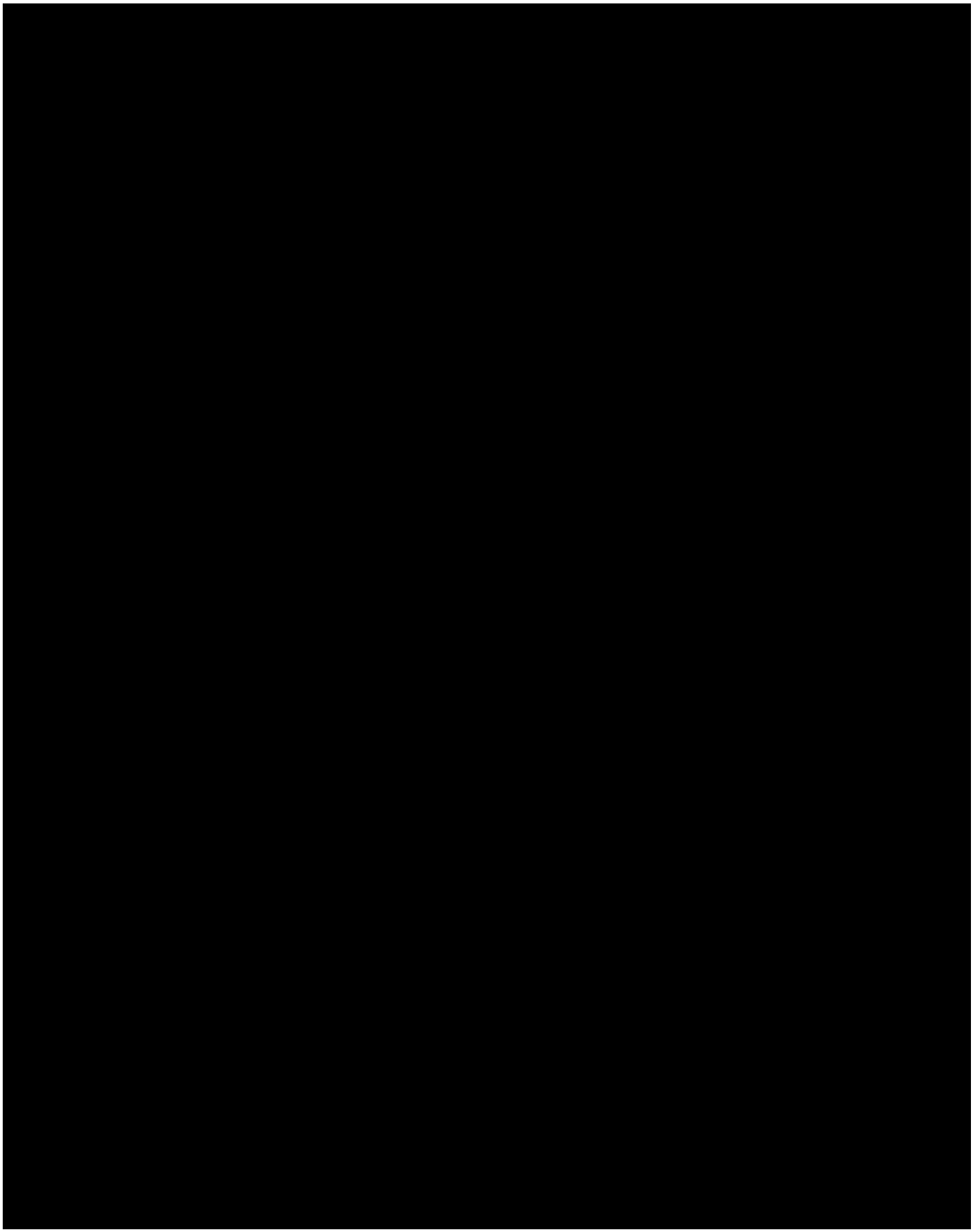
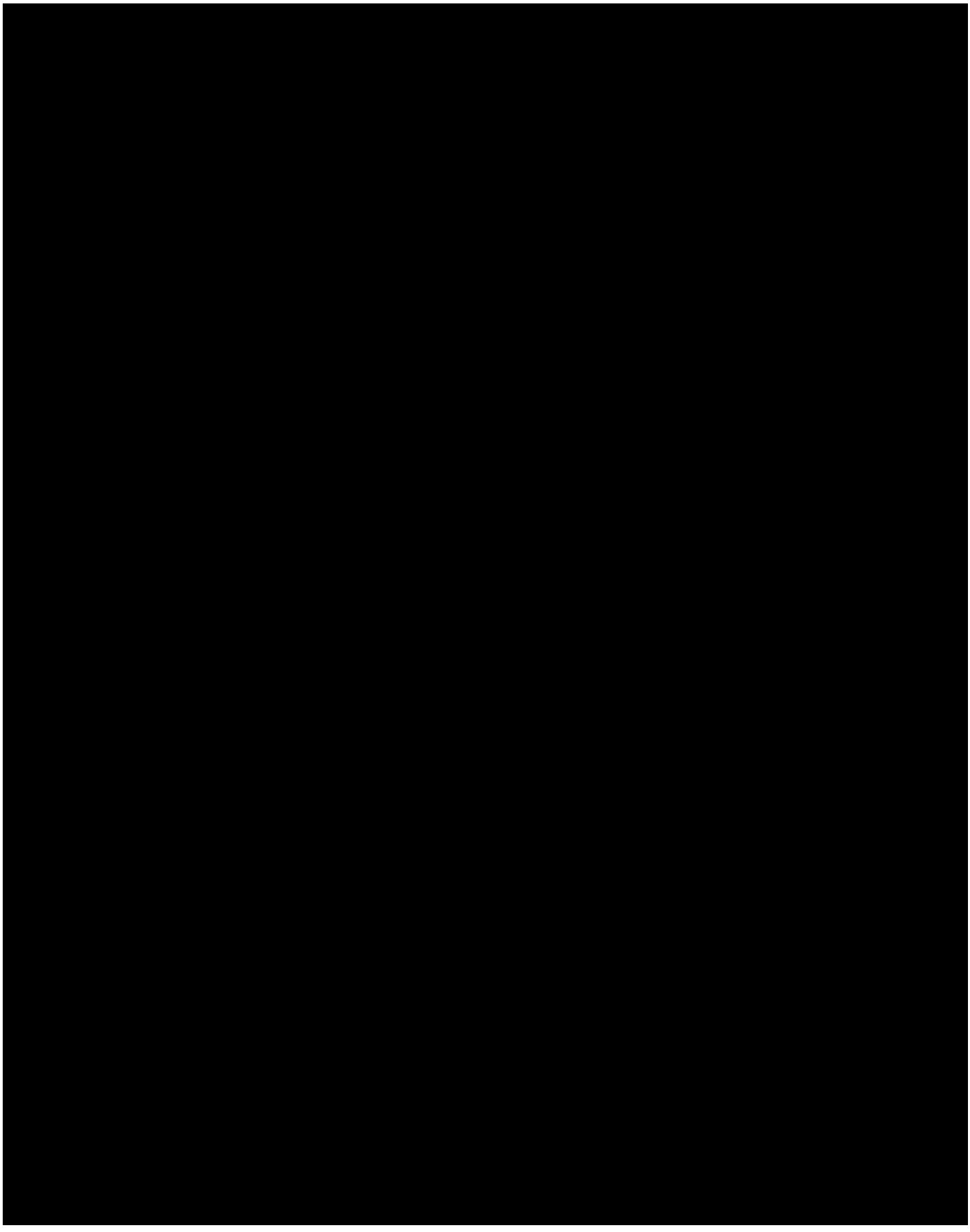


Figure ATT_DTH Post RLPS
Kaplan-Meier estimates of time to event



UKALL 14 transplant and MRD data

Background to the data presented

UKALL 14 (NCT01085617, open 2010-2018) has completed recruitment, but for some patients, therapy is ongoing and some data is not yet available. Below is a listing showing the treatment given for patients who had an MRD positive/negative result at our key stratification time point as well as survival data.

It's relevant that the NICE committee be aware that our UKALL14 MRD stratification timepoint is immediately after the second induction, namely after two courses of intensive chemotherapy. Patients must subsequently undergo either 5 more courses of consolidation therapy plus two years of maintenance OR one more course of therapy followed by allogeneic stem cell transplant (alloSCT).

Of note, patients with MRD positive ALL at our relevant timepoint were allowed by the BLAST study to be enrolled at this timepoint as the amount of therapy received was deemed equivalent to the '3 courses' eligibility stated in BLAST eligibility criteria. Two such patients are noted below and are excluded from survival analyses.

It is important to note the other 'high risk' factors such as well as MRD were used to allocate transplant on the UKALL14 protocol – presenting white cell count, certain genetic abnormalities and age >40 years. For this reason, we are able to analyse the outcome data of those who proceeded to allo but had achieved MRD negativity despite the ALL having other high-risk features. This makes the analysis quite powerful in showing the predictive value of the MRD measurement for less good alloSCT outcome among a group of patients who are already considered to have high risk ALL for other reasons. The hazard ratios for all of the outcome measures are all around [redacted] and are [redacted] giving a [redacted] indicator of the magnitude of the impact which we hope will assist in modelling relevant scenarios based on the activity of blinatumomab in the BLAST study.

456 patients aged 25-65 years with B-cell Ph- ALL were recruited to UKALL14

- 103 were MRD negative at the informative timepoint
- 37 had a positive outside quantitative range (POQR) result - these are grouped with MRD negative for the analysis because 1) they were treated as negative 2) prior data shows the outcome of patients with a POQR result segregates with negative
- 67 had an indeterminate result. This means that MRD was detected but that the patient specific assay developed didn't meet the require standard to give out a quantitative result. Again, these patients are grouped with MRD negative for analysis because they were treated as MRD negative per protocol as it was felt inappropriate to escalate therapy on the basis of an indeterminate result. However, they differ from those with POQR as in MRD was definitely detected
- [redacted] were MRD positive at the informative timepoint
- [redacted] were not assessable for MRD at the key timepoint (due to variety of reasons ranging from died of therapy toxicity, through to not assessable for MRD due to specimen issues). They are excluded from these analyses.

Patients with MRD positive ALL (N= [redacted]) : subsequent treatment allocations

Stem cell transplant (SCT): N=[redacted]
SCT after Blinatumomab N= [redacted] (these were two patients who went from UKALL14 to the BLAST study due to high level MRD)
SCT Without Blinatumomab N=[redacted]

Currently unknown: N=[redacted]
SCT planned: [redacted]
No treatment allocation yet known: [redacted]

No SCT: N=[redacted]
Further consolidation and maintenance chemo only: [redacted]
Relapsed during intensification or consolidation: [redacted]

Patients with MRD negative ALL (N=[redacted]) : subsequent treatment allocations

Died post phase 2 induction N=[redacted]

SCT: N=[redacted]
SCT N=[redacted]

Currently unknown: N=[redacted]
SCT planned: [redacted]
Currently unknown: [redacted]

No SCT: N=[redacted]
Further consolidation and maintenance chemo only: [redacted]
Relapsed or died during intensification or consolidation: [redacted]

1. **Proportion of patients (N=[redacted])who were MRD positive and proceeded to SCT**
   - [redacted] Myeloablative Conditioned (MAC) SCT
   - [redacted] Reduced Intensity Conditioned (RIC) SCT
   - [redacted] unknown (no allocation form but SCT was given)
   - [redacted] off trial - had been given blinatumomab as per BLAST study between induction and SCT
   - [redacted] off trial having had a haploidentical SCT wich was not allowed per protocol

A further six patients were allocated SCT as per protocol but we do not yet have data as to whether they have been given as the forms have not yet been returned

- Registered for a MAC, N=[redacted]
- Off trial for a non-protocol mismatched unrelated donor SCT, N=[redacted]
- Non-trial protocol haploidentical SCT, N=[redacted]
- Non-trial additional bridging chemo as currently unfit for TBI (plan was to proceed to SCT when fit enough), N=[redacted]

Overall, [redacted] ([redacted]) have been confirmed as having received SCT. Potential increase to maximum of [redacted] ([redacted]) when all data available

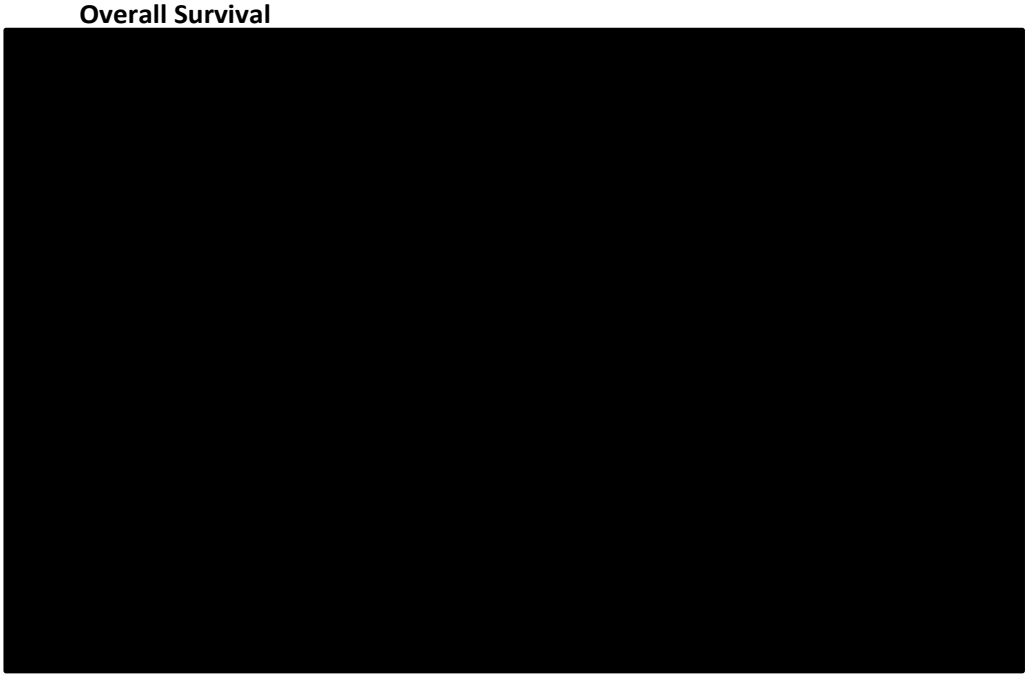
2. EFS, OS and RR for patients undergoing any time of HSCT - split by MRD positive/negative
   The two patients given Blinatumomab as per BLAST study pre SCT have been excluded
   Any patients where we do not yet have evidence that an allocated transplant was definitely given have also been excluded

	Events/N	HR (95% CI)	p-value	3 year rate
EFS*				
MRD negative	[redacted]	[redacted]	[redacted]	[redacted]
MRD positive	[redacted]	[redacted]		[redacted]
OS				
MRD negative	[redacted]	[redacted]	[redacted]	[redacted]
MRD positive	[redacted]	[redacted]		[redacted]
Relapse risk				
MRD negative	[redacted]	[redacted]	[redacted]	[redacted]
MRD positive	[redacted]	[redacted]		[redacted]

All endpoints are measured from the date of randomisation. *Events are relapse or death.

Event Free Survival

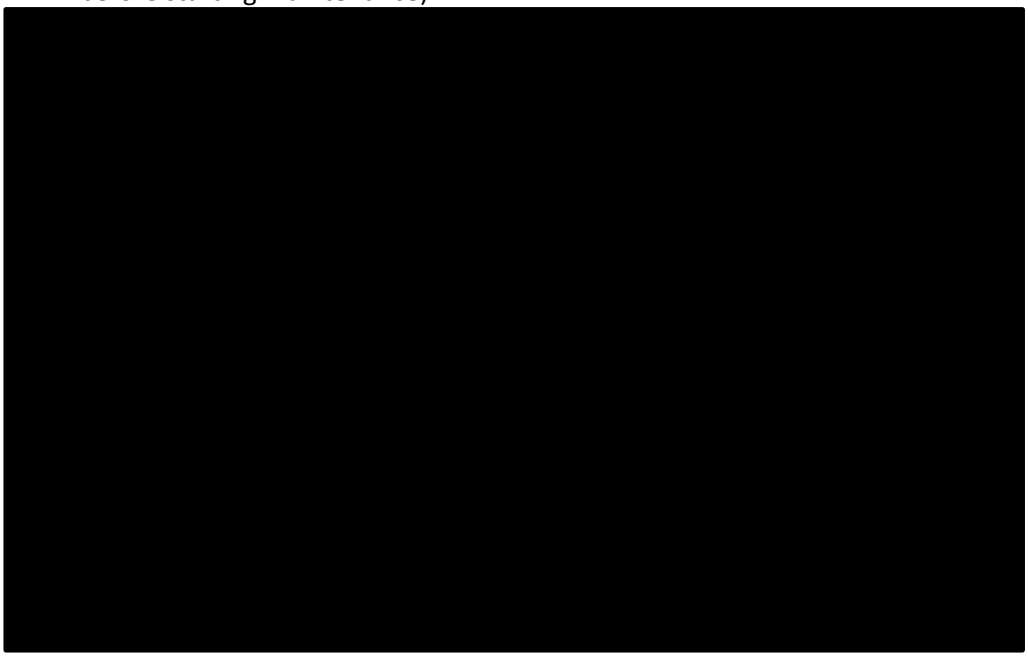
Overall Survival



Time to relapse

3) Outcome for MRD +/- who do not proceed to HSCT

EFS – patients treated with chemo only post induction (includes patients who relapsed or died before starting maintenance)



Overall Survival

Time to relapse

Blinatumomab for acute lymphoblastic leukaemia for people with minimal residual disease activity in remission: A Single Technology Appraisal

Addendum - ERG critique of additional evidence submitted by the company

Paul Tappenden, Professor of Health Economic Modelling

Andrew Metry, Research Associate

Daniel Pollard, Research Associate

ScHARR, University of Sheffield

30th April 2019

1. Introduction

In February 2019, the NICE Appraisal Committee published its Appraisal Consultation Document[1] (ACD) on the use of blinatumomab for treating acute lymphoblastic leukaemia (ALL) in remission with minimal residual disease (MRD) activity. The recommendation given in the ACD is as follows: *"The committee was minded not to recommend blinatumomab as an option for treating acute lymphoblastic leukaemia in adults with Philadelphia chromosome-negative CD19-positive B-precursor whose disease is in first or second complete remission with minimal residual disease (MRD) of at least 0.1%."* (NICE ACD,[1] February 2019).

The NICE ACD[1] requested that the company provide further clarification and analyses. According to the ACD, these should include:

- A revised cost-effectiveness analysis reflecting the current treatment pathway and comparing blinatumomab with standard care. The revised economic model should:
    - Include costs, health-related quality-of-life (HRQoL) estimates and outcomes associated with the current treatment pathway for people with relapsed or refractory (R/R) ALL
    - Include the proportion of people with and without MRD after blinatumomab treatment and how many have haematopoietic stem cell transplantation (HSCT)
    - Incorporate an explicit causal link between the probability of HSCT and relapse-free survival (RFS) and overall survival (OS) in both groups
    - Explicitly model a cure for people whose disease is expected to be cured and include scenario analyses considering different cure fractions and cure points
    - Factor in the different positions in the treatment pathway at which HSCT might be given
- The latest available evidence on survival outcomes after HSCT
- The latest trial data cut.

In April 2019, the company submitted two health economic models: (i) an updated version of their partitioned survival model, and (ii) a new semi-Markov model. The company also submitted a general ACD response document[2] and two appendices[3, 4] which describe the methods and results of the updated/new models. At the request of the ERG, the company submitted further documentation which provides additional detail regarding various aspects of the new/updated models (costing estimates, weighted Kaplan-Meier curves by event and further details on the weighting of TOWER patients).[5]

This ERG addendum provides a brief summary of the new/updated models, together with a critique of the main issues identified within each model. It should be noted that a Patient Access Scheme (PAS) is in place for inotuzumab ozogamicin (IO). The analyses presented in this addendum reflect the list price for this product. The results of all analyses including the PAS for IO are contained in a separate confidential appendix.

2. Company's updated partitioned survival model

2.1 Overview of the company's updated partitioned survival model

The company's original partitioned survival model is described in detail in the company's submission[6] (CS) and the ERG report.[7] The company's updated partitioned survival model uses the same structure and parameters as the analysis previously presented in the CS[6] (referred to by the company as their "key scenario analysis"). The company's key scenario analysis uses the base case model and simply adds on an incremental cost and incremental quality-adjusted life year (QALY) gain to patients leaving the relapse-free state (excluding those who die).

2.2 Amendments to company's previous key scenario analysis

The company's updated partitioned survival model applies three key changes to the original key scenario analysis:

1. IO is now included as a downstream treatment for relapsed disease
2. The proportions of patients receiving blinatumomab/IO for relapsed disease have been amended
3. The cost calculations for downstream blinatumomab for relapsed disease have been amended.

Table 1 summarises the incremental QALYs and costs applied to patients receiving blinatumomab/IO for relapsed disease in the company's updated partitioned survival model.

Table 1: Company's updated partitioned survival model - incremental QALYs and costs applied to patients receiving blinatumomab/IO for relapsed disease

Additional QALY gain / cost	Value	Source and description of calculation
Blinatumomab QALYs	+1.98	NICE T450.[8] Incremental QALY gain associated with blinatumomab (no prior salvage).
IO QALYs	+1.98	Assumed to the be the same as blinatumomab
Blinatumomab costs	[redacted]	NICE TA450.[8] Based on medication and administration costs for blinatumomab (including the PAS for blinatumomab).
IO costs	£85,147	NICE TA541.[9] Micro-costed based on the mean number of IO doses and associated inpatient days reported in TA541, the list price of IO and the cost of an inpatient day of £805.10. Excludes the PAS for IO.

QALY – quality-adjusted life year; IO - inotuzumab ozogamicin; PAS – Patient Access Scheme; TA – technology appraisal

The ERG notes that Appendix 1 of the company's ACD response[3] includes an error relating to the proportions of patients who receive blinatumomab/IO for relapsed disease. The proportions of patients receiving each downstream treatment for relapsed disease (by initial treatment group) are summarised in Table 2.

Table 2: Company's updated partitioned survival model and original "key scenario analysis" - assumed proportions of patients receiving downstream treatments for relapsed disease

Salvage therapy for relapsed disease	Treatment group	
	Blinatumomab	Standard care
Company's original "key scenario analysis"[6]		
Salvage chemotherapy alone*	0%	30%
Blinatumomab	0%	70%
Inotuzamab ozogamicin	0%	0%
Company's updated partitioned survival model[3]		
Salvage chemotherapy alone*	0%	0%
Blinatumomab	0%	50%
Inotuzamab ozogamicin	100%	50%

** No additional benefit or cost applied*

2.2 Company's updated partitioned survival model - results

The results of company's updated partitioned survival model are presented in Table 3. Based on the probabilistic version of the model (assuming the unrestricted Gompertz function for RFS and the log normal mixture cure model for OS), blinatumomab is expected to generate an additional 2.00 QALYs at an additional cost of [redacted] compared with standard care: the corresponding incremental cost-effectiveness ratio (ICER) for blinatumomab versus standard care is £20,024 per QALY gained. The deterministic version of the updated model produces a similar ICER of £18,818 per QALY gained. The updated model suggests that the probability that blinatumomab produces more net benefit than standard care chemotherapy at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively.

Table 3: Company's updated partitioned survival model – central estimates of cost-effectiveness

Probabilistic model							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	13.23	7.67	[redacted]	5.47	2.00	[redacted]	**£20,024**
Standard care	7.76	5.67	[redacted]	-	-	-	-
Deterministic model							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	14.25	7.79	[redacted]	4.61	2.11	[redacted]	**£18,818**
Standard care	9.63	5.68	[redacted]	-	-	-	-

LYG – life year gained; QALY – quality-adjusted life year
** Undiscounted*

2.3 ERG critique of company's updated partitioned survival model

The ERG's critique of the company's original model and "key scenario analysis" are presented in Section 5.3.4 of the original ERG report.[7] The ERG has several concerns regarding the company's updated partitioned survival model; these are discussed below.

(i) Cure points determined separately for RFS and OS based on parametric models

The ERG's preferred model applied a fixed cure point at 5-years for all surviving patients. This cure timepoint was based on clinical advice received by the ERG (see ERG report,[7] Section 5.4). The company's revised partitioned survival model does not include this assumption; instead, the timepoints at which cure is assumed are determined by the parametric functions for RFS and OS. These timepoints differ between the two endpoints.

(ii) Concerns regarding the curves selected for the company's base case model

The updated partitioned survival model uses the company's original OS curve selections (log normal mixture cure models for both treatment groups). The clinical advisors to the ERG suggested three alternative plausible OS functions (generalised gamma (unrestricted); RCS Weibull (unrestricted); and Weibull Mixture (cure + unrestricted). These have not been considered in the company's updated analyses.

(iii) Latest BLAST data-cut not used

The updated partitioned model uses the same OS and RFS functions as the company's original model; these have not been re-estimated using the latest data-cut of BLAST.

(iv) Concerns regarding the incorporation of downstream costs and benefits for patients with relapsed disease

The ERG's main concern regarding the implementation of the company's key scenario analysis (and the updated partitioned survival model) is that the additional costs and QALYs associated with downstream treatments for relapsed disease are not structurally related to the core OS model. The company's approach crudely applies additional QALY gains to relapsed patients but does not consider whether those patients have the propensity to gain them. Further, whilst this analysis implies an improvement in survival (and potentially cure), the impact on the predicted OS curves cannot be directly estimated using the updated partitioned survival model.

(v) Concerns regarding the included costs of downstream treatments for relapsed disease

With respect to downstream treatments for relapsed disease, the company's updated partitioned survival model includes only the acquisition and administration costs of salvage therapy using blinatumomab and/or IO. Post-relapse HSCT costs remain the same as those in the company's original partitioned survival model.[6] The TOWER trial[10] suggests that blinatumomab does not increase HSCT over standard chemotherapy in patients with relapsed disease, whereas the INO-VATE trial[11] suggests that IO leads to more HSCT compared with standard chemotherapy. The ERG believes that the model should account for additional costs of HSCT in those patients who receive IO.

(vi) Blinatumomab and IO are assumed to have the same impact on QALYs in the relapsed setting

The company's updated partitioned survival model assumes that downstream IO and blinatumomab for relapsed disease will produce the same incremental QALY gains. The ERG was unable to assess whether this is reasonable as many of the results from the committee papers for the IO appraisal[9] (TA541) have been redacted.

2.4 Additional ERG exploratory analyses using the company's updated partitioned survival model

The ERG undertook two additional exploratory analyses using the company's updated partitioned survival model:

ERG exploratory analysis 1: Inclusion of a fixed 5-year cure point for all surviving patients

This analysis is in line with the ERG's preferred version of the company's original model (see ERG report,[7] Section 5.4).

ERG exploratory analysis 2: Exploration of ERG's clinical advisors' preferred OS functions

The ERG's clinical advisors stated preferences for the generalised gamma (unrestricted), RCS Weibull (unrestricted) and Weibull mixture (cure + unrestricted). Within this analysis, the company's updated partitioned survival model was evaluated using these three alternative OS functions; high and low ICERs were estimated for each scenario based on the full range of RFS curves fitted by the company.

The results of the ERG's exploratory analyses are summarised in Table 4 and Table 5. As shown in Table 4, the inclusion of a fixed 5-year cure point for all surviving patients increases the probabilistic ICER for blinatumomab versus standard care to £22,433 per QALY gained. Table 5 summarises the ICER ranges associated with the three OS models preferred by the ERG's clinical advisors; these OS models lead to ICERs in the range £15,176 to £26,753 per QALY gained.

Table 4: Company's updated partitioned survival model, ERG exploratory analysis 1 - inclusion of a 5-year cure point, probabilistic model

Company's updated partitioned survival model – cure point determined by parametric curves							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	13.23	7.67	[redacted]	5.47	2.00	[redacted]	**£20,024**
Standard care	7.76	5.67	[redacted]	-	-	-	-
Company's updated model with fixed 5-year cure point							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	13.72	7.89	[redacted]	4.95	1.78	[redacted]	**£22,433**
Standard care	8.77	6.12	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year
** Undiscounted*

Table 5: Company's updated partitioned survival model, ERG exploratory analysis 2 – ICER ranges using ERG clinical advisors' preferred OS functions (low-high ICER range determined by RFS curve given the selected OS model), deterministic model

OS model	Low ICER	High ICER
Generalised gamma (U)	£21,742	£26,753
RCS Weibull (U)	£20,976	£24,562
Weibull Mixture (Cure + U)	£15,176	£18,991

U – unrestricted; ICER – incremental cost-effectiveness ratio

3. Company's new semi-Markov model

3.1 Overview of the company's new semi-Markov model

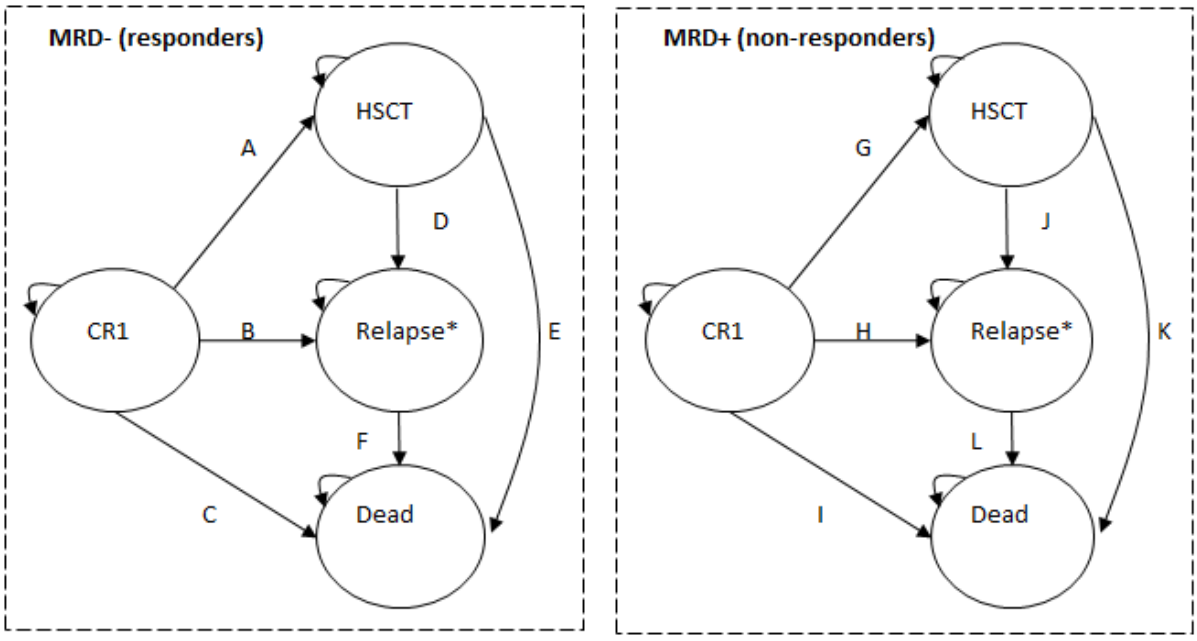
The company's new semi-Markov model compares: (a) blinatumomab for up to 4 cycles, followed by pre-relapse HSCT for a proportion of patients, followed by post-relapse salvage therapy using IO versus (b) standard chemotherapy (based on the UKALL14 trial maintenance regimen) for up to 2 years, followed by pre-relapse HSCT for a proportion of patients, followed by post-relapse salvage therapy using either IO or blinatumomab. The analysis also includes costs of post-relapse HSCT in both treatment groups.

The semi-Markov model adopts a 50-year (lifetime) horizon with a 42-day cycle length. The model structure is comprised of four health states: (i) first complete haematological remission (CR1); (ii) pre-relapse HSCT; (iii) relapse and (iv) dead. Within each treatment group, the modelled population is sub-divided into those patients who achieve an MRD response and those who do not; this 4-state structure is replicated for both MRD responders and MRD non-responders. The model assumes an MRD response rate of 83.56% for blinatumomab (from BLAST[12]) and 8.00% for standard care (based on expert opinion[13]).

The semi-Markov approach allows the model to incorporate time- and state-dependent event risks conditional on time since model entry (in CR1) and conditional on time since health state entry (within the two intermediate model health states of HSCT and relapse). Each of the intermediate health states include 44 tunnel states; given the 42-day cycle length, this corresponds to a maximum sojourn time of 5 years in each state. During each cycle, patients transition between the model health states according to time and state-dependent event risks based on *de novo* analyses of time-to-event data from BLAST,[12] the historical control study[6] and the TOWER study[10] (in relapsed patients). Patients who remain event-free after 5-years in each state are assumed to be cured; the subsequent risk of death in cured patients is modelled using uplifted general population mortality risks (assuming a 4-fold increase over general population mortality risk).

The structure of the company's semi-Markov model is presented in Figure 1. Within the figure, each permitted model transition is denoted by an alphabetic letter; the data sources and parametric assumptions used to inform each of these transitions are summarised in Table 6.

Figure 1: Company's semi-Markov model structure (drawn by the ERG)



** Treatment for relapse assumed to be IO/blinatumomab (50:50 split) in standard care comparator group and exclusively IO in the blinatumomab group*

The semi-Markov model for each MRD response sub-population operates as follows. Patients enter the model in the CR1 health state. Patients transition to the other health states (pre-relapse HSCT, relapse or dead) according to time-dependent probabilities based on the following permitted transitions:

- Patients who are in the CR1 state may remain in their current state, undergo pre-relapse HSCT, experience relapse or die;
- Patients who are in the pre-relapse HSCT state may remain in their current state, relapse or die;
- Patients who are in the relapse state may remain in their current state or die.

Within the semi-Markov model, the timepoint at which cure is assumed is dependent on the event(s) that the patient has previously experienced:

- Patients who do not relapse from CR1 within 5 years are subsequently assumed to be cured (cure point = 5 years since model entry)
- Patients who undergo pre-relapse HSCT (from CR1) and do not subsequently experience relapse are assumed to be cured 5 years after they entered the pre-relapse HSCT state (cure point = CR1 sojourn time plus 5 years – i.e. more than 5 years but less than 10 years since model entry)

- Patients who experience relapse and do not die within 5 years of relapse are assumed to be cured 5 years after they entered the relapse state (cure point = CR1 sojourn time plus 5 years, with additional HSCT sojourn time of 5-years if the patient has undergone a transplant– i.e. more than 5 years but less than 15 years since model entry).

The use of HSCT after relapse is not explicitly captured in the model structure; instead, outcomes for these patients are embedded within the OS parametric curves fitted to time-to-event data from the blinatumomab group of the TOWER study[10] (with ATT-adjustment). The costs of post-relapse HSCT are captured separately, based on weighted averages for each MRD response sub-population.

Total health outcomes and costs for each treatment group are estimated as the sum of the outcomes and costs estimated within the MRD responder and MRD non-responder sub-populations.

3.2 Semi-Markov model parameters

The semi-Markov model uses the same evidence sources to inform parameters relating to risks of relapse, HSCT and death as the updated partitioned survival model (BLAST,[12] the historical control study[6] and TOWER[10]). However, the semi-Markov model estimates time-to-event outcomes conditional on treatment received, MRD response and the patient's current health state. As such, this leads to a different definition of the model parameters compared with the company's partitioned survival model. The company's semi-Markov model includes parametric curves fitted to seven datasets:

- *Dataset 1:* BLAST CR1 MRD responders – time from study entry to HSCT, relapse or death
- *Dataset 2:* BLAST CR1 MRD non-responders – time from study entry to HSCT, relapse or death
- *Dataset 3:* BLAST MRD responders post-HSCT – time to relapse or death (time zero adjusted to transplant time)
- *Dataset 4:* BLAST MRD non-responders post-HSCT – time to relapse or death (time zero adjusted to transplant time)
- *Dataset 5:* Historical control study CR1 MRD responders/non-responders - time from study entry (adjusted) to HSCT, relapse or death (ATT-adjusted)
- *Dataset 6:* Historical control study MRD responders/non-responders post-HSCT – time to relapse or death (time zero adjusted to transplant time, ATT-adjusted)
- *Dataset 7:* TOWER relapsed subgroup (ATT-adjusted).

With the exception of survival outcomes for patients with relapsed disease, event risks are assumed to be treatment-specific (e.g. the probability of relapse following HSCT is different between the blinatumomab and standard care treatment groups).

The company re-analysed each of these datasets using what they refer to as a "competing risk framework." This involved estimating the survival distribution for a particular transition (event) and censoring patients who experience other competing risks at the time of the event; for example, the re-estimated Kaplan-Meier function for the transition from CR1 to HSCT counts the receipt of HSCT as an event and censors the events of relapse and death prior to HSCT.

Table 6 summarises the parametric distributions for each transition within the semi-Markov model. The alphabetic letters in the left hand column of the table correspond to those used to denote specific transitions in Figure 1.

Table 6: Company's semi-Markov model - summary of time-to-event data used to inform health state transitions

Transition	Description	Source	N events	N at risk	Best-fitting (using BIC)	Company's curve
Blinatumomab group						
A	Blin, MRD-, CR1 to HSCT	BLAST MRD responder subgroup[12]	46	61	Log normal cure	Log normal cure
B	Blin, MRD-, CR1 to Relapse		7		Exponential	Gompertz
C	Blin, MRD-, CR1 to Dead		1		Gompertz cure†	Exponential
D	Blin, MRD-, HSCT to Relapse		11	46	Exponential	Exponential cure
E	Blin, MRD-, HSCT to Dead		13		Exponential cure	Exponential cure
F	Blin, MRD-, Relapse to Dead	TOWER – blinatumomab group (ATT-adjusted)[10]	7.43*	13.03*	Exponential	Gompertz (restricted)
G	Blin, MRD+, CR1 to HSCT	BLAST MRD non-responder subgroup[12]	7	12	Log normal	Log normal
H	Blin, MRD+, CR1 to Relapse		4		Exponential	Gompertz
I	Blin, MRD+, CR1 to Dead		1		Gompertz cure†	Exponential
J	Blin, MRD+, HSCT to Relapse		0	7	n/a (no events)	Exponential
K	Blin, MRD+, HSCT to Dead		5		Exponential	Gompertz
L	Blin, MRD+, Relapse to Dead	TOWER – blinatumomab group (ATT-adjusted)[10]	7.43*	13.03*	Exponential	Gompertz (restricted)
Standard care group						
A	SC, MRD-, CR1 to HSCT	Historical control study (ATT-adjusted)[6]	15.78*	62.68*	Gompertz	Gompertz
B	SC, MRD-, CR1 to Relapse		40.30*		Gompertz	Gompertz
C	SC, MRD-, CR1 to Dead		2.74*		Exponential	Exponential
D	SC, MRD-, HSCT to Relapse		4.62*	15.78*	Exponential	Weibull cure
E	SC, MRD-, HSCT to Dead		1.52*		Exponential	Log normal
F	SC, MRD-, Relapse to Dead	TOWER – blinatumomab group (ATT-adjusted)[10]	7.43*	13.03*	Exponential	Gompertz (restricted)
G	SC, MRD+, CR1 to HSCT	Same as standard care MRD responders				
H	SC, MRD+, CR1 to Relapse					
I	SC, MRD+, CR1 to Dead					
J	SC, MRD+, HSCT to Relapse					
K	SC, MRD+, HSCT to Dead					
L	SC, MRD+, Relapse to Dead					

Blin – blinatumomab; SC – standard care; MRD – minimal residual disease; BIC – Bayesian Information Criterion; N – number; ATT - Average treatment effect on the treated

** Whilst not explicitly stated in the company's ACD response, the ERG believes these values are effective sample sizes from the ATT-weighted populations*

† This option cannot be selected in the model – the second-best fitting curve in both cases is the exponential

The semi-Markov model uses the same health state utility values as those used in the updated partitioned survival model. The costs of downstream blinatumomab/IO are the same as those used in the updated partitioned survival model (see Table 2). Costs associated with HSCT were calculated separately for relapse-free and relapsed patients, with a single QALY loss used to reflect lower HRQoL during the 5 year period post-transplant.

3.4 Company's semi-Markov model - results

Table 7 presents the results of the company's semi-Markov model. Based on the probabilistic version of the model, blinatumomab is expected to generate an additional 2.08 QALYs at an additional cost of [redacted]; the corresponding ICER is £27,257 per QALY gained. The deterministic ICER is lower at £25,645 per QALY gained. The company's probabilistic sensitivity analysis (PSA) suggests that the probability that blinatumomab produces more net benefit than standard care chemotherapy at WTP thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively.

Table 7: Company's semi-Markov model – central estimates of cost-effectiveness‡

Probabilistic model†							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	11.98	6.48	[redacted]	3.98	2.08	[redacted]	**£27,257**
Standard care	8.00	4.40	[redacted]	-	-	-	-
Deterministic model							
Option	**LYGs***	**QALYs**	**Costs**	**Inc. LYGs***	**Inc. QALYs**	**Inc. costs**	**Incremental cost per QALY gained**
Blinatumomab	12.14	6.56	[redacted]	4.06	2.12	[redacted]	**£25,645**
Standard care	8.08	4.44	[redacted]	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year
** Undiscounted*
† The version of the semi-Markov model supplied by the company included PSA results; however, the PSA sub-routine did not function for the ERG
‡ The model produces an estimated cure probability of 45.39% for blinatumomab and 26.78% for standard care

The ERG notes that the semi-Markov model produces absolute estimates of survival and QALYs for each treatment group which are noticeably lower than those generated from the updated partitioned survival model, although the incremental QALY gains are similar (see Table 3 and Table 7). Given the limitations of each model (see Section 2.3 and Section 3.5), it is difficult to determine the root cause of these differences.

3.5 ERG critique of company's semi-Markov model

3.5.1 Comments relating to verification of the company's semi-Markov model

The ERG was given limited time to verify the model. The ERG was able to scrutinise the calculations in one of the four MRD sub-population Markov traces and to check the application of the cost and utility calculations. During this process, the ERG identified a minor implementation error in the QALY loss

calculations (the disutilities are applied to the wrong tunnel states after year 2); however, correcting this issue appears to have little impact on the model results. The implemented model appears to be generally in line with its description within Appendix 2 of the company's additional evidence submission.[4]

3.5.2 Comments on company's semi-Markov model structure

The ERG believes that, at least to some degree, the company's semi-Markov structure addresses the majority of concerns raised by the Appraisal Committee in the ACD.[1] In contrast to the company's partitioned survival model, the semi-Markov model:

(a) Explicitly models health outcomes and costs for patients with or without MRD response following treatment with blinatumomab
(b) Includes explicit causal links between the receipt of pre-relapse HSCT, relapse and survival
(c) Allows some patients to go straight to HSCT whilst relapse-free (noted as a concern regarding the company's original partitioned survival model in the NICE ACD[1] [page 7])
(d) Includes a structural assumption of cure conditional on prior clinical events (receipt of HSCT and/or relapse). This means that patients who experience relapse may still achieve cure as a consequence of downstream treatments (blinatumomab or IO with/without subsequent post-relapse HSCT). The ERG believes this is more clinically plausible than the assumption of a fixed cure point for all patients which does not consider relapse history (the ERG's preferred assumption within the company's original partitioned survival model structure).
(e) Allows event risks to be conditioned on time since entry into each model health state; this is achieved through the use of tunnel states.
(f) Explicitly incorporates time-to-event outcomes for patients receiving downstream IO/blinatumomab for relapsed disease.

However, the ERG notes that the company's semi-Markov model structure is subject to some limitations and anomalies:

(a) Patients who undergo pre-relapse HSCT are penalised through the use of a later cure point than that applied to the CR1 state. The cure point for CR1 is 5 years. The cure point for patients entering the pre-relapse HSCT state is 5 years after entry into that state (i.e. CR1 sojourn time plus 5 years). This leads to a paradoxical situation whereby patients who remain relapse-free and proceed to transplant may only be considered cured at a later timepoint than those who remain relapse-free but never proceed to HSCT. The ERG is unsure whether it is possible to resolve this issue within the company's new model structure.
(b) The use of cure points of 5 years in each health state may be overly conservative. The use of 5-year cure points in all health states means that patients who undergo a late transplant and subsequently suffer a late relapse might only be considered cured after almost 15 years. The ERG is unsure whether this is clinically realistic.

(c) The model structure only explicitly links HSCT to cure in those patients who receive HSCT prior to relapse. Survival outcomes for relapsed patients are modelled using a single parametric curve which does not explicitly consider post-relapse HSCT or its impact on OS. Post-relapse HSCT costs are applied to a proportion of patients who relapse, but are not related to downstream salvage treatment. This may not be appropriate as the TOWER study[10] suggests that blinatumomab does not increase HSCT use in patients with relapsed disease, whereas the INO-VATE study[11] suggests that IO does increase HSCT use in this population.

3.5.2 Comments on evidence used to inform company's semi-Markov model

Whilst the evidence sources used to inform the time-to-event parameters of the company's semi-Markov model are the same as those used for the updated partitioned survival model (i.e. BLAST,[12] the historical control study[6] and the TOWER trial[10]), the definition of the parameters themselves are necessarily different due to the structure of the new model. The company has undertaken new analyses to estimate these parameters using the latest data-cut of the BLAST study.[12] The ERG's has several concerns regarding these new analyses; these are described below.

(i) Inappropriate method for handling competing risks

Based on the information provided in Appendix 2 of the company's ACD response,[4] the approach used by the company to deal with competing risks (censoring competing events which are not of interest) does not appear to be correct. The literature on competing risks analysis (e.g. Putter *et al*[14] and various others) describes the censoring approach taken by the company as an example of a method which fails to handle competing risks appropriately. Specifically, the problem with censoring events not of interest is that this may violate a key assumption underlying the Kaplan-Meier estimator: the assumption of independence of the censoring distributions.[14] The ERG believes that a more appropriate approach for handling competing risks would involve the use of the cumulative incidence function (CIF) to estimate the marginal probability of the event of interest in the presence of competing events. However, this would require a re-analysis of the underlying individual patient-level time-to-event data from BLAST[12] and the historical control study.[6] The ERG believes that the company's approach is likely to have inflated the risk of each event; as the company's method does not use the CIF to account for competing risks, the ERG is uncertain regarding the extent of the bias in the company's model predictions.

(ii) Small numbers of events and patients at risk

As noted in Appendix 2 of the company's additional evidence submission,[4] several time-to-event datasets for specific transitions feature very small numbers of patients at risk and small numbers of events; this is particularly evident within the MRD non-responder subgroup from BLAST[12] (see Table 6). Similarly, the effective sample sizes for the conditional event probabilities from the ATT-weighted

historical control study data are also very small. This leads to considerable uncertainty in the model predictions and difficulties in selecting the appropriate parametric model for each transition.

(iii) Questionable rationale for curve selection

The company fitted more than 15 different parametric models to estimate transition probabilities between model health states. As noted above, the small numbers of events and patients at risk makes curve selection challenging. Table 1 of Appendix 2 of the company's additional evidence submission includes a brief rationale for the distributions selected for use in the company's base case analysis. However, the reasons given are not always consistent: some curves were selected on the basis of the BIC, whereas others were chosen to accommodate certain assumptions (e.g. cure). In addition, in some instances, the company provides a rationale for selecting a particular curve, but that rationale would have been better justified through the selection of an alternative curve (for example, for the standard care group, the company selected the Weibull cure model for HSCT to relapse on the basis of BIC and the cure assumption, whereas the exponential cure model has a lower BIC and also assumes cure).

Given the structural assumption of a maximum cure point of 5 years in each health state, the ERG believes that the consideration of the plausibility of the extrapolated curves for each transition is largely irrelevant. This is because the tail of each modelled curve (after 5 years) is overridden by the cure assumption and therefore has no bearing on the model results. As most of the event-specific Kaplan-Meier functions include follow-up to 5 years, the ERG believes that it would be more appropriate to select preferred time-to-event functions on the basis of their statistical goodness-of-fit (e.g. using the Bayesian Information Criterion [BIC]).

(iii) Concerns regarding model-predicted RFS and OS

The ERG has concerns regarding the RFS and OS predictions generated using the company's semi-Markov model. Figure 2 presents a comparison of the Kaplan-Meier curves and the semi-Markov model predictions for RFS. Figure 3 presents a comparison of the Kaplan-Meier curves and the semi-Markov model predictions for OS including blinatumomab/IO as downstream treatments for relapsed disease (this model applies the restricted Gompertz post-relapse OS function for the blinatumomab group from TOWER[10]). Figure 4 presents a comparison of the Kaplan-Meier curves and the semi-Markov model predictions for OS excluding blinatumomab/IO as downstream treatments for relapsed disease (this model applies the restricted Gompertz post-relapse OS function for the standard chemotherapy group from TOWER[10]).

Figure 2: Company's semi-Markov model – relapse-free survival, model includes blinatumomab/IO as downstream treatments for relapsed ALL

Figure 3: Company's semi-Markov model – overall survival, model includes blinatumomab/IO as downstream treatments for relapsed ALL

Figure 4: Company's semi-Markov model – overall survival, model excludes blinatumomab/IO as downstream treatments for relapsed ALL

With respect to these model predictions, the ERG notes the following observations:

- The company's semi-Markov model provides predictions of RFS which appear to provide a good fit to the Kaplan-Meier curves (see Figure 2).
- Predicted OS from the company's base case semi-Markov model appears to provide a good visual fit to the Kaplan-Meier OS curves (see Figure 3). However, the ERG believes that this is a misleading signal of model validity, as the curves should not match. The base case semi-Markov model includes blinatumomab/IO as downstream treatments. Due to the timing of the retrospective historical control study (study completion date June 2014), the ERG considers it unlikely that any sizeable proportion of patients could have received blinatumomab or IO following disease relapse within this study. As these downstream treatments have been shown to improve OS in the relapsed setting, it would seem reasonable to expect the modelled OS projections from the company's base case semi-Markov model to be higher than the Kaplan-Meier estimates.
- When the post-relapse OS function fitted to data from the standard chemotherapy group of TOWER[10] is instead used to model OS for relapsed patients, the semi-Markov model no longer provides a good fit to the Kaplan-Meier curves in either treatment group (see Figure 4). The ERG would expect the predictions from this version of the model to match the Kaplan-Meier curves. Instead, predicted OS appears to be underestimated in both treatment groups, but the extent of the bias appears to be greater in the standard chemotherapy comparator group.

The ERG believes that this problem may be a consequence of one or more of the following issues: (a) inappropriate parametric functions selected to inform one or more transitions; (b) inappropriate assumptions regarding the timing of cure in one or more of the model's health states, or (c) inappropriate handling of competing risks. The ERG has concerns that any cost-effectiveness results generated using the company's semi-Markov model may not be reliable.

3.6 Additional ERG exploratory analyses using the company's semi-Markov model

The ERG undertook two sets of exploratory analyses using the company's semi-Markov model:

ERG exploratory analysis 1: Parametric time-to-event functions selected according to BIC

Parametric functions were selected according to their BIC (see Table 6). Owing to limitations in model functionality, the curves with the lowest BIC could not be selected for the transitions from CR1 to dead in the blinatumomab group; instead the second-best fitting curves (exponential) were applied.

ERG exploratory analysis 2: Use of different timepoints for cure in each state

Within these analyses, the impact of assuming cure points of 3-, 4- and 5-years was explored.

All ERG analyses were undertaken using the deterministic version of the company's model as the PSA sub-routine in the company's semi-Markov model did not function correctly. The ERG believes that the probabilistic ICERs would likely be slightly higher than those presented in Table 8.

Table 8: Company's semi-Markov model, ERG exploratory analysis results, deterministic model

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	Incremental cost per QALY gained
Semi-Markov model – company's curve selections, 5-year cure timepoint							
Blinatumomab	12.14	6.56	[redacted]	4.06	2.12		**£25,645**
Standard care	8.08	4.44	[redacted]	-	-	-	-
Semi-Markov model – company's curve selections, 4-year cure timepoint							
Blinatumomab	12.50	6.72	[redacted]	4.05	2.11		**£25,479**
Standard care	8.44	4.61	[redacted]	-	-	-	-
Semi-Markov model – company's curve selections, 3-year cure timepoint							
Blinatumomab	13.13	7.03	[redacted]	4.00	2.09		**£25,551**
Standard care	9.13	4.94	[redacted]	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 5-year cure timepoint							
Blinatumomab	10.39	5.75	[redacted]	4.57	2.39		**£25,106**
Standard care	5.81	3.37	[redacted]	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 4-year cure timepoint							
Blinatumomab	11.41	6.23	[redacted]	4.87	2.52		**£23,237**
Standard care	6.54	3.71	[redacted]	-	-	-	-
Semi-Markov model – curves selected according to lowest BIC, 3-year cure timepoint							
Blinatumomab	12.69	6.84	[redacted]	5.03	2.60		**£21,874**
Standard care	7.66	4.24	[redacted]	-	-	-	-

** Undiscounted*

LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental

The ERG's exploratory analyses produced ICERs in the range £21,874 to £25,645 per QALY gained. The ERG notes that using BIC to select parametric functions and altering the timepoints for cure do not resolve the ERG's concerns regarding poor model fit described in Section 3.5. As such, the ERG is unclear regarding the reliability of the ICERs generated using the company's semi-Markov model.

4. Other factors which may influence the cost-effectiveness of blinatumomab for MRD+ ALL

In December 2018, NICE issued a positive CDF recommendation for the use of tisagenlecleucel for the treatment of R/R B-cell ALL in people aged up to 25 years.[15] The availability of this therapy will have a significant impact on downstream costs and outcomes for some patients with relapsed ALL. However, the company's models assume a starting age of around 45 years; as such, this therapy is not relevant to the population considered within the company's model. However, tisagenlecleucel may be a relevant downstream option for a subset of patients who are eligible for treatment under the marketing authorisation for blinatumomab for MRD+ ALL. The impact on the ICER for blinatumomab in the MRD+ indication is unclear.

5. ERG comments on whether blinatumomab meets NICE's End of Life criteria

The original CS[6] and the company's ACD response[2] argue that blinatumomab for MRD+ ALL meets NICE's End of Life (EoL) criteria on the basis of median estimates of OS. The company's ACD response also draws reference to the pragmatic interpretation of the EoL criteria within the appraisals of blinatumomab and IO in the relapsed setting.[16, 17] As discussed in the ERG report,[7] median OS and mean OS estimates from the model diverge considerably as a consequence of the inclusion of an assumption of cure for a proportion of patients. The ERG notes that the company's partitioned survival and semi-Markov models produce mean OS estimates for the standard care group of 7.76 years and 8.00 years, respectively (see Table 3 and Table 7). As such, the ERG does not believe that blinatumomab meets NICE's EoL criteria.

6. References

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