NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Kite, a Gilead company**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Leukaemia Care
   b. NCRI-ACP-RCP-RCR

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Sophie Wheldon, Advocacy Officer – patient expert, nominated by Leukaemia Care
   b. Professor David Marks, Director Bristol BMT Unit/Head ALL program – clinical expert, nominated by Kite

There were no public comments on the appraisal consultation document received through the NICE website.

5. **Evidence Review Group critique of company comments on the ACD**

6. **Evidence Review Group threshold analyses**

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

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Brexucabtagene autoleucel for treating relapsed for refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

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.

Comments submitted by the company (Kite, a Gilead company) in response to the appraisal consultation document are included in the committee papers. These were considered by the committee. Please refer to the Final Appraisal Document for information.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
1	Patient expert	NA	One of the points made in the ACD (3.9) state that the committee does not believe that patients who have received CAR T cells have the same quality of life as the general population. I would like to clarify that I was not in disagreement with the clinical experts when I discussed the emotional, financial and immunological impact of my experience with receiving tisagenlecleucel, and I very much agree that patients can return to a near-normal life after CAR T therapy, which is what I feel I have been able to do since receiving the treatment myself in 2019. I don't believe that the correct context for my comments was used in this decision. My point was that the benefits of this treatment in getting my life back far outweighed the emotional and financial impacts which were faced during the earlier stages of my treatment with my experience of CAR T. In terms of the regular appointments with immunology and my healthcare team, I do not believe that this hinders my quality of life at all. I feel that it actually improves it, as I know that there is a team of people who are always looking out for me, and that they are there with solutions for me if I face issues with infection. This provides me with a lot of reassurance in my day to day life, and does not prevent me from doing the daily activities that I am now able to do since having my treatment, including completing my education, socialising with friends and loves ones, going to work, and contributing to society in general - all of which would not have been possible if I was not able to have CAR T therapy. I would therefore ask for the committee to reconsider their reasoning with this point.	Thank you for your comment. The committee considered this comment and the comments made in the committee meeting around quality of life after CAR T-cell treatment. Please see section 3.10 of the Final Appraisal Document for further detail. In summary, the committee noted the comments from clinical and patient experts that the benefits of treatment outweighed the negative impacts, and that disease monitoring provides reassurance and does not affect the ability to perform daily activities. However, it agreed that compared to the general population, a population who have had relapsed or refractory B-cell acute lymphoblastic leukaemia and brexucabtagene autoleucel treatment was likely to have a lower quality of life.
2	Patient	NA	I was concerned to read that the committee state that they are	Thank you for your comment. The committee

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
	expert		unsure of how a cure can be defined for patients aged over 26 receiving autologous anti-CD19-transduced CD3+ cells, despite expecting the treatment to be clinically effective as per the clinical evidence. Patients like myself who received tisagenlecleucel aged under 25 are defined as being cured after 3 years, which was defined by the previous NICE appraisal (ID544). The clinical experts also explained to the committee that relapses after 12 months are very unlikely. I would like to reflect the concerns raised by Leukaemia Care's response and ask the committee to re-evaluate their definition of when a patient can be considered as cured using the same criteria as they have used in the previous CAR T appraisals for ALL and using the information from the clinical experts.	considered the evidence from ZUMA-3 to estimate the clinical effectiveness of brexucabtagene autoleucel (previously referred to as autologous anti-CD19-transduced CD3+ cells; see section 3.4 of the Final Appraisal Document). It noted that the results for overall survival suggested that this treatment could be potentially curative. The committee considered the opinion of clinical experts that relapses after 12 months are infrequent. However, it also noted that there were uncertainties with the clinical evidence which meant that the assumption of cure was uncertain. The model used in decision making assumed that after 3 years, the population who had not relapsed after brexucabtagene autoleucel were cured, with a standardised mortality ratio and utility multiplier applied. The committee noted that based on the evidence presented, it was uncertain if this treatment is curative, but that the company's economic model was appropriate for decision making.
3	Patient expert	NA	The committee state that the clinical evidence shows that the treatment is expected to be clinically effective. I feel it would be unfair to limit the use of CAR T therapy to those aged under 25 by not recommending the treatment to the older age group. This treatment has completely changed my life, in fact, it gave me another chance at life. It is terrifying to consider that, if I had been just a few years older at the time of my relapse, I may not have been given the opportunity to live beyond Christmas of that year. I therefore believe that the committee should reconsider their decision to allow other patients to access this treatment to allow	Thank you for your comment. The committee considered the equalities issues highlighted in this comment (see section 3.17 of the Final Appraisal Document). It was aware that a different CAR T-cell treatment is available through the Cancer Drugs Fund for people aged under 26 and that there is an unmet need for people aged 26 years and over. It noted that the decision to recommend brexucabtagene autoleucel was based on the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			them to explore a potential cure and for them to be able to truly 'live' again.	clinical and cost effectiveness evidence available for this appraisal and the committee could not recommend a technology for a particular population based on the fact that another technology appraisal did not include that population.
4	Patient expert	NA	I would like to stress to the the importance of equality and access to treatments to the committee. Allowing a larger population of patients to access this treatment would significantly improve the outcomes for patients who, in particular, are not able to find a suitable stem cell donor and whom are overall less likely to achieve a cure without having equitable access to CAR T products. I believe that everyone who has ALL who could potentially benefit from CAR T therapy should be able to access it.	Thank you for your comment. The committee considered the equalities issues highlighted in this comment (see section 3.17 of the Final Appraisal Document). It specifically considered the population who are unable to have an allogenic stem cell transplant, including people who are less likely to identify a suitable stem cell donor. However, the committee was not presented with any cost effectiveness evidence which meant that this population could be taken into consideration separately. Therefore, it was only able to make a decision based on the full population included in the decision problem. Based on the clinical and cost effectiveness evidence presented for the population in the decision problem, the committee concluded that brexucabtagene autoleucel should be recommended for with the Cancer Drugs Fund.
5	Clinical expert	NA	Page 19: I don't understand what the summary is saying about age inequality. The language is not clear There is a basic age inequality issue here which the committee has not addressed. Nor have they addressed the patients who are not transplant eligible but would be fit enough to receive CAR T. (this is also in effect a discrimination against older patients)	Thank you for your comment. The committee considered the equalities issues highlighted in this comment (see section 3.17 of the Final Appraisal Document). It also specifically considered the population who are unable to have an allogenic stem cell transplant, including older people who are less likely to be eligible. However, the committee was not presented with any cost effectiveness evidence which meant that this population

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
				could be taken into consideration separately. Therefore, it was only able to make a decision based on the full population included in the decision. Based on the clinical and cost effectiveness evidence presented for the population in the decision problem, the committee concluded that brexucabtagene autoleucel should be recommended for use with the Cancer Drugs Fund.
6	Clinical expert	NA	*'a curative treatment effect is uncertain' (page 8)* The committee is inconsistent. Tisagenlecleucel was approved long before this therapy was shown to be curative. As I have said before, the results are broadly consistent with this CAR T cell, and we are better at dealing with CAR T toxicity now (disease relapse after 12 months is uncommon)	Thank you for your comment. The committee considered the evidence from ZUMA-3 to estimate the clinical effectiveness of brexucabtagene autoleucel (see section 3.4 of the Final Appraisal Document). It noted that the results for overall survival suggested that this treatment could be potentially curative. The committee considered the opinion of clinical experts that relapses after 12 months are infrequent. However, it also noted that there were uncertainties with the clinical evidence which meant that the assumption of cure was uncertain. The model used in decision making assumed that after 3 years, the population who had not relapsed after brexucabtagene autoleucel were cured, with a standardised mortality ratio and utility multiplier applied. The committee noted that based on the evidence presented, it was uncertain if this treatment is curative, but that the company's economic model was appropriate for decision making.
7	Clinical expert	NA	*The ERG stated that the sensitivity analysis was not sufficiently powered to detect a difference. It also noted that an allo-SCT could have provided a survival advantage to the people who had had one* This is illogical and is 'having it both ways' If there is no evidence that alloSCT provides a survival advantage	Thank you for your comment. This statement has been updated in the Final Appraisal Document for clarity (see section 3.11). Given that the sensitivity analysis was not sufficiently powered to detect a difference, the ERG

Comment number	Type of stakeholder	Organisation name	Stakeholder comment	NICE Response
			then it is only fair to assume there is none. Remember that it is not UK practice to automatically do a consolidative transplant, we would test this drug as stand-alone therapy	noted that it could not be determined if an allogenic stem cell transplant could have provided a survival advantage for the people in ZUMA-3 who received this treatment. The ERG stated that it was therefore appropriate to include the costs and quality-adjusted life years (QALYs) associated with the allogenic stem cell transplants used in the trial, given that the potential benefits are included in the clinical data that informs the model. It modelled these costs and QALYs for 18% of the population included in the treatment arm of the model, which aligns with the proportion of people who received allogenic stem cell transplant in ZUMA-3. The committee agreed that the ERG's approach was appropriate.
8	Clinical expert	NA	Page 14: I totally agree (with Kite's submission) that fewer staff are required to look after a CAR T patient. 60K is a gross overestimate of the cost of a CAR T patient	Thank you for your comment. An updated figure for the CAR T-cell delivery costs has been agreed between the company and NHS England at £41,101. For further detail on how this figure was derived, see section 3.12 of the Final Appraisal Document.
9	Clinical expert	NA	I have no doubt that this therapy is effective. That is also the opinion of Jae Park (New York), Matthias Stelljes (Muenster), Josep Ribera (Barcelona) and Andre Schuh (Toronto). (We discussed this at a virtual meeting yesterday). To be frank I don't think the ERG's opinion carries as much weight as the combined view of ALL CAR T experts worldwide	Thank you for your comment. The committee considered the evidence from ZUMA-3 to estimate the clinical effectiveness of brexucabtagene autoleucel, as well as statements from clinical experts (see section 3.4 of the Final Appraisal Document). The committee concluded that treatment with brexucabtagene autoleucel could be clinically effective, but a curative treatment effect is uncertain. The recommendation is based on a consideration of both clinical and cost-effectiveness.

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10	Patient organisation	Leukaemia Care	The ACD papers commented that it was uncertain whether autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (CAR-T) would be considered a cure. This was because analysis conducted by the ERG did not distinguish between people who had an allogeneic stem cell transplant (SCT) before treatment with CAR-T and those who did not, meaning survival benefit could not be solely attributed to the treatment being appraised. However, the clinical expert said that the treatment could potentially lead to a cure in some people and that curative outcomes can be seen in the real-world evidence of those in the indication in question. Additionally in the experience of the patient expert, CAR-T appears to have been curative. We would therefore like the committee to reconsider CAR-T's curative effects and accept more uncertainty in light of the innovation this represents to patients, and to give people over 25 years old equal access to a treatment with great clinical benefit.	Thank you for your comment. The committee considered the evidence from ZUMA-3 to estimate the clinical effectiveness of brexucabtagene autoleucel (previously referred to as autologous anti-CD19-transduced CD3+ cells; see section 3.4 of the Final Appraisal Document). It noted that the results for overall survival suggested that this treatment could be potentially curative. The committee considered the opinion of clinical experts that relapses after 12 months are infrequent. However, it also noted that there were uncertainties with the clinical evidence which meant that the assumption of cure was uncertain. The model used in decision making assumed that after 3 years, the population who had not relapsed after brexucabtagene autoleucel were cured, with a standardised mortality ratio and utility multiplier applied. The committee noted that based on the evidence presented, it was uncertain if this treatment is curative, but that the company's economic model was appropriate for decision making.
11	Patient organisation	Leukaemia Care	Secondly, we ask the committee to re-evaluate the point at which the treatment is considered a cure. It would be unfair and unreasonable to define cure differently to what is seen in people with the same diagnosis who can receive existing CAR-T treatments, such as tisagenlecleucel. In the appraisal of tisagenleleucel for ALL patients under 25 (ID554), a cure of 3 years was considered appropriate. We therefore request an explanation from the committee on why their decision on the curative duration of CAR-T differs from the appraisal ID554. Furthermore, we believe there ought to be consistency on this point between all ALL CAR-T appraisals. Other clinical characteristics, such as the efficacy in	Thank you for your comment. The model used in decision making assumed that after 3 years, the population who had not relapsed after brexucabtagene autoleucel treatment were cured, with a standardised mortality ratio and utility multiplier applied. The committee noted that based on the evidence presented, it was uncertain if this treatment is curative, but that the company's economic model was appropriate for decision making.

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			subgroups, has been assumed to be the same between different products in similar populations (point 3.5 in the ACD), and therefore it would be unreasonable not to apply other clinical similarities such as cure assumptions.	
12	Patient organisation	Leukaemia Care	We are concerned about the committee's conclusion that people who have CAR-T do not have the same quality of life as the general population in the long-term (point 3.9). We request that the committee explain why they arrived at such a final conclusion, when there was a significant amount of uncertainty in the discussion surrounding this. It currently appears as though the patient expert's comment on ongoing immunology appointments has informed the conclusion too heavily. This is because the committee failed to frame the point in the correct context. For those who are cured with CAR-T, the benefits of extended life when a patient has run out of other options far outweigh the QoL implications. Additionally, the negative QoL impact on a patient's friends and family members should CAR-T not be available in this setting would be significant, as the patient would alternatively likely be put on best supportive care with a short life expectancy. Finally, routine hospital appointments can help to alleviate health-related anxiety as patients feel monitored clinically.	Thank you for your comment. The committee considered this comment and the comments made in the committee meeting around quality of life after CAR T-cell treatment. Please see section 3.10 of the Final Appraisal Document for further detail. In summary, the committee noted the comments from clinical and patient experts that the benefits of treatment outweighed the negative impacts, and that disease monitoring provides reassurance and does not impact the ability to perform daily activities. However, it agreed that compared to the general population, a population who have had relapsed or refractory B-cell acute lymphoblastic leukaemia and brexucabtagene autoleucel was likely to have a lower quality of life.
13	Patient organisation	Leukaemia Care	We believe it has not been made clear whether the trial only included patients who had relapsed, or whether it could also have included patients who were undergoing bridging therapy. We believe this might have an impact on the uncertainty of CAR-T being curative and therefore seek further clarification from the committee on this point.	Thank you for your comment. No evidence was presented by the company to demonstrate a difference in effectiveness between people who had relapsed and people who were undergoing bridging therapy. Please see the company's submission, document B, table 6 in the committee papers for further information on the eligibility criteria for ZUMA-3.

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14	Patient organisation	Leukaemia Care	The committee concluded CAR-T cannot be put into the Cancer Drugs Fund (CDF). We believe this is both an unfair and unreasonable conclusion, given that other CAR-T products that aim to achieve very similar outcomes for patients have previously been entered into the CDF, such as with the NICE appraisal for tisangenleleucel for the treatment of relapsed or refractory ALL patients under the age of 25. As a result, we request the committee explain why they made a different decision on the suitability for this treatment in the CDF to other committees.	Thank you for your comment. The committee considered the consultation comments received from all stakeholders as well as scenarios which demonstrated that it is plausible that brexucabtagene autoleucel could be cost-effective. Therefore, the committee concluded that brexucabtagene autoleucel meets the criteria for use within the Cancer Drugs Fund (see section 3.16 of the Final Appraisal Document).
15	Patient organisation	Leukaemia Care	Additionally, we consider the committee's decision that the treatment has no plausible potential to be cost effective, and therefore excluded from the CDF, to be unreasonable. We ask the committee to clarify whether any of the scenarios presented are cost-effective and for NICE to clarify how many ICERs should be in the range that NICE considers costs effective to be considered on the CDF.	Thank you for your comment. For the committee to make a recommendation in the Cancer Drugs Fund (CDF), it needs to be satisfied that clinical uncertainty can be resolved within the CDF and that it has been presented with a scenario which it considers plausible resulting in an incremental cost effectiveness ratio (ICER) that is considered a cost-effective use of NHS resources. There is no set number of scenarios which should be within a cost-effective range that determines the suitability for the CDF. Following the second appraisal committee meeting, the committee was presented with scenarios which it considered plausible that were within a cost-effective range. Therefore, the committee concluded that brexucabtagene autoleucel meets the criteria for use within the CDF (see section 3.16 of the Final Appraisal Document).
16	Patient organisation	Leukaemia Care	Due to a review of the original NHS tariff cost of CAR-T delivery, NHS England revised their cost from £96,016 to £65,415. The ACD states that some costs included in the NHS estimate of £65,415 were already captured in the company's model and therefore reduced the price further to arrive at a final figure of £60,000. However, there is no further detail in the ACD about how and why	Thank you for your comment. An updated figure for the CAR T-cell delivery costs has been agreed between the company and NHS England at £41,101. For further detail on how this figure was derived, see section 3.12 of the Final Appraisal Document.

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			the figure of £60,000 was arrived at. We believe a failure to explain this does not give us the full opportunity to be involved and to comment. We are therefore requesting greater transparency over the decision making that led to this final figure, from both NICE and NHSE; not to provide this information would be procedurally unfair and unreasonable.	
17	Patient organisation	Leukaemia Care	It is unreasonable for the committee to disregard the findings of the ZUMA-3 trial. The ACD states that ZUMA-3 may be better source of information on treatment effects in the correct population and it would unreasonable not to use the best source of information for the question, which is in regard specifically to understand the effect of the treatment on the NHS population.	Thank you for your comment. Section 3.4 of the Final Appraisal Document explains how the committee considered the findings of the ZUMA-3 trial.

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over

Company response to NICE appraisal consultation document (ACD) [ID1494]

6th January 2023

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Abbreviations

Abbreviation	Definition
ACD	Appraisal Consultation Document
ACM	Appraisal committee meeting
ASH	American Society of Hematology
BM	Bone marrow
CAR-T	Chimeric antigen receptor T-cell
CDF	Cancer Drugs Fund
CI	Confident Interval
CNS	Central Nervous System
CR	Complete Remission
CRh	Complete Remission with Partial Hematologic Recovery
CRi	Complete Remission with Incomplete Hematologic Recovery
DCO	Data Cutoff date
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ERG	Evidence Review Group
ESS	Effective sample size
GvHD	Graft-versus-host disease
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HRU	Healthcare Resource Use
HSCT	Haemopoietic Stem Cell Transplant
ICER	Incremental cost-effectiveness ratio
IPD	Individual Patient Data
ITC	Indirect treatment comparison
mITT	Modified Intention-to-treat
IVIg	Intravenous immunoglobulin
KM	Kaplan-Meier
LVD	Longest Vertical Dimension
LY	Life years
MAA	Managed Access Agreement
MAIC	Matching-Adjusted Indirect Comparison
MLL	Mixed Lineage Leukaemia
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health & Care Excellence
NR	Not reached
OCR	Overall Complete Remission
OS	Overall Survival; not fully defined Page 14
PD	Progressive Disease
PH	Proportional hazards

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PR	Partial Remission
QALY	Quality-adjusted life year
SCT	Stem Cell Transplant
SmPC	Summary of Product Characteristics
SMC	Scottish Medicines Consortium
SMR	Standardised Mortality Ratio
STC	Simulated Treatment Comparison
STDEV	Standard Deviation
TRM	Transplant-Related Mortality
TSD	Technical Support Document
UK	United Kingdom

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Executive summary

The Company is grateful for the opportunity to respond to the appraisal consultation document (ACD). While we are disappointed that KTE-X19 did not receive an initial positive recommendation for treating adults >25 years of age with relapsed/refractory B-cell ALL, we are pleased that the appraisal committee recognizes that there is a significant unmet need for effective treatments in this population, particularly in the context of the availability of a CAR-T for R/R ALL patients 25 years of age or younger.

In the ACD, the Committee noted that uncertainty remains in relation to long-term durability of effect with KTE-X19. Specifically, this relates to long-term mortality risk following treatment with KTE-X19, as well as long-term quality of life. In addition, the committee considered that the cost of allo-SCT's performed in ZUMA-3 should be included in the model, and that the NHS tariff provides the best estimate for the cost of delivering CAR-T in England. Notably, the committee stated that the NHS tariff value should be reviewed if any new evidence is presented, and as described in our response to Topic 5, the company and NHS England have come to an agreement on the appropriate tariff.

In Section 3.13 of the ACD (page 16-17), the Committee sets out its preferred assumptions. We have addressed several of these topics in our response to the ACD in the following sections, noting that the two with the biggest impact on the model are Topic 1 (method of indirect comparison) and Topic 2 (long-term mortality relative to general population). Where appropriate, the Company has carried out additional scenario analyses, the results of which are reported within this response.

Summary conclusions are as follows:

1. **Methods for indirect treatment comparison (Topic 1)**
    - The committee preferred the Evidence Review Group's (ERG's) proportional hazards approach, whereby the inverse of the hazard ratio (HR) from the Company's matching-adjusted indirect treatment comparison (MAIC) was applied to the ZUMA-3 survival curve to derive a survival curve for inotuzumab (1).

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- The Company stands by its position that a naïve indirect comparison is appropriate for inotuzumab on the basis that the ERG's preferred approach is flawed for the following reasons:
    i. The ERG's preferred HR was derived from an unanchored MAIC, a method known to be at high risk of bias according to NICE Technical Support Document 18. The ERG's method is further compromised by a small effective sample size (significantly below 30).
    ii. The ERG's preferred HR lacks face validity based on the transitivity assumption; that is, it does not align with the HR that would be generated through an indirect comparison between the HR of KTE-X19 vs. blinatumomab in SCHOLAR-3 and the HR from a published anchored MAIC and simulated treatment comparison (STC) of inotuzumab vs. blinatumomab. The Company's preferred naïve HR, on the other hand, is similar (via STC) or identical (via anchored MAIC) than the HRs generated assuming transitivity.
    iii. The survival curve generated using the ERG's approach generates survival estimates for inotuzumab that lack face validity given the poor prognostic characteristics being adjusted to; short-term survival is overestimated, and the cure fraction is unrealistically high when considering the stem-cell transplant (SCT) rate and post-SCT survival rate observed in INO-VATE (2).

2. Long-term risk of mortality for KTE-X19 treated patients relative to the general population (Topic 2)

- The committee's preferred source for estimating the standardised mortality ratio (SMR) is from a trial that spanned 1970-2002 and in which ALL patients only made up ~10% of the population. This source is selected on the flawed assumption that all patients to receive KTE-X19 in clinical practice will have received a prior allo-SCT; an SMR of 4 is therefore inappropriate.
- Use of an SMR of 4 was appropriate for TA541, as inotuzumab is a treatment for which long-term outcomes are contingent on allo-SCT, this is not the case for KTE-X19.

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- Active GvHD is an exclusion criterion for KTE-X19 (as stated in the SmPC). As such, even the KTE-X19 treated patients that will have received a prior SCT are expected to be at a lower risk of long-term mortality relative to the population that informs the SMR of 4.
- As ZUMA-3 is the most generalisable trial to UK clinical practice, any increase to the SMR over the company's base case should adopt a blended SMR of 2.2 based on prior SCT in ZUMA-3 (38%).

3. Long-term quality of life for KTE-X19 treated patients relative to the general population (Topic 3)

- The ERG's rationale for applying a utility decrement to cured patients is flawed given the large difference in short vs long-term health-related quality of life (HRQoL).
- The ERG's key argument is that it is unrealistic to assume no HRQoL decrement in cured patients if there is an increased mortality risk compared to the general population.
- The ERG chose a mid-point between the HRQoL of responding patients in ZUMA-3 and the general population, which is disproportionate to the mortality risks of a patient who has recently undergone treatment vs. one considered cured of their ALL. This is contradictory to the ERG's rationale that mortality and HRQoL are correlated.
- We fundamentally disagree with the rationale that mortality and HRQoL are correlated, given that mortality can be driven by acute events that do not impact HRQoL on a daily basis in cured patients.
- The Company stands by its assertion that patients who have been cured by treatment with a CAR-T will over the longer-term have the HRQoL of the general population (which already captures the HRQoL of cancer survivors and patients who have received other aggressive treatments and interventions). The Company's position is not unreasonable.

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4. **Inclusion of allo-SCT related costs & QALY loss in the economic model (Topic 4)**
    - Allo-SCT's performed in ZUMA-3 were pre-planned either due to high-risk prognostic factors and/or limited long-term data on KTE-X19 at time of enrolment.
    - The Company considered the sensitivity analysis to be informative despite lacking statistical power as it showed little or no difference between transplanted and non-transplanted patients, based on patient numbers similar to those anticipated to be treated with KTE-X19 in clinical practice.
    - [redacted] Therefore, no survival advantage is expected in patients who received a pre-planned allo-SCT whilst in remission in ZUMA-3.
    - Further support comes from the observation that survival of patients who received allo-SCT in ZUMA-3 far exceeded that of patients who received SCT following treatment with other therapies for ALL, suggesting that the survival benefit came from KTE-X19, not the allo-SCT.
    - Uncertainties regarding allo-SCT rates and survival estimates could be addressed by data collection in the Cancer Drugs Fund (CDF).

5. **NHS tariff for delivery of CAR-T treatment (Topic 5)**
    - Since the first committee meeting for this appraisal, an agreed tariff cost of £41.1k for CAR T-cell therapy has been accepted for the parallel cancer drugs fund review of axicabtagene ciloleucel for treating diffuse large B-cell lymphoma after 2 or more systematic therapies [ID3980] (administration costs cover the first 3 months of care, excluding the cost of bridging therapy, consolidation SCT and hypogammaglobulinemia management).
    - We believe that NHS England have confirmed that £41.1k (with the costs for bridging chemotherapy drugs and its administration, SCT and IVIg in addition to this) would appropriately reflect the cost of delivery of treatment for this appraisal and have included this in our updated base case.
    - We consider the £41.1k to be a substantial overestimate based on the available real-world evidence on the costs and resource use of CAR-T delivery. Using published NHS reference costs for allo- and auto-SCT and a US study as a

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reference point, we demonstrate that the costs in the economic model are perfectly aligned with the published evidence and that the proposed NHS England tariff may be more than double the actual costs to the NHS. In our revised base case, we therefore include the £41.1k tariff cost but remove all costs up to day 100 other than CAR-T acquisition, SCT and subsequent therapy.

Finally, in section 3.15 of the ACD we note that the committee considered that data collection in the CDF would not address the uncertainties in the post-cure mortality rate (Topic 2) and utility value (Topic 3). This directly contradicts the conclusions of TA677, which considered the use of KTE-X19 in mantel-cell lymphoma. In that appraisal, while the committee acknowledged the uncertainty with respect to long-term mortality and quality of the life, KTE-X19 was approved for the CDF on the basis of an SMR of 1.09 and the company base case assumption of general population quality of life after 5 years of progression-free survival (with decrements only considered as scenarios). We note that 5 years lies outside the data collection period within the CDF. Furthermore, "quality of life experienced by long-term survivors" is specifically listed within the TA677 Managed Access Agreement (MAA) as an item to be addressed via data collection within the CDF. Based on these justifications, we believe many of the ERG base case assumptions preferred by committee to be flawed. Whilst we accept the updated NHS tariff for delivery of KTE-X19, we present our arguments against the remainder of the committees preferred assumptions herein. We have therefore updated our base-case with the updated tariff of £41.1k (see Table 1).

Table 1: Company's ACD revised base case cost-effectiveness estimates

Interventions	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER
Overall population					
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,690
Ph- population					
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£33,044
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,602
Ph+ population					
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	£38,302
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

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It can be seen that all ICERs lie below the willingness-to-pay threshold for end-of-life therapies of £50,000 per QALY gained, demonstrating that KTE-X19 not only provides significant benefits in terms of improved patient prognosis, but is a cost-effective treatment for the National Health Service (NHS) in England and Wales.

In the absence of a CAR-T option for patients with R/R ALL over the age of 25, patients unable to access allo-SCT, either due to contraindications, lack of a matched donor, or remission status, are left with no potentially curative treatment option, with standard of care associated with median overall survival of 5-8 months. It is vital that both clinicians and patients have access to this innovative therapy, which, if recommended for use by NICE, will truly represent a paradigm shift in the treatment of adults over the age of 25 with R/R B-cell ALL. NICE recommendation would also ensure that patients of all ages with R/R B-cell ALL are able to access CAR-T therapy, a particularly important point in the context of allo-SCT eligibility, which decreases with age.

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Topic 1 Methods for indirect treatment comparison

ACD section 3.6: *The ERG also suggested using inverse hazard ratios derived from the MAIC analysis applied to the ZUMA-3 arm as baseline (an inverse hazard ratio method)...It considered this a reasonable approach since the company believes that matching patients to other studies rather than ZUMA-3 would be inappropriate…The committee concluded that it preferred the inverse of the hazard ratios method, over the MAIC and naive comparisons*.

Company response:

- The Company stands by its position that a naïve indirect comparison is appropriate for inotuzumab on the basis that the ERG's preferred approach is flawed.
- The ERG's preferred HR is flawed because it was derived from an unanchored MAIC, a method known to be at high risk of bias according to NICE Technical Support Document (TSD) 18. The ERG's method is further compromised by a small effective sample size (significantly below 30).
- The ERG's preferred HR lacks face validity based on the transitivity assumption; that is, it does not align with the HR that would be generated through an indirect comparison between the HR of KTE-X19 vs. blinatumomab in SCHOLAR-3 and the HR from a published anchored MAIC and STC of inotuzumab vs. blinatumomab (see section 1.3).
- The survival curve generated using the ERG's approach generates survival estimates for inotuzumab that lack face validity given the poor prognostic characteristics being adjusted to; short-term survival is overestimated, and the cure fraction is unrealistically high when considering the stem-cell transplant (SCT) rate and post-SCT survival rate observed in INO-VATE.

1.1 Summary

The Company's approach to comparison with inotuzumab was a naïve indirect comparison, in which survival curves were fitted independently to the ZUMA-3 and INO-VATE individual patient data (IPD). The ERG preferred a proportional hazards approach, whereby the inverse of the HR from the Company's MAIC was applied to

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the ZUMA-3 survival curve to derive a survival curve for inotuzumab. The ERG's rationale for this approach was that it maintained generalisability to the treated population (by using ZUMA-3 as the baseline survival curve) while adjusting for differences in the ZUMA-3 and INO-VATE populations (MAIC HR rather than naive).

The Company believes the assumption of proportional hazards to be flawed and disputes that the HRs from the MAICs should be the preferred source for the following reasons:

1) The ERG's value was obtained from an unanchored MAIC, which requires that all effect modifiers and prognostic variables be adjusted for. NICE TSD 18 states that "*This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate" also that "unanchored methods for population adjustment are problematic and should not be used when anchored methods can be applied*." (3).
2) The ERG's unanchored MAIC HRs were underpinned by a small sample size, an effective sample size (ESS) of [redacted] which is well below the preferred lower limit of 30. This compounds the uncertainty associated with an unanchored MAIC. For reference, The ESSs for the SCHOLAR-3 comparison vs. blinatumomab and naïve comparison vs. inotuzumab were substantially higher at [redacted] and [redacted] respectively.

We further demonstrate in sections 1.2 to 1.3 below that the ERG's proportional hazards (PH) approach using the MAIC HRs lacks validity:

3) Based on the transitivity assumption, the ERG's MAIC HR is not in line with that predicted when considering the HR from SCHOLAR-3 (the comparison which both the ERG and committee preferred vs. blinatumomab) and the HRs from a published anchored MAIC of inotuzumab vs. blinatumomab (4). That simple exercise estimates a HR for KTE-X19 vs. inotuzumab of [redacted] vs. the naïve HR of [redacted] preferred by the Company and the MAIC HR of [redacted] preferred by the ERG (see section 1.2)
4) The ERG's approach produces survival curves for inotuzumab that lack face validity as the survival estimates are unrealistically high. Given that KTE-X19 is targeted at a population with poorer prognostic factors than patients recruited

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to the INO-VATE study (2), the predicted survival curves for inotuzumab using the ERG's approach are better than expected given the observed survival curves from the INO-VATE study (see section 1.3). The ERG's predicted median OS of 10.35 months is in stark contrast to the Company's median OS of 7.59 months.

5) The ERG's approach generates cure fractions which are unrealistically high in contrast to observed pre-SCT and post-SCT survival rates from the INO-VATE study. The ERG's estimates lack face validity given that the population of patients likely to be treated with KTE-X19 is one unlikely to achieve SCT with existing therapies (see section 1.3).
6) The ERG criticised the SCHOLAR-3 analysis of KTE-X19 vs. blinatumomab because it matched to Phase 2 ZUMA-3 data rather than pooled Phase 1 and 2 data. We demonstrate that both the baseline characteristics and the survival outcomes differ little between the ZUMA-3 Phase 2 and pooled Phase 1 and 2 populations (see section 1.4).

1.2 The ERG's preferred approach is flawed because the transitivity assumption of indirect treatment comparisons does not hold

The key assumption underlying the validity of an indirect treatment comparison (ITC) is transitivity. The underlying assumption of ITC is that we can learn about the true relative effect of B versus C via treatment A by combining the true relative effects A versus B and A versus C. Transitivity requires that intervention A is similar when it appears in A versus B studies and A versus C studies with respect to characteristics (effect modifiers) that may affect the two relative effects (5).

Due to the single-arm nature of the ZUMA-3 trial, an anchored ITC was not possible and thus effectiveness against each comparator has been assessed in isolation. However, as discussed at technical engagement, an anchored MAIC/STC was published by Proskorovsky et al. (2019) that compared inotuzumab vs. blinatumomab (4). The Committee accepts that the SCHOLAR-3 analysis is representative of the treatment effect of KTE-X19 vs. blinatumomab, therefore it follows that the approximate treatment effect of KTE-X19 vs. inotuzumab should be derived by bridging to inotuzumab via the published inotuzumab vs. blinatumomab MAIC/STC using a simple Bucher approach (Bucher et al., 1997) (6) (see Figure 1). While this network is not anchored by randomised controlled trials both the comparisons of KTE-

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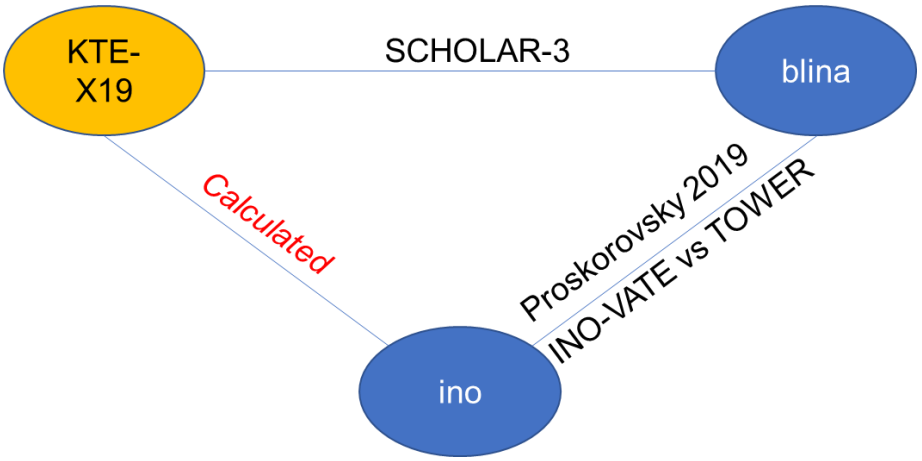
X19 vs. blinatumomab and those of inotuzumab vs. blinatumomab have been adjusted for in the Company's approach, noting that the hazard ratio for KTE-X19 vs. blinatumomab from the SCHOLAR-3 analysis [redacted] aligned closely with that of the naïve comparison vs. TOWER [redacted], 21-month regulatory subgroup). In the Proskorovsky analysis, adjustments using the MAIC vs. STC approaches improved the inotuzumab naïve HR of 1.06 vs. blinatumomab to 0.96 and 1.01, respectively (4)

Figure 1: network diagram of adjusted indirect comparisons



Key ino: inotuzumab; blina; blinatumomab

Based on the transitivity assumption, the HR of KTE vs inotuzumab can be calculated as:

$$HR_{KTE\text{-}X19\ vs.\ blinatumomab} * (1/HR)_{inotuzumab\ vs.\ blinatumomab}$$

The Company's approach produces sensible HRs whereas the ERG's approach produces a significantly higher HR.

Table 2 (highlighted in blue) shows that using the Proskorovsky MAIC and STC to derive a treatment effect for KTE-X19 vs. inotuzumab produces HRs of [redacted] and [redacted] using Proskorovsky's MAIC and STC respectively. These values are either identical or better than the naïve HR of [redacted] generated using the Company's naïve approach (highlighted in green). In contrast, the ERG's preferred approach (highlighted in red) produced a significantly higher HR, at [redacted].

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Table 2: Treatment effect of KTE-X19 vs. inotuzumab; comparison of methods

Comparison		Source	ESS	HR (CI)
A	KTE-X19 vs. blinatumomab	SCHOLAR-3 matched patient-level analysis	53	0.39 (0.23, 0.68)
B	KTE-X19 vs. blinatumomab	Naïve comparison vs. TOWER		0.37 (0.24, 0.57)
C	Inotuzumab vs. blinatumomab	Proslorovsky et al., 2019 anchored MAIC (4)	83/75 (Ino/SoC)	0.96 (0.61, 1.50)
D	Inotuzumab vs. blinatumomab	Proslorovsky et al., 2019 STC (4)	142/135 (Ino/SoC)	1.01 (0.65, 1.59)
E	KTE-X19 vs. inotuzumab (ERG approach)	Company's MAIC	[redacted]	[redacted]
F	KTE-X19 vs. inotuzumab (Company's approach)	Company's naïve ITC	[redacted]	[redacted]
G	KTE-X19 vs. inotuzumab (calculated using transitivity assumption; MAIC)	A * 1/C		[redacted]
H	KTE-X19 vs. inotuzumab (calculated using transitivity assumption; STC)	A * 1/D		[redacted]

Key: HR, hazard ratio; ino, inotuzumab; MAIC, matching-adjusted indirect comparison; SoC, standard of care; STC, simulated treatment comparison.

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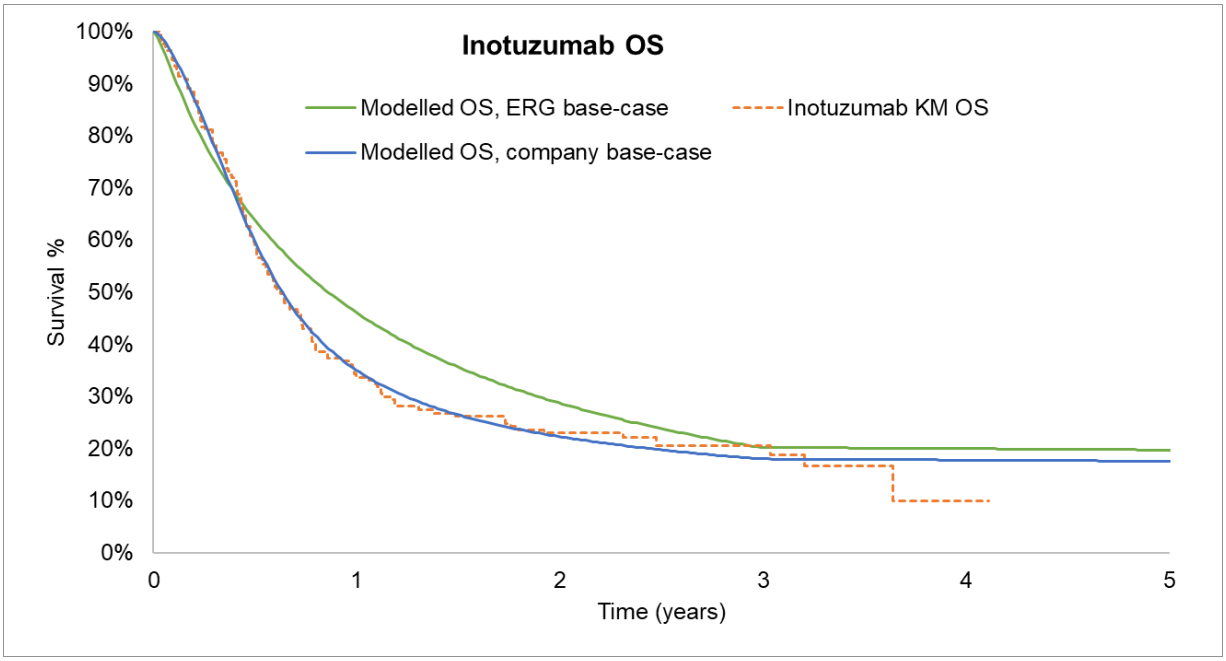
1.3 The ERG's preferred survival curves for inotuzumab lack face validity when compared with the results of INO-VATE

An important element of survival analysis is face validity. The ERG's PHs method of deriving survival curves for inotuzumab uses a lower HR for KTE-X19 vs. inotuzumab ([redacted] than the naïve approach preferred by the Company [redacted]) and therefore produces an inotuzumab survival curve that is more favourable than that observed in the INO-VATE study (see Figure 2 and Table 3). This lacks face validity given that KTE-X19 is targeted at a population unlikely to achieve SCT and given key prognostic factors in ZUMA-3 compared with INO-VATE (2).

Figure 2: Comparison of ERG's vs. Company's inotuzumab OS survival curves vs. INO-VATE



Key: KM, Kaplan-Meier; OS, overall survival

Table 3: Comparison of inotuzumab OS in ERG vs. Company base-case

Year	Proportion alive in inotuzumab arm	
	ERG base-case	Company base-case
1	46%	35%
2	29%	22%
3	20%	18%
4	20%	18%
5	20%	18%

Note: patients alive after 3 years are assumed to be cured and assume the mortality rate of the general population multiplied by a standardised mortality ratio of 1.09 (Company base case) or 4 (ERG base case).

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It can be seen, in Table 4, that ZUMA-3 patients had, on balance, more unfavourable prognostic factors than patients in INO-VATE. The exceptions are ECOG performance status and duration of first remission, which would only be expected to lead to better OS for inotuzumab once adjusted for if, and only if, *all other prognostic factors were equal between the two studies.*

Table 4: Comparison of key prognostic factors between INO-VATE and ZUMA-3

	ZUMA-3	INO-VATE	Difference
	Phase 1+2 combined >25 years	Inotuzumab arm	
Age (years), mean	48	47	1
ECOG score (%)			
0	28	38	10
1	72	49	23
2	0	13	13
Philadelphia +ve (%)	22	13	9
Prior SCT (%) (any)	40	18	22
1 prior line of therapy (%)	19	69	50
2 prior lines of therapy (%)	33	30	3
>2 prior lines of therapy (%)	47	1	46
Primary refractory (%)	31	16	15
Duration of first remission <12 months (%)	28	59	31
Prior blinatumomab (%)	49	0	49
Prior inotuzumab (%)	22	NR	

Key: ECOG, Eastern Cooperative Oncology Group; mITT, modified intention-to-treat;. NR: not reported; SCT: stem-cell transplant. Source: Kantarjian, 2016 (3) and Gilead data on file (7).

Better prognosis in ZUMA-3

Worse prognosis in ZUMA-3

Equal (≤5% difference)

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The median OS estimated by the ERG is 10.4 months which is unrealistically high and has not been validated by clinicians. The Company's approach is considered more appropriate as the predicted median OS is more realistic at 7.6 months (Figure 2) vs. the reported median of 7.7 months in INO-VATE (2). The better short-term survival in the ERG's survival curve is clearly a consequence of not only their preferred MAIC HR, which is less favourable than the naïve HR, but also the choice of a proportional hazards approach which has visibly led to a poor fit to the observed inotuzumab data.

As a reminder, the Company's model assumed that all patients who survived beyond 3 years were cured, regardless of intervention and modality of cure, whether via SCT or CAR-T. The cured fraction under the ERG's preferred analysis is 10% higher than the Company's (20% vs. 18%) which is unrealistically high. The Company's base-case cure assumption of 18% for inotuzumab was already generous compared with the outcomes observed in INO-VATE: in INO-VATE 48.2% (79 of 164) patients were reported to have received an SCT of which 67.1% (53 of 79) subsequently died. This leaves a maximum potential cure fraction of 15.9% vs. the ERG's estimate of 20%. Over the longer term, while the cure fraction in the ERG's analyses is only 2% more than in the Company's, the difference is extrapolated over the remaining 49 years of the model, thus the QALY difference compared with the Company's analysis accrues over a long-time horizon. This small difference in cure fraction alone leads to an increase of £1,725 in the Company's base case ICER vs. inotuzumab.

1.4 The results of SCHOLAR-3 are generalisable to the pooled Phase 1 and 2 dataset

The ERG has commented that it would have preferred that SCHOLAR-3 data were matched to both Phase 1 and Phase 2 data. The SCHOLAR-3 analysis was the key analysis undertaken to support the regulatory approval of KTE-X19. For all avoidance of doubt, we present below a comparison of both the baseline characteristics of pooled Phase 1 and Phase 2 data vs. Phase 2 alone (Table 5) as well as the ZUMA-3 Kaplan-Meier curves (Figure 3).

In terms of baseline characteristics, those with a difference of more than 5% in Phase 2 vs Phase 1 + 2 pooled were the % male (+6%), complex karyotype (+7%), relapse post all-SCT (+7%) and % bone marrow blasts after bridging chemotherapy (-6%).

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These small differences in baseline characteristics have visibly not led to any material difference in prognosis as evidenced in the Kaplan-Meier plots in Figure 3.

Table 5: Comparison of baseline characteristics of phase 2 vs. pooled phase 1 and 2

Baseline characteristics	Phase 2 (n = 55)	Phase 1 + 2 combined (n=78)
Age, median (range), y	40 (19, 84)	43 (18, 84)
Age category, n (%)		
< 65 years	47 (85)	[redacted]
≥ 65 years	8 (15)	[redacted]
Male, n (%)	33 (60)	[redacted]
ECOG performance status, n (%)		
0	16 (29)	[redacted]
1	39 (71)	[redacted]
Philadelphia chromosome t(9:22) mutation, n (%)	15 (27)	[redacted]
MLL translocation t(4:11) of Myc translocation t(8:14), n (%)	2 (4)	[redacted]
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	14 (25)	[redacted]
Low hypodiploidy (30–39 chromosomes), n (%)	1 (2)	[redacted]
Near triploidy (60–78 chromosomes), n (%)	1 (2)	[redacted]
Number of lines of prior therapy, n (%)		
1	10 (18)	[redacted]
2	19 (35)	[redacted]
≥3	26 (47)	[redacted]
Prior blinatumomab, n (%)	25 (45)	[redacted]
Prior inotuzumab ozogamicin, n (%)	12 (22)	[redacted]
Prior allogenic SCT, n (%)	23 (42)	[redacted]
Prior autologous SCT, n (%)	2 (4)	[redacted]
Prior radiotherapy, n (%)	13 (24)	[redacted]
Refractory, n (%)		
Primary refractory	18 (33)	[redacted]
R/R after ≥ 2 lines of therapy	43 (78)	[redacted]
R/R post-allo-SCT	24 (44)	[redacted]

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Baseline characteristics	Phase 2 (n = 55)	Phase 1 + 2 combined (n=78)
First relapse with remission ≤ 12 months	16 (29)	[redacted]
BM blasts at screening, median % (range)	65 (5.01–100)	[redacted]
BM blasts at baseline, median % (range)	60 (0–98)	[redacted]
BM blasts after bridging chemotherapy, median % (range)	59 (0–98)	[redacted]
BM blasts >25% at baseline, n (%)	40 (73)	[redacted]
Extramedullary disease at screening, n (%)	6 (11)	[redacted]
CNS disease at baseline, n (%)		
CNS-1	55 (100)	[redacted]
CNS-2	0 (0)	[redacted]

Key: BM, bone marrow; CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; LVD, longest vertical dimension; MLL, mixed lineage leukaemia; NR, no response; PD, progressive disease; PR, partial remission; SCT, stem cell transplant; STDEV, standard deviation.

Figure 3: Comparison of outcomes of phase 2 vs. pooled phase 1 and 2

Key: KM, Kaplan-Meier; EFS, event-free survival; OS, overall survival

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Table 6: Comparison of OS in phase 2 vs. pooled phase 1 and 2, ZUMA-3

Month	Overall survival – KTE-X19	
	Pooled phase 1 and 2 dataset (n=78)	Phase 2 dataset (n=55)
0	[redacted]	100%
3	[redacted]	83%
6	[redacted]	80%
9	[redacted]	73%
12	[redacted]	71%
15	[redacted]	66%
18	[redacted]	59%
21	[redacted]	47%
24	[redacted]	N/A

Note: The SCHOLAR-3 analysis has not yet been conducted in the over-25 patients.

Topic 2 Long-term risk of mortality for KTE-X19 treated patients relative to the general population

ACD section 3.8: *The clinical expert highlighted that the main risk of the disease relapsing is during the first year after treatment and that after that, relapse is unlikely. He further explained that the risk of dying was associated with having an allo-SCT. This is because of the risk of graft-versus-host disease. The clinical expert added that it is rare that people who have had a CAR T-cell therapy develop graft-versus-host disease [GvHD]. The committee understood that the risk of dying was linked to allo-SCT before the CAR T-cell therapy. So, it considered that the true standardised mortality ratio for this population would be aligned to the value proposed by ERG (a standardised mortality ratio of 4).*

Company response:

- The risk of dying is not linked to the risk of allo-SCT because all KTE-X19 patients are not expected to receive allo-SCT before CAR T-cell therapy; a standardised mortality ratio (SMR) of 4 is therefore inappropriate.
- Use of an SMR of 4 was appropriate for TA541, as inotuzumab is a treatment for which long-term outcomes are contingent on allo-SCT, this is not the case for KTE-X19.

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- Active GvHD is an exclusion criterion for KTE-X19 (as stated in the SmPC). As such, KTE-X19 treated patients are expected to be at a lower risk of long-term mortality relative to the population that informs the SMR of 4.
- The Company is of the opinion, should a higher SMR be adopted, that a blended SMR of 2.20 based on prior allo-SCT in ZUMA-3 (38%) is appropriate because long-term outcomes with KTE-X19 are not contingent on allo-SCT.
- Although the committee considered that collection of data in the CDF would not resolve this issue (ACD section 3.15), KTE-X19 was previously recommended for the CDF in the mantle-cell indication (TA677) on the basis of the Company's proposed SMR of 1.09.

2.1 Summary

The committee heard from clinical experts that the main risk of disease relapse is during the first year after treatment, and that after that relapse is unlikely. In addition, the clinical expert described how the increased risk of dying was associated with having an allo-SCT, primarily as a result of the risk of GvHD. Despite this distinction between allo-SCT and CAR-T with relation to long-term risk of mortality, the committee determined that the ERG's approach of using an SMR of 4.0 which was applied for TA541, sourced from Martin *et al.,* (2010), a paper that tracked long-term outcomes in patients – only 10% of which had ALL - surviving more than 5 years after haemopoietic stem cell transplant (HSCT) between 1970-2002 was most appropriate. The committee decision appears to be predicated on the flawed assumption that all patients to receive KTE-X19 in clinical practice will have previously received an allo-SCT.

In the appraisal of inotuzumab (TA541) where an SMR of 4 was used for decision-making, it was very clearly in the context of HSCT, as stated in section 6.2.2 of the ERG report '*most HSCT patients would continue to experience an elevated mortality compared to the general population*' (8). Whilst an SMR based on HSCT was appropriate for inotuzumab, a treatment for which long-term outcomes are contingent on allo-SCT, this is not appropriate for KTE-X19.

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Taking into consideration the committee's understanding that risk of death is linked to allo-SCT before the CAR-T cell therapy, we firmly contest the conclusion that an SMR based on long-term outcomes with HSCT that spanned 1970-2002 is appropriate. Instead, we would propose a blended SMR that uses the proportion of patients with prior SCT in ZUMA-3 (38%). As the study that is most generalisable to UK clinical practice, we consider this the most appropriate source for decision-making.

Finally, patients with active GvHD are not eligible for KTE-X19, as stated in the SmPC. We note the clinical expert at committee (ACD section 3.8): '*He [the clinical expert] further explained that the risk of dying was associated with having an allo-SCT. This is because of the risk of graft-versus-host disease*.'.

Therefore, not only do we contest the decision to use an SMR of 4, which was premised on the assumption that 100% of those treated with KTE-X19 in UK clinical practice will have received a prior SCT, we also anticipate that those that have received a prior SCT will be at a lower risk of long-term mortality as a result of eligibility being contingent on no active GvHD.

2.2 Committee decision is not aligned to positioning of KTE-X19 in clinical practice

In making their decision, '*the committee understood that the risk of dying was linked to allo-SCT before the CAR-T cell therapy*', which the clinical expert explained was due to the risk of GvHD, a risk not associated with CAR-T (ACD section 3.8). As such, the committee's conclusion that people receiving KTE-X19 are likely to be at a higher risk of mortality than the general population, and decision to use a source relating to long-term outcomes with HSCT is predicated on the flawed assumption that all patients to receive KTE-X19 in clinical practice will have received a prior SCT.

As described in the company submission, KTE-X19 is positioned for the treatment of adult patients 26 years of age and above with R/R B-cell precursor ALL, who fulfil one of the following criteria:

- Have relapsed post-SCT
- Are ineligible for SCT (on the basis of age, frailty, comorbidities or other criteria)

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- Are unlikely to achieve SCT via existing bridging therapies (primary refractory, relapsed within 12 months, failed ≥2 lines of prior therapy)

Based on this positioning, a large proportion of patients receiving KTE-X19 will not have had a prior allo-SCT, either due to a contraindication, or due to not achieving the complete remission required for eligibility. We strongly believe that the proportion without a prior allo-SCT is likely to be a majority in clinical practice.

For instance, in the pivotal trial of KTE-X19, ZUMA-3, only [redacted] ([redacted] of 63 subjects) in the combined Phase 1 + 2 population >25 years of age treated at target dose had received a prior allo-SCT at baseline. We note the committee preference for the inverse of hazard ratios method for indirect comparison, which by inference suggests they consider ZUMA-3 to be the trial population most generalisable to UK clinical practice. As such, our position is that a blended SMR between the company submission (1.09) and ERG preferred assumption based on 100% prior SCT (4.00) is most appropriate. We discuss this in detail in the following sub-section but based on the proportion of allo-SCT received in ZUMA-3, we propose applying an SMR of 2.20.

Data from the UKALL14 study of standard induction chemotherapy vs standard induction therapy + rituximab in adult ALL provides additional support for our approach (9). In this study, which took place between 2012 and 2017 in the UK, 54% received allo-SCT as first-line consolidation due to high-risk features, which included both myeloablative and reduced intensity conditioning, aligned to current practice with SCT. Notably, UKALL14 excludes adults >65 years of age, none of whom are expected to be eligible for allo-SCT. As such, 54% is an overestimate.

Furthermore, trials of treatments which constitute standard of care in England, specifically inotuzumab and blinatumomab provide another source of evidence. Long-term survival with these treatments is largely contingent on subsequent SCT, with the Scottish Medicines Consortium even restricting usage of inotuzumab to patients for whom the intent is to proceed to SCT (10). In this context, one would expect the clinical trials of blinatumomab and inotuzumab to set an upper limit to likely SCT usage with SoC. Notably, in TOWER, only 24% (65 of 271 subjects) went on to receive allo-SCT (11), whilst the final report for INO-VATE stated 48.2% (79 of 164 subjects) went on to receive allo-SCT at any time after study treatment (2).

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As the most generalisable study to UK clinical practice, we consider the 38% prior SCT in ZUMA-3 as the most appropriate figure for decision making. This figure also sits approximately halfway between that found in trials of SoC comparator therapies, providing further rationale for its adoption.

We explored a scenario in the model where the SMR applied to cured patients was a weighted average of the ERG's preferred SMR (4) and that of the company (1.09). The SMR was weighted by the proportion of KTE-X19 patients in ZUMA-3 who had received an allo-SCT. The SMR of 4 was applied to those that had received an allo-SCT whilst 1.09 was applied to the remaining proportion of patients. The proportion of allo-SCT recipients ([redacted] was informed by the proportion who had received prior SCT at baseline ([redacted] out of 63 patients) in the ZUMA-3 population ≥26 years of age. This resulted in an SMR of 2.20. The results for this scenario are reported in Table 7.

Table 7: Scenario assuming a weighted average SMR (2.20) based on % of allo-SCT in ZUMA-3

Comparator	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALYs)	Company base-case ICER
Overall population					
Inotuzumab	[redacted]	5.735	[redacted]	£26,126	£23,690
Ph- population					
Blinatumomab	[redacted]	6.644	[redacted]	£36,716	£33,044
Inotuzumab	[redacted]	4.871	[redacted]	£29,302	£26,602
Ph+ population					
Ponatinib	[redacted]	7.083	[redacted]	£42,325	£38,302
Inotuzumab	[redacted]	5.660	[redacted]	£25,506	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

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2.3 The ERG SMR source is not generalisable to KTE-X19 in R/R adult ALL

The ERG proposed a standardised mortality ratio of 4, sourced from a study in relapsed or refractory B-cell acute lymphoblastic leukaemia in which the mortality risk ranged between 4 and 9. It noted that it had chosen the lowest value in the study, which was a conservative approach.

(ACD section 3.8, pp.11)

The company have several concerns with the ERG's preferred source, as well as the way it has been represented in the ACD. The Martin *et al.,* (2010) paper investigates long-term survival in patients receiving HSCT in a range of cancers from 1970-2002 (12). Contrary to the ACD which represents Martin *et al*., (2010) as a study in R/R B-cell ALL, only 11% of 5-year survivors (279 of 2,574 subjects) had a diagnosis of ALL, with far more subjects diagnosed with acute myeloid leukaemia (552 of 2,574 subjects) or chronic myeloid leukaemia (799 of 2,574 subjects). As such, the generalisability of this study from a patient population perspective is questionable (12).

Secondly, and most importantly, this study exclusively relates to patients who had received a HSCT. The clinical expert at committee was clear that the risk of dying was associated with having an allo-SCT, because of the risk of GvHD. As such, and as already described in Section 2.2, a study investigating long-term risk of mortality in patients who received a HSCT is not generalisable to use of KTE-X19 in UK clinical practice and is likely to over-estimate the long-term SMR.

Finally, the characterisation of an SMR of 4 as a conservative estimate is somewhat disingenuous. As described in the committee papers for TA541, this approach was used to mitigate concerns about the historic nature of the cohort in the ERG's preferred source: '*The ERG acknowledges that many of the studies are derived from historic cohorts and hence may over-estimate mortality compared to current practice*.'. This is especially relevant during the current appraisal, which is taking place five years on from the inotuzumab appraisal, and 50 years after data collection began on the ERG's preferred source (8). For example, there were 17 deaths caused by hepatitis C observed in the HSCT study. All of these occurred prior to 1990, when hepatitis C screening of transplantation and transfusion donors became available (12). Furthermore, the UKALL12 study published in 2008 observed a 36% transplant-

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related mortality (TRM) at 2 years, whereas UKALL14 observed only 19.6% TRM at 4 years, providing UK-specific evidence for the improved safety of SCT through developments such as reduced-intensity chemotherapy (13, 14). As such, we would challenge any characterisation of the SMR of 4 being a conservative estimate, or some sort of middle ground, in the context of this appraisal.

The clinical expert at committee '*explained that the risk of dying was associated with having an allo-SCT. This is because of the risk of graft-versus-host disease*.'. Notably, active GvHD is included as a reason to delay treatment under the 'special warnings and precautions for use' section of the SmPC for KTE-X19 (15). It is further stated that KTE-X19 treatment should be delayed until this has resolved.

Real-world evidence in the UK supports the exclusion of ALL patients with active GvHD from eligibility for CAR-T. In an analysis of all patients discussed for treatment with tisagenlecleucel up to 15th June 2022, it was reported that of 148 patients screened, three were ineligible due to GvHD (16).

Therefore, not only do we contest the assumption that 100% of those treated with KTE-X19 in UK clinical practice will have received a prior SCT, but we also anticipate that those that have received a prior SCT will be at a lower risk of long-term mortality as a result of eligibility for KTE-X19 being contingent on no active GvHD.

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Topic 3 Long-term quality of life for KTE-X19 treated patients relative to the general population

ACD section 3.9: *The company's model assumed that people who had autologous anti-CD19-transduced CD3+ cells and whose disease had not progressed after 3 years of treatment would have the same health-related quality of life as that of the same age- and sex-matched general population in the UK. The ERG had received clinical advice that there is cumulative toxicity from previous therapies, and that the disease itself reduced quality of life. Therefore, the ERG proposed a utility multiplier of 0.92 applied to the general population utility values to adjust for lower quality of life. This was a midpoint between the utility value after the infusion and before relapse, and the general population of a similar age. The clinical experts explained that there is not enough evidence in CAR T-cell therapies to support either approach. People can live a near normal life after treatment with the new technology and can return to daily activities soon after having a CAR T-cell therapy. The clinical expert also explained that CAR T-cell therapy can lead to better quality of life because the treatment is given in an outpatient setting and so people need less time in hospital.*

Company response:

- The ERG's rationale for applying a utility decrement to cured patients is flawed given the large difference in short vs long-term health-related quality of life (HRQoL).
- The ERG's key argument is that it is unrealistic to assume no HRQoL decrement in cured patients if there is an increased mortality risk compared to the general population.
- However, the ERG chose a mid-point between the HRQoL of responding patients in ZUMA-3 and the general population, which is disproportionate to the mortality risks of a patient who has recently undergone treatment vs. one considered cured of their ALL. This is contradictory to the ERG's rationale that mortality and HRQoL are correlated.

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- Furthermore, we fundamentally disagree with the rationale that mortality and HRQoL are correlated, given that mortality can be driven by acute events that do not impact HRQoL on a daily basis in cured patients.
- The Company stands by its assertion that patients who have been cured by treatment with a CAR-T will over the longer-term have the HRQoL of the general population (which already captures the HRQoL of cancer survivors and patients who have received other aggressive treatments and interventions).
- Although the committee considered that collection of data in the CDF would not resolve this issue (ACD section 3.15), KTE-X19 was previously recommended for the CDF in the mantle-cell indication (TA677) on the basis of the Company's base case, which assumed general population utility after 5-years progression-free. Furthermore, "quality of life experienced by long-term survivors" is specifically listed within the TA677 MAA document(17) as an item to be addressed via data collection.

3.1 Summary

The committee preferred a HRQoL decrement to be applied to cured patients because they had understood that people whose disease has not progressed will have a worse health-related quality of life than the general population because of the risks associated with CAR T-cell treatments and the effect of previous therapies. The ERG argued that it is unrealistic to assume no HRQoL decrement in cured patients if there is an increased mortality risk compared to the general population.

As discussed in ACM1 and highlighted within the ACD, mortality risk for CAR-T recipients is greatest during the short-term period following treatment. The short-term mortality risks, which are largely ALL-specific, are far less likely to have an impact on the long-term HRQoL of cured patients. The ERG's post-cure utility decrement, set at half the pre-cure utility decrement, is therefore disproportionate to the mortality risk pre- vs post-cure.

Furthermore, in assuming a relationship between mortality risk and HRQoL, the ERG is assuming that mortality risk is linked with the same morbidities that lead to poor quality of life. We previously demonstrated in Topic 2 that patients treated with KTE-X19 would not be subject to GvHD and therefore would sustain no decrement with

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respect to this mortality risk. A further potential cause of mortality, infection, is more frequent with GvHD and is not incurred on a chronic basis. The underlying reason for being at higher risk of infection, that of a weakened immune system, is not uncommon throughout the general population and likely captured within general population utility values given the average age of the cohort receiving KTE-X19.

3.2 The ERG's utility decrement is disproportionate to the mortality risk

In the ERG's critique of the company's response to technical engagement, they state, *'The ERG therefore maintains its logic that "the assumption that patients are cured without residual comorbidities would not appear consistent with the assumption that patients have an increased risk of death compared to the age- and sex-matched population" and maintains its utility multiplier of 0.92'.* The ERG's rationale for applying a utility multiplier for cured patients is thus directly linked to the application of a SMR.

The ERG applied a multiplier which represented the mid-point between the utility value after the infusion and before relapse and the general population of a similar age. However, as stated in the ACD, the risk of death is far greater in the short-term. As discussed in the previous section, section 3.8 of the ACD states '*the clinical expert highlighted that the main risk of the disease relapsing is during the first year after treatment and that after that, relapse is unlikely. He further explained that the risk of dying was associated with having an allo-SCT.'*

Furthermore, as discussed in Topic 2 patients treated with KTE-X19 would not be at risk of GvHD, one of the key risk factors leading to increased mortality post-SCT Sohl *et al*., 2018 and a significant contributor to the ERG's preferred SMR (18). If KTE-X19 patients are at low risk of GvHD then it follows that GvHD is not a contributor to HRQoL. A mid-point between the short-term disutility of R/R-ALL and general population utility is therefore disproportionate given the relative mortality risk post- vs. pre-cure timepoint and is not in alignment with the ERG's rationale.

3.3 HRQoL is not necessarily correlated with mortality risk

We disagree fundamentally with the assumption that a higher long-term mortality risk is necessarily associated with poorer HRQoL. For example, another major contributor to mortality post-SCT is infection; however, infection would not impact HRQoL on a chronic basis but rather may occur acutely in response to a weakened immune system. As the committee are well aware following the COVID-19 pandemic, a large

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proportion of the population are at higher risk of mortality due to weakened immune systems (including cancer survivors and those taking immunosuppressants for other conditions) and their daily HRQoL would already be captured within general population estimates for this age group. This is not the case for tisagenlecleucel for example, which concerns a far younger group of patients.

In summary, we firmly refute the ERG's assertion that higher post-cure mortality justifies the post-cure utility decrement proposed by the ERG. Table 8, presented below, provides a summary of the utility assumptions accepted for cured patients in previous appraisals of relevance. As can be seen in Table 8, the committee's preferred utility assumptions for this appraisal are in general pessimistic compared with those accepted in previous appraisals. Furthermore, in TA677 (KTE-X19 in mantle-cell lymphoma), while a higher post-cure mortality rate was assumed in the base case a post-cure utility decrement was only considered as a scenario by the committee. The only appraisals in which a utility decrement was applied in the base case were those for tisagenlecleucel and inotuzumab. The mean age of patients offered tisagenlecleucel is approximately 12 (based on the ENSIGN study in the tisagenlecleucel committee slides)(8). The general population at this age is largely naïve to cancer treatments, let alone treatment for other conditions that would be prevalent in the general population at the baseline age in ZUMA-3 of 46 years. Long-term survival with inotuzumab is contingent on allo-SCT and post-cure utility decrements allocated to inotuzumab in that appraisal would not apply to KTE-X19 for reasons discussed in this and the previous sections.

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Table 8: Utility assumptions applied in previous appraisals of relevance

Technology appraisal	Post-cure QoL assumption	ERG	Committee
Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA559)	General population utility	York	Committee C
Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554)	Event-free survival utility value (0.91) allocated to the long-term survivors	York	Committee C
Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma (TA677)	The same health-related quality of life as the general population.	York	Committee A
Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (TA541)	Committee concluded that utility values 5 years post-transplant are likely to be between those presented in Kurosawa *et al.,* (2016) (0.76) and the value for the general population (0.88).	York	Committee C
Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (TA450)	General population utility.	Warwick	Committee A

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Topic 4 Exclusion of allo-SCT related costs

ACD Section 3.10: *The company stated that the technology is not planned to be used after [Note: should be before] an allo-SCT in UK clinical practice. It had done a sensitivity analysis adjusting for overall survival, censoring for allo-SCT, and no statistical difference was found. The ERG stated that the sensitivity analysis was not sufficiently powered to detect a difference. It also noted that an allo-SCT could have provided a survival advantage to the people who had had one. The clinical experts stated that allo-SCT would be considered for some people whose disease had relapsed after having a CAR T-cell therapy and who were well enough to have this procedure.*

Company response:

- The statistical analysis of overall survival, censoring for allo-SCT in ZUMA-3, was based on patients who received a pre-planned allo-SCT.
- The Company considered the sensitivity analysis to be informative despite lacking statistical power as it showed little or no difference between transplanted and non-transplanted patients, based on patient numbers similar to those anticipated to be treated with KTE-X19 in clinical practice.
- Allo-SCT's performed in ZUMA-3 were pre-planned either due to high-risk prognostic factors and/or limited long-term data on KTE-X19 at time of enrolment.
- [redacted] of 14 subjects to receive subsequent SCT were in CR/CRi per central assessment, with [redacted] per investigator and [redacted] in a patient with extramedullary disease per investigator.
- [redacted], therefore no survival advantage is expected in patients who received a pre-planned allo-SCT in ZUMA-3.
- Further support comes from the observation that survival of patients who received allo-SCT in ZUMA-3, despite their high-risk features, far exceeded that of patients who received SCT following treatment with other therapies for ALL., suggesting that the survival benefit came from KTE-X19, not the allo-SCT.
- Uncertainties regarding allo-SCT rates and survival estimates could be addressed by data collection in the Cancer Drugs Fund.

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4.1 Summary

The committee preferred the ERG's approach, including the costs & QALY loss aligned to ZUMA-3 where, 14 out of 78 subjects had an allo-SCT post treatment with KTE-X19. This cost & QALY impact was not included in the economic model, based on the understanding that allo-SCT would not be used after KTE-X19 in clinical practice, as well as the fact that allo-SCTs in ZUMA-3 were pre-planned rather than in response to worsening prognosis. Furthermore, in a sensitivity analysis censoring for allo-SCT, overall survival appeared independent of subsequent allo-SCT.

The ERG had stated the sensitivity analysis was not sufficiently powered, and the committee concluded that allo-SCT costs and QALY loss should be included in the model for people having KTE-X19.

Of the 14 of 78 subjects to receive allo-SCT in ZUMA-3:

- [redacted] of 14 had achieved CR/CRi per central assessment, with [redacted] achieving CRi per investigator assessment. [redacted] had achieved partial remission per investigator assessment.
- Of the [redacted] subjects for which the study investigator provided a reason [redacted] were pre-planned due to poor prognostic factors, and the other [redacted] were due to uncertainty about the long-term data relating to KTE-X19 at the time of study enrolment.
- [redacted] received an allo-SCT following treatment with subsequent therapy.

As posed by the ERG for clarification question A2, the fact that almost all these allo-SCTs were not in response to a decline in prognosis, and instead pre-planned in patients who had achieved remission, is supportive of the statement that survival is independent of allo-SCT. Further support for this statement comes from the aforementioned sensitivity analysis, which found no statistically significant difference between those who received subsequent allo-SCT in ZUMA-3 and those who did not.

Therefore, the company re-state our view that patients in ZUMA-3 did not benefit from allo-SCTs performed in ZUMA-3, and use of subsequent allo-SCT is not anticipated in UK clinical practice. As such, we maintain our position that allo-SCT should not be included as a subsequent treatment option for patients who receive KTE-X19 in the

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economic model (inclusion of the [redacted] who received KTE-X19 following subsequent therapy only increases the ICER by £100). Furthermore, the uncertainty relating to this assumption could clearly be addressed via data collection in the Cancer Drugs Fund, given that the majority of relapses and deaths occur in the shorter term.

4.2 Allo-SCT in ZUMA-3 were pre-planned & performed for patients in remission

As explored at clarification, the ERG were of the belief that if allo-SCTs performed in ZUMA-3 were in response to a decline in prognosis following KTE-X19 treatment, this would confound the statement that survival is independent of subsequent allo-SCT.

[redacted] Clearly, based on the clinician feedback received during ACM1 that "*allo-SCT would be considered for some people whose disease had relapsed after having a CAR T-cell therapy and who were well enough to have this procedure."*, the vast majority of allo-SCTs carried out during ZUMA-3 would not be carried out in clinical practice. Furthermore, this expectation could be confirmed via data collection in the CDF.

Table 9: Summary characteristics of patients that received an allo-SCT subsequent to KTE-X19 in ZUMA-3

	mITT Phase 1 and 2, (n = 14)
Pre-planned/transplanted due to high-risk features*	[redacted] for which data were available ([redacted])*
Prior allogeneic SCT	[redacted]
Primary refractory	[redacted]
First remission <= 12 months12 months	[redacted]
R/R after >=2 lines of therapy	[redacted]
In CR/CRi	[redacted]
Transplanted following salvage therapy	[redacted]
Note: [redacted]	

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4.3 Sensitivity analysis demonstrates that survival in ZUMA-3 was independent of allo-SCT

The Company reiterates that a sensitivity analysis of OS in patients with an overall complete response (OCR) stratified by receipt of allo-SCT, demonstrated that OS in responders appeared to be independent of subsequent allo-SCT (Figure 4). Kaplan-Meier estimates of OS for non-transplanted patients at 1 year and 2 years were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively (Table 10). While OS is numerically lower in those not transplanted following this period, numbers are too low to draw conclusions. In the following section, we further demonstrate that the OS of the transplanted patients exceeds that seen in R/R-ALL patients transplanted following other treatments and that by inference, a large proportion of the survival benefit comes from KTE-X19 and not transplantation.

Figure 4: Kaplan-Meier plot of OS for OCR subjects using investigator review by subsequent allogeneic SCT group

Data cutoff date = 23/07/21; Phase 1 + 2 target dose
Key: CI, confidence interval; NE, not evaluable; NR, not reached; OCR, overall complete remission; SCT, stem cell transplant.
Source: (3).

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Table 10: OS outcomes for OCR subjects using investigator review by subsequent allogeneic SCT group

	KTE-X19 + Subsequent SCT (N = [redacted])	KTE-X19 alone (N = [redacted])	All OCR Subjects (N = 58)
Number of subjects, n	[redacted]	[redacted]	58
Death, n (%)	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]
Death after DCO, n (%)	[redacted]	[redacted]	[redacted]
Alive on or after DCO, n (%)	[redacted]	[redacted]	[redacted]
Full withdrawal of consent, n (%)	[redacted]	[redacted]	[redacted]
Lost to follow-up, n (%)	[redacted]	[redacted]	[redacted]
KM median (95% CI) OS (months)	[redacted]	[redacted]	[redacted]
Min, Max OS (months)	[redacted]	[redacted]	[redacted]
Survival rates (%) (95% CI) by KM estimation at			
6 months	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]
42 months	[redacted]	[redacted]	[redacted]
48 months	[redacted]	[redacted]	[redacted]
54 months	[redacted]	[redacted]	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]	[redacted]	[redacted]

Data cutoff date = 23Jul2021.
Abbreviations: CI, confidence interval; DCO, data cutoff date; KM, Kaplan-Meier; NE, not estimable; NR, not reached; OS, overall survival; OCR, overall complete remission; SCT, stem cell transplant.
Note: Overall survival for subjects treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. '+' indicates censoring.

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4.4 The outcomes of transplanted patients in ZUMA-3 exceed those of patients transplanted following other therapies

As summarised in Table 10, 1- and 2-year survival in OCR patients in ZUMA-3 who received allo-SCT was [redacted] and [redacted] respectively, with the median not yet reached, despite the high proportion of these patients with high-risk features (see Table 9).

In contrast, outcomes were worse following SCT for comparator treatments in R/R-ALL: In INO-VATE, of the complete response/complete response with incomplete haematological recovery (CR/CRi) patients who received allo-SCT post inotuzumab (n=71), median survival was 12.6 months (9.3, 27.7) and 2 year survival was 39.4% (28.1, 50.5) compared with a median OS of 7.1 (5.6, 10.8) months and 2 year survival of 13.1% (5.4, 24.4) for patients with no follow-up HSCT, HR 0.55 (97.5% CI, 0.32, 0.95) p=0.0065 (2).

In TOWER, which notably excluded Ph+ patients, among patients treated with blinatumomab who achieved CR, CRh or CRi, there was not enough evidence that patients receiving HSCT had a survival benefit compared with those who did not (p=0.69) (11). Therefore, based on outcomes from INO-VATE, at most 55% of the survival benefit can be attributed to the SCT, although the company firmly believes the data from the subgroup of transplanted patients from ZUMA-3 demonstrate survival to be robust in the absence of allo-SCT. Despite this, we have carried out a scenario analysis whereby 50% of the costs and QALY loss of allo-SCT are included in the model in the following section.

4.5 Scenario analysis assuming only a proportion of the costs of transplantation are included

Following on from the previous section, we carry out scenario analyses whereby either 50% of the costs and QALY loss of allo-SCT are included in the economic model.

In the ZUMA-3 population, 14 out of 78 (18%) of KTE-X19 patients (Phase 1 and 2 combined dataset) received subsequent allo-SCT. The ERG's preferred base-case, which includes allo-SCT as a subsequent treatment for KTE-X19 patients, assumes that all patients who received a subsequent allo-SCT in ZUMA-3 would receive this as a subsequent treatment in the real-world clinical setting. The cost-effectiveness model

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captures the cost and HRQoL decrement associated with allo-SCT for patients who receive this treatment. We explored a scenario in the model whereby only a proportion of the costs and utility decrement associated with allo-SCT are applied. In the first scenario, we include 50% of the costs and QALY loss of allo-SCT (Table 11).

Table 11: Cost-effectiveness results, scenario assuming 50% of allo-SCT costs and QALY loss

Comparator	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALYs)	Company base-case ICER*
Overall population					
Inotuzumab	[redacted]	6.934	[redacted]	£26,491	£23,690
Ph- population					
Blinatumomab	[redacted]	8.059	[redacted]	£35,730	£33,044
Inotuzumab	[redacted]	5.889	[redacted]	£29,922	£26,602
Ph+ population					
Ponatinib	[redacted]	8.579	[redacted]	£40,771	£38,302
Inotuzumab	[redacted]	6.842	[redacted]	£25,962	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

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Topic 5 NHS tariff

ACD section 3.11 *The committee was concerned that the company's costs underestimated the true cost of delivering autologous anti-CD19-transduced CD3+ cells. It noted that the company's cost was significantly less than the figure provided by NHS England. It noted that it was difficult to compare the company's cost with the NHS England tariff because they were reported differently. In the absence of an HRG, the NHS England estimate was the best available source for the costs of delivering CAR T-cell therapy. The committee considered that some costs included in the NHS estimate of £65,415 were already captured in the company's model. It concluded that a CAR T-cell administration cost of £60,000 was more relevant for decision making, but this value should be reviewed if any new evidence is presented.*

Company response:

- The tariff proposed by NHS England is unrepresentative of the true cost of delivering CAR T-cells because it was based on a prospective costing exercise at only one NHS centre
- The Company's estimate of the true cost of delivering CAR T-cells is more appropriate because it follows published methods and NICE guidance on the costing of cell therapy products.
- The NHS England tariff does not adjust for proportions receiving CAR-T infusion and surviving over the costing period.
- Real-world studies have demonstrated that treatment with CAR-T consumes substantially less healthcare resource than other potential modalities of cure such as allo- or auto-SCT. Using published NHS reference costs for allo- and auto-SCT and a US study as a reference point, we demonstrate that the costs in the economic model are perfectly aligned with the published evidence.
- Conversely, using the same published NHS reference costs and study, the NHS tariff may overestimate costs by over double the actual cost to the NHS.

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5.1 Summary

The committee applied a tariff cost of £65,415. NHS England explained that it worked with a single NHS trust to provide a reasonable distribution of the total tariff costs across the different phases of treatment. NHS England explained that there is not a Healthcare Resource Group (HRG) that captures CAR T-cell therapies. It also commented that a key difference between its estimate of costs and the company's costs is the number of staff who look after people who have had CAR T-cell therapy. Since publication of the ACD NHS England has agreed a lower tariff of £41.1k for the Cancer Drugs Fund re-appraisal of axicabtagene ciloleucel for treating diffuse large B-cell lymphoma after 2 or more systematic therapies [ID3980].

Whilst we believe that the tariff issue is resolved at £41.1k when appropriate like for like changes have been made, we feel we need to reiterate our objection to the original position in the ACD. Following the first committee meeting for this appraisal, the Committee adopted a CAR-T administration cost of £60,000. We are confident the issue of the uncertainty of cost of treatment has now been resolved by NICE and NHS England as set out above, but as £60,000 is referred to in the published ACD would like to take the opportunity to reiterate that we remain deeply concerned about any use of this figure, given the lack of the clarity on the proposed tariff coverage, and apparent over-estimation of costs proposed by NHS England as previously communicated.

The Company has been given access to NHS England's tariff costing sheet and compared it with the costs included in the economic model. The costs in the economic model sum up to £26,902 vs. the NHS England's tariff of £41.1k when considered over the same time period of up to 100 days post-infusion. We have therefore updated our base case to adopt a tariff of £41.1k but have in exchange removed all healthcare resource costs other than the acquisition cost of KTE-X19, the costs of subsequent treatment and the cost of subsequent allo-SCT up to day 100 in the model, as we believe the £41.1k remains a substantial overestimate based on our analyses below:

- The tariff cost is based on a prospective micro costing exercise at one UK centre, whereas NICE methods specify that NHS reference costs should be used, as these represent actual costs incurred by multiple NHS trusts submitting data. The Company has applied published NHS reference costs in

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its costing approach, in line with both NICE methods and those recommended in Hettle et al (2017)(19).

- The tariff cost includes costs incurred from identification and work-up up to day 100 post-infusion. In the model, the ERG applied the tariff as a lump sum replacing other individual costs that had been applied in the model to the proportion of patients alive and receiving different stages of treatment such as pre-conditioning and infusion. Thus, the tariff cost appears to assume that all patients incur the costs of treatment over 100 days of follow-up whereas in the ZUMA-3 study, 96% of patients proceeded to infusion and [redacted] of patients had died by 100 days (economic model estimate), so a substantial proportion of the costs included in the tariff would not be incurred for the average patient targeted for KTE-X19 treatment.
- The tariff is far higher than the costs identified by the Company in a targeted literature review. The review identified six recently published studies that provide absolute or comparative cost data for CAR T-cell therapies and/or allo- and/or autologous stem cell transplant (auto-SCT) (20-26). Across all studies, the mean total hospitalization costs associated with inpatient CAR T-cell administration was £35,402 (converted value, including US studies where healthcare costs are far higher). In a large-scale process analysis study in Switzerland, total costs associated with CAR T-cell therapy administration were shown to be 29% lower than costs associated with auto-SCT administration including 29% lower staff costs, 69% lower concomitant medication and material costs and 9% lower surcharge costs (Ring, Grob et al. 2022). A 29% reduction in the cost of auto-SCT in the UK NHS (£17,570 according to published NHS reference costs, see Table 12) equates to only £12,475.
- Both allo- and auto- SCT were shown to incur substantially higher non-pharmacy costs than treatment with CAR-T in the study presented by Cui *et al.,* (2022) (26) at the recent American Society of Hematology (ASH) conference (1) (see Table 12). Shorter hospital stays for CAR-T therapy patients contributed to this cost differential. The costs of CAR-T delivery (excluding acquisition costs) in that study were 57% lower than those of allo-SCT and 24% lower than those of auto-SCT. The Company's estimate of CAR-T delivery cost was similarly 57% lower than the NHS reference costs of allo-SCT but 53%

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higher than those of auto-SCT. In stark contrast, the proposed NHS England tariff for CAR-T delivery is only 34% lower than the NHS reference costs of allo-SCT and 134% *higher* than the costs of auto-SCT. The NHS England tariff therefore appears to be substantially overestimated when considering the published NHS reference costs for comparator modalities of cure and the relative costs of treatment observed from real-world evidence in the US.

Table 12: Comparison of costs of CAR-T vs. allo- and auto-SCT

Treatment	Cost source	CAR-T	Allo-SCT	Auto-SCT
UK NHS costs				
CAR-T	NHS England proposed tariff (up to day 100)	£41.1k		
CAR-T	The Company model costing (all HRU costs up to day 100, excluding CAR-T acquisition)	£26,902		
Stem cell harvest	UK NHS reference cost SA187 (N=83)		£4,774	£4,774
SCT	UK NHS reference cost, weighted average of sibling, volunteer unrelated and haplo-identical donor allo-graft, adults (N=14). UK NHS reference cost, auto-graft, adults (N=26)		£57,868	£13,374
SCT	Total cost stem cell harvest and graft		£62,642	£17,570
NHS England CAR-T tariff vs. SCT NHS reference costs		**Reference**	**66%**	**234%**
The Company model CAR-T costs vs. SCT NHS reference cost		**Reference**	**43%**	**153%**
US costs, Cui e*t al.,* (2022)(26)				
CAR-T	Tecartus™ published US list price (price assuming 20% manufacturer rebate)(27, 28)	$373,000 ($298,400)		
All	Pharmacy costs (minus 80% of the published list price of Tecartus™ for CAR-T)	$31,670	$57,701	$44,770
SCT	Non-pharmacy costs	$41,375	$111,594	$51,778
All	Total costs (minus CAR-T acquisition costs)	$73,045	$169,295	$95,548
CAR-T US costs (minus CAR-T acquisition) vs. SCT US costs		**Reference**	**43%**	**76%**

Key : HRU, healthcare resource use.

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The cost-effectiveness results with the tariff applied are reported in Table 13 and represent the updated company base-case following the ACD.

Table 13: Updated Company base-case cost-effectiveness results, with tariff for KTE-X19 delivery

Comparator	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALYs)
Overall population				
Inotuzumab	[redacted]	6.934	[redacted]	£23,690
Ph- population				
Blinatumomab	[redacted]	8.059	[redacted]	£33,044
Inotuzumab	[redacted]	5.889	[redacted]	£26,602
Ph+ population				
Ponatinib	[redacted]	8.579	[redacted]	£38,302
Inotuzumab	[redacted]	6.842	[redacted]	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

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Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

Consultation on the appraisal consultation document – deadline for comments 5pm on 20 December 2022. Please submit via NICE Docs.

	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):	**Leukaemia Care**
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]

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	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.
Example 1	We are concerned that this recommendation may imply that ……..
1	The ACD papers commented that it was uncertain whether autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (CAR-T) would be considered a cure. This was because analysis conducted by the ERG did not distinguish between people who had an allogeneic stem cell transplant (SCT) before treatment with CAR-T and those who did not, meaning survival benefit could not be solely attributed to the treatment being appraised. However, the clinical expert said that the treatment could potentially lead to a cure in some people and that curative outcomes can be seen in the real-world evidence of those in the indication in question. Additionally in the experience of the patient expert, CAR-T appears to have been curative. We would therefore like the committee to reconsider CAR-T's curative effects and accept more uncertainty in light of the innovation this represents to patients, and to give people over 25 years old equal access to a treatment with great clinical benefit.
2	Secondly, we ask the committee to re-evaluate the point at which the treatment is considered a cure. It would be unfair and unreasonable to define cure differently to what is seen in people with the same diagnosis who can receive existing CAR-T treatments, such as tisagenlecleucel. In the appraisal of tisagenleleucel for ALL patients under 25 (ID554), a cure of 3 years was considered appropriate. We therefore request an explanation from the committee on why their decision on the curative duration of CAR-T differs from the appraisal ID554. Furthermore, we believe there ought to be consistency on this point between all ALL CAR-T appraisals. Other clinical characteristics, such as the efficacy in subgroups, has been assumed to be the same between different products in similar populations (point 3.5 in the ACD), and therefore it would be unreasonable not to apply other clinical similarities such as cure assumptions.
3	We are concerned about the committee's conclusion that people who have CAR-T do not have the same quality of life as the general population in the long-term (point 3.9). We request that the committee explain why they arrived at such a final conclusion, when there was a significant amount of uncertainty in the discussion surrounding this. It currently appears as though the patient expert's comment on ongoing immunology appointments has informed the conclusion too heavily. This is because the committee failed to frame the point in the correct context. For those who are cured with CAR-T, the benefits of extended life when a patient has run out of other options far outweigh the QoL implications. Additionally, the negative QoL impact on a patient's friends and family members should CAR-T not be available in this setting would be significant, as the patient would alternatively likely be put on best supportive care with a short life expectancy. Finally, routine hospital appointments can help to alleviate health-related anxiety as patients feel monitored clinically.
3	We believe it has not been made clear whether the trial only included patients who had relapsed, or whether it could also have included patients who were undergoing bridging therapy. We believe this might have an impact on the uncertainty of CAR-T being curative and therefore seek further clarification from the committee on this point.
4	The committee concluded CAR-T cannot be put into the Cancer Drugs Fund (CDF). We believe this is both an unfair and unreasonable conclusion, given that other CAR-T products that aim to achieve very similar outcomes for patients have previously been entered into the CDF, such as with the NICE appraisal for tisangenleleucel for the treatment of relapsed or refractory ALL patients under the age of 25. As a result, we request the committee explain why they made a different decision on the suitability for this treatment in the CDF to other committees.
6	Additionally, we consider the committee's decision that the treatment has no plausible potential to be cost effective, and therefore excluded from the CDF, to be unreasonable. We ask the committee to clarify whether any of the scenarios presented are cost-effective and for NICE to clarify how many ICERs should be in the range that NICE considers costs effective to be considered on the CDF.
5	Due to a review of the original NHS tariff cost of CAR-T delivery, NHS England revised their cost from

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	£96,016 to £65,415. The ACD states that some costs included in the NHS estimate of £65,415 were already captured in the company's model and therefore reduced the price further to arrive at a final figure of £60,000. However, there is no further detail in the ACD about how and why the figure of £60,000 was arrived at. We believe a failure to explain this does not give us the full opportunity to be involved and to comment. We are therefore requesting greater transparency over the decision making that led to this final figure, from both NICE and NHSE; not to provide this information would be procedurally unfair and unreasonable.
6	It is unreasonable for the committee to disregard the findings of the ZUMA-3 trial. The ACD states that ZUMA-3 may be better source of information on treatment effects in the correct population and it would unreasonable not to use the best source of information for the question, which is in regard specifically to understand the effect of the treatment on the NHS population.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- 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 under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- 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.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
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]

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	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.
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 comment as follows.
1	In section 3.4 it states: **The ERG explained that results supporting an assumption of cure with autologous anti-CD19-transduced CD3+ cells were uncertain, because the analyses did not distinguish between people who had an allo-SCT before treatment with autologous anti-CD19-transduced CD3+ cells and those who did not. Therefore, it was unclear if any survival benefit resulted from treatment with autologous anti-CD19-transduced CD3+ cells or from an allo-SC** Our experts do not agree with this statement. One expert notes that this was not an accurate reflection of the conversation and recalls discussing consolidation allografts post CAR-T, not pre. In patients who have relapsed following an allogeneic transplant and went on to autologous anti-CD19-transduced CD3+ cells the allogeneic transplant has already failed and is not contributing to any stated potential survival benefit. All patients relapsed post allograft are incurable, so any cure is related to the autologous anti-CD19-transduced CD3+ cells not the allograft.
2	**The inverse hazard ratio analysis is preferred over matching-adjusted indirect comparisons and naive comparisons** Our experts note that this is difficult as whilst inverse of the hazard ratios method is chosen over the MAIC and naive comparisons, all are compromises.
3	**People having autologous anti-CD19-transduced CD3+ cells are likely to be at a higher risk of mortality than the general population** Our experts believe the data is lacking if patients post autologous anti-CD19-transduced CD3+ cells are likely to be at a higher risk of mortality than the general population, it is only an unproven assumption that the true standardised mortality ratio for this population would be aligned to the value proposed by ERG (a standardised mortality ratio of 4), which may well be too pessimistic.
4	**People who have had autologous anti-CD19-transduced CD3+ cells do not have the same quality of life as the general population** Our experts believe that the assessment that people who have had autologous anti-CD19-transduced CD3+ cells do not have the same quality of life as the general population at 3 years post treatment is an unproven assumption. QoL is correctly observed to be adversely affected by previous treatments and allografts, however patients post anti-CD19-transduced CD3+ cells may well expect to have a QoL more favourable than the midpoint between the utility value after the infusion and before relapse and the general population of a similar age. Anti-CD19-transduced CD3+ cells are well tolerated, and toxicity is managed easily, often in the outpatient setting.
5	**Allo-SCT costs and QALY loss should be included in the model for people having autologous anti-CD19-transduced CD3+ cells** Our experts note that the UK ALL community agree they do not plan to consolidate autologous anti-CD19-transduced CD3+ cells with an allograft in remission. There may be patients eligible for autologous anti-CD19-transduced CD3+ cells with no ability to have an allograft or who have previously had an allograft. It is a highly unlikely situation there would be many (if any) UK patients

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	who have relapsed post autologous anti-CD19-transduced CD3+ cells who would be eligible for an allograft. They would have to re-enter a complete remission first which would be virtually impossible.
6	**The equalities issues cannot be addressed through this technology appraisal The clinical expert noted that people from minority ethnic backgrounds can sometimes find it difficult to identify a suitable match for a curative allo-SCT. For this reason, autologous anti-CD19-transduced CD3+ cells could potentially offer improved outcomes in this population. The committee noted that the company had not positioned autologous anti-CD19-transduced CD3+ as an alternative for people who are eligible for allo-SCT (such as people from minority ethnic backgrounds). The committee was also aware that this technology appraisal cannot change how suitable matches are identified. It agreed that this could not be addressed in this technology appraisal given the information available at this time. The committee noted that the company's marketing authorisation states that this technology is for people 26 years and over. The patient and clinical expert noted that if this technology is not recommended it would leave people above this age without access to a potentially curative treatment option. The committee acknowledged this issue and recalled that NICE can only make recommendations on companies marketing authorisations. It was also aware that some religious groups such as Jehovah's witnesses may not accept technologies or procedures derived from blood (such as allo-SCT). These people would normally have best supportive care. The committee acknowledged that if autologous anti-CD19-transduced CD3+ cells does become an available treatment option, some people may choose not to have this treatment because it contains human blood products. Accordingly, this is not viewed as an equality issue. For these reasons, the committee concluded that the equality issues cannot be addressed through this technology appraisal.** Our experts do not agree that this technology appraisal cannot be considered as an equality issue. Whilst our experts understand the committee's opinion, we have a clinical scenario of relapsed refractory B acute lymphoblastic leukaemia being less likely to be cured if patients are over 25 years, have no donor based on ethnicity, or unsuitable for allograft based on age or religion. Our experts believe this should be taken into consideration.

Insert extra rows as needed

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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.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
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:	Sophie Wheldon

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	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.
Example 1	We are concerned that this recommendation may imply that ……..
1	One of the points made in the ACD (3.9) state that the committee does not believe that patients who have received CAR T cells have the same quality of life as the general population. I would like to clarify that I was not in disagreement with the clinical experts when I discussed the emotional, financial and immunological impact of my experience with receiving tisagenlecleucel, and I very much agree that patients can return to a near-normal life after CAR T therapy, which is what I feel I have been able to do since receiving the treatment myself in 2019. I don't believe that the correct context for my comments was used in this decision. My point was that the benefits of this treatment in getting my life back far outweighed the emotional and financial impacts which were faced during the earlier stages of my treatment with my experience of CAR T. In terms of the regular appointments with immunology and my healthcare team, I do not believe that this hinders my quality of life at all. I feel that it actually improves it, as I know that there is a team of people who are always looking out for me, and that they are there with solutions for me if I face issues with infection. This provides me with a lot of reassurance in my day to day life, and does not prevent me from doing the daily activities that I am now able to do since having my treatment, including completing my education, socialising with friends and loves ones, going to work, and contributing to society in general - all of which would not have been possible if I was not able to have CAR T therapy. I would therefore ask for the committee to reconsider their reasoning with this point.
2	I was concerned to read that the committee state that they are unsure of how a cure can be defined for patients aged over 26 receiving autologous anti-CD19-transduced CD3+ cells, despite expecting the treatment to be clinically effective as per the clinical evidence. Patients like myself who received tisagenlecleucel aged under 25 are defined as being cured after 3 years, which was defined by the previous NICE appraisal (ID544). The clinical experts also explained to the committee that relapses after 12 months are very unlikely. I would like to reflect the concerns raised by Leukaemia Care's response and ask the committee to re-evaluate their definition of when a patient can be considered as cured using the same criteria as they have used in the previous CAR T appraisals for ALL and using the information from the clinical experts.
3	The committee state that the clinical evidence shows that the treatment is expected to be clinically effective. I feel it would be unfair to limit the use of CAR T therapy to those aged under 25 by not recommending the treatment to the older age group. This treatment has completely changed my life, in fact, it gave me another chance at life. It is terrifying to consider that, if I had been just a few years older at the time of my relapse, I may not have been given the opportunity to live beyond Christmas of that year. I therefore believe that the committee should reconsider their decision to allow other patients to access this treatment to allow them to explore a potential cure and for them to be able to truly 'live' again.
4	I would like to stress to the the importance of equality and access to treatments to the committee. Allowing a larger population of patients to access this treatment would significantly improve the outcomes for patients who, in particular, are not able to find a suitable stem cell donor and whom are overall less likely to achieve a cure without having equitable access to CAR T products. I believe that everyone who has ALL who could potentially benefit from CAR T therapy should be able to access it.
5	
6	

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than 1 set of comments from each organisation.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**UK NCRI group**]
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:	[**Professor David Marks**]

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Example 1	We are concerned that this recommendation may imply that ……..
1	Page 19: I don't understand what the summary is saying about age inequality. The language is not clear There is a basic age inequality issue here which the committee has not addressed. Nor have they addressed the patients who are not transplant eligible but would be fit enough to receive CAR T. (this is also in effect a discrimination against older patients)
2	*'a curative treatment effect is uncertain' (page 8)* The committee is inconsistent. Tisagenlecleucel was approved long before this therapy was shown to be curative. As I have said before, the results are broadly consistent with this CAR T cell, and we are better at dealing with CAR T toxicity now (disease relapse after 12 months is uncommon)
3	*The ERG stated that the sensitivity analysis was not sufficiently powered to detect a difference. It also noted that an allo-SCT could have provided a survival advantage to the people who had had one* This is illogical and is 'having it both ways' If there is no evidence that alloSCT provides a survival advantage then it is only fair to assume there is none. Remember that it is not UK practice to automatically do a consolidative transplant, we would test this drug as stand-alone therapy
4	Page 14: I totally agree (with Kite's submission) that fewer staff are required to look after a CAR T patient. 60K is a gross overestimate of the cost of a CAR T patient
5	I have no doubt that this therapy is effective. That is also the opinion of Jae Park (New York), Matthias Stelljes (Muenster), Josep Ribera (Barcelona) and Andre Schuh (Toronto). (We discussed this at a virtual meeting yesterday). To be frank I don't think the ERG's opinion carries as much weight as the combined view of ALL CAR T experts worldwide
6	

Insert extra rows as needed

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Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal: ERG comments on company's response to the Appraisal Consultation Document.

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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1 Introduction

In October 2022, the NICE Appraisal Committee considered autologous anti-CD19-transduced CD3+ cells for treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults (henceforth the technology and indication are referred to as KTE-X19 and R/R ALL respectively for brevity). This meeting resulted in NICE publishing an Appraisal Consultation Document (ACD) which did not recommend the use of KTE-X19.[1]

The company's response to the ACD[2] includes a response document, structured around five 'topics' together with updated version of the executable model. This document provides a commentary on the company's ACD response and should be read in conjunction with the original company submission (CS),[3] the ERG report,[4] the company's response to Technical Engagement (TE)[5] and the ERG's critique of this response.[6] Many of the topics raised by the company in its TE response have been raised again in its response to the ACD so there is considerable overlap between the ERG's response to TE and this document.

Section 2 provides a description of the company's ACD response by topic and the ERG's critique of these points. Section 3 presents the results of the company's updated base case incremental cost-effectiveness ratios (ICER), expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained, together with ICERs from scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 4.

All results presented in this document include the Patient Access Scheme (PAS) discount for KTE-X19 ([redacted]), which is unchanged from the Appraisal Committee meeting. The results of the company's analyses when applying the confidential PASs for blinatumomab, inotuzumab ozogamicin (henceforth referred to as inotuzumab for brevity), ponatinib, and tocilizumab (which is used to treat cytokine release syndrome a potential adverse event) are presented in a separate confidential appendix.

2 ERG summary and critique of the company's TE response

This ERG addendum is structured around the five topics contained in company's response to the ACD which are detailed in Sections 2.1 to 2.5. These sections summarise the issues as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new ICERs generated when using the company's preferred assumptions. Each section also includes, where appropriate, the ERG's opinion on the new data and assumptions. The impact of these assumptions on the ICER is presented in Section 3 alongside the company's preferred ICER and the ERG's exploratory analyses.

For reference, the company's updated ICER after the ACD is shown in Table 1.

Table 1: Company's ACD revised base case cost-effectiveness estimates

Interventions	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER
Overall population					
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,690
Ph- population					
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	£33,044
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£26,602
Ph+ population					
Ponatinib	[redacted]	[redacted]	[redacted]	[redacted]	£38,302
Inotuzumab	[redacted]	[redacted]	[redacted]	[redacted]	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

The ERG identified an implementation error in the latest company model related to the survival estimates for people receiving ponatinib treatment. This is detailed in Section 2.6.

2.1 Topic 1: Methods for indirect treatment comparison

Within the ACD, the Appraisal Committee preferred the use of the inverse hazard ratio (HR) derived from the company's unanchored matching-adjusting indirect comparison (MAIC) applied to the ZUMA-3 population, as did the ERG. The company, however, still prefers using relative treatment effect estimates from the naïve indirect treatment comparison (ITC).

The company states that the ERG's preferred HR is flawed as it was derived from an unanchored MAIC, which is a method subject to a high risk of bias[7] and with a small effective sample size (ESS). NICE's Decision Support Unit Technical Support Document number 18 (TSD18)[7] states that unanchored methods should not be used when anchored methods can be applied and the company has provided analyses with an anchored MAIC in the ACD response. The ERG notes that this is contrast to the company's submission[3] which stated that "*In the context of the evidence base available (single-arm trial data), it was not feasible to perform an anchored indirect treatment comparison to evaluate the comparative effectiveness of KTE-X19 versus relevant comparators. As such, both naïve ITCs and matching-adjusted indirect comparisons (MAICs) were conducted in line with the NICE decision support unit (DSU) technical support document (TSD) 18*."

The company states that the ERG's preferred HR for KTE-X19 compared with inotuzumab lacks face validity based on a transitivity assumption. This is because the "*transitivity assumption of indirect treatment comparisons does not hold*" because "*the ERG's approach produced a significantly higher HR*" of [redacted] compared with the HR generated using the Proskorovsky study[8] (which was an anchored ITC between inotuzumab and blinatumomab) and SCHOLAR-3 ([redacted] using MAIC and [redacted] using simulated treatment comparison [STC]). The company notes that in contrast, the naïve HR of [redacted] is similar to the HR generated using the Proskorovsky study and SCHOLAR-3.

The company additionally states that the overall survival (OS) curve for inotuzumab lacks face validity as the OS is greater than observed in INO-VATE given that patients in ZUMA-3 had, "*on balance, more unfavourable prognostic factors than patients in INO-VATE*". Table 4 in the company's response to the ACD, which is reproduced in Table 2, provides a comparison of key prognostic factors between ZUMA-3 and INO-VATE. The company considers the naïve comparison more appropriate as the median from this analysis is more aligned to the reported median survival in INO-VATE compared with the unanchored MAIC approach. The company also states that the cure fraction produced using the unanchored MAIC at 20% is unrealistically high compared with the 18% produced by the naïve comparison.

Table 2: Comparison of key prognostic factors between INO-VATE and ZUMA-3 (reproduced from company's ACD response Table 4)

	ZUMA-3	INO-VATE	Difference
	Phase 1+2 combined >25 years	Inotuzumab arm	
Age (years), mean	48	47	1
ECOG score (%)			
0	28	38	10
1	72	49	23
2	0	13	13
Philadelphia +ve (%)	22	13	9
Prior SCT (%) (any)	40	18	22
1 prior line of therapy (%)	19	69	50
2 prior lines of therapy (%)	33	30	3
>2 prior lines of therapy (%)	47	1	46
Primary refractory (%)	31	16	15
Duration of first remission <12 months (%)	28	59	31
Prior blinatumomab (%)	49	0	49
Prior inotuzumab (%)	22	NR	

Key: ECOG, Eastern Cooperative Oncology Group; mITT, modified intention-to-treat; NR: not reported; SCT: stem-cell transplant. Source: Kantarjian, 2016 [9] and Gilead data on file [10].

Better prognosis in ZUMA-3

Worse prognosis in ZUMA-3

Equal (≤5% difference)

In response to the ERG's criticism that it would prefer to see the SCHOLAR-3 data matched to pooled Phase 1 and 2 results from ZUMA-3, rather than Phase 2 data alone, the company has provided the Kaplan-Meier plots for pooled Phases 1 and 2 and Phase 2 (See Figure 3 of the company's response to the ACD). The company states that small differences in baseline characteristics (provided in Table 5 of the company's response to the ACD) "*have visibly not led to any material difference in prognosis*". However, the company did not provide any additional ICERs based on matching SCHOLAR-3 data to the pooled dataset.

Whilst the ERG acknowledges the high-risk of bias in unanchored MAICs, the ERG believes that these are strongly preferable to naïve indirect treatment comparisons. TSD 18,[7] which is used by the company to criticise the unanchored MAIC, states that where there are only single-arm studies or disconnected networks that "*unanchored MAIC or STC can be used to improve on "unadjusted" or naïve indirect comparisons by taking into account the different distributions of prognostic factors and effect modifiers in the two studies. (In the same way that MAIC and STC may improve upon standard "adjusted" indirect comparison by taking account of the distribution of effect modifiers.)*" TSD 18 states that "*it is essential that submissions include information on the likely bias attached to the estimates, due to unobserved prognostic factors and effect modifiers distributed differently in the trials*." The company undertook the MAIC but appears not to have discussed which potential prognostic factors and treatment effect modifiers were unobserved in the studies. Given the choice between adjusting for observed and known prognostic factors and treatment effect modifiers, or ignoring these factors, the ERG believes that using an unanchored MAIC is the optimal choice, particularly when there are known imbalances in prognostic factors between populations as shown in Table 2. Therefore, using the inverse of the MAIC such that the efficacy of other treatments in the ZUMA-3 population can be estimated is believed by the ERG to be much more appropriate than a naïve comparison, as there are key differences between the populations. The EAG notes that if the populations were balanced the unanchored MAIC would return the same result as the naïve comparison.

The ERG also notes that a naïve count of the number of prognostic factors that favour or disfavour a study, as the company appears to have done, may produce misleading results. The relative importance of each factor must be considered, and it could be the case that the two factors (ECOG Score 2 and duration of first remission being less than 12 months) where INO-VATE has a worse prognosis (see Table 2) are much more influential factors than the remaining factors combined. Additionally, for factors which are categorical variables, a simple count may be misleading; Table 2 indicates that there is a worse prognosis in ZUMA-3 related to ECOG score alone (2 worse prognoses compared with 1 better prognosis), however, clinical input indicates that the INO-VATE study would have a worse prognosis due to the greater numbers of patients with ECOG Score 2.

The ERG disagrees with the company's claim that the ERG's unanchored MAIC produced a significantly higher HR than the HR derived using the Proskorovsky study and SCHOLAR-3 as consistency checking shows that the result produced by the unanchored MAIC is consistent with the result produced via the indirect comparison based on the Proskorovsky study and SCHOLAR-3 (p-value=0.89 for MAIC used in Proskorovsky and p-value=0.80 for STC used in Proskorovsky).

The ERG agrees that an anchored MAIC is preferable to an unanchored MAIC, however, the ERG notes that the anchored ITC in the Proskorovsky study was criticised by Song *et al*.[11] on the grounds that the

analysis failed to match the number of prior salvage therapies which presents a key difference between the two trials analysed, and different subsets of treatment effect modifiers for different outcomes were matched without providing a convincing rationale. In response to the criticism, Proskorovsky *et al*.[12] acknowledge that failing to adjust for two or more lines of prior salvage therapies could have led to an overestimation of the treatment effect for OS and updated the analysis adjusting for more baseline covariates. The updated analysis shows that the estimated HR for OS is 0.90 (95% confidence interval [CI]: 0.51-1.58) from the MAIC and 0.85 (95% CI: 0.50-1.43) from the STC. Using the results from the updated analysis, the HR derived using the Proskorovsky study and SCHOLAR-3 would be [redacted] from MAIC and [redacted] from STC; these values are similar to the HR obtained from the ERG's preferred approach [redacted].

The ERG highlights that it is inappropriate to compare the ERG-preferred survival curve for inotuzumab with the observed data from INO-VATE because the differences observed in the trial population between ZUMA-3 and INO-VATE and the ERG's survival curve reflect the results after population adjustment. If the populations are noticeably different, then it would be expected that the adjusted survival curve should not match the unadjusted survival curve reported in the study. Contrastingly, it would be expected that the results from a naïve analysis are very similar to the source data as there have been no adjustments. The EAG therefore believes that the company's argument cannot reasonably be used to support a claim that its approach is more valid.

The ERG notes that there are some differences in the Kaplan-Meier survival functions between Phase 2 and pooled Phase 1 and 2 data, especially in the tail area of the curves. These differences (even if small in magnitude) could have an impact in the economic analysis and the ERG would have preferred this analysis to be formally undertaken.

In conclusion, the ERG remains concerned that the naïve comparisons do not reflect the true relative treatment effect of KTE-X19 and prefers the unanchored MAIC results. These results are aligned with the company's updated indirect comparisons using an anchored MAIC (between inotuzumab and blinatumomab) to generate an estimate between KTE-X19 and blinatumomab. Additionally, in the absence of analyses using pooled Phase 1 and Phase 2 data for SCHOLAR-3 analysis, the generated results use Phase 2 data alone. The impact of this exclusion on the ICER is unknown.

Finally, the ERG notes that Section 3.4.20 of the current NICE Methods Manual[13] states that: "*In all cases when evidence is combined using adjusted indirect comparisons or network meta-analysis frameworks, trial randomisation must be preserved. It is not acceptable to compare results from single treatment arms from different randomised trials. If this type of comparison is presented, the data will be treated as observational in nature and associated with increased uncertainty.*" As such, it appears

that the naïve comparison preferred by the company is viewed as not acceptable in the Methods Manual.[13]

2.2 Topic 2: Long-term risk of mortality for KTE-X19 treated patients relative to the general population.

The company disagrees with the NICE Appraisal Committee's (and the ERG's) view that a standardised mortality ratio (SMR) of 4 should be applied to long-term survivors after KTE-X19 treatment. The company states that clinical opinion is that relapse after the first year is unlikely and that the increased risk of dying was associated with graft-versus-host disease (GvHD) following allogeneic stem cell transplant (allo-SCT). The company notes that people receiving KTE-X19 would not routinely receive allo-SCT and thus the estimate of an SMR of 4 is inappropriate. The company's base case uses an SMR of 1.09, but the company has explored a scenario where this value was set equal to 2.20. This value was calculated by the company noting that [redacted] of 63 ([redacted]) people had an allo-SCT in ZUMA-3 and estimated a blended SMR of 2.20 using an SMR of 1.09 for those patients without allo-SCT and an SMR of 4 for those with allo-SCT. The company also provides supportive evidence that the use of allo-SCT as a first line treatment ranges from 24% to 54%.

The ICERs increased by approximately £3000 when an SMR of 2.20 was used with the values shown in Table 3.

Table 3: Scenario assuming a weighted average SMR (2.20) based on % of allo-SCT in ZUMA-3

Comparator	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALYs)	Company base-case ICER
Overall population					
Inotuzumab	[redacted]	5.735	[redacted]	£26,126	£23,690
Ph- population					
Blinatumomab	[redacted]	6.644	[redacted]	£36,716	£33,044
Inotuzumab	[redacted]	4.871	[redacted]	£29,302	£26,602
Ph+ population					
Ponatinib	[redacted]	7.083	[redacted]	£42,325	£38,302
Inotuzumab	[redacted]	5.660	[redacted]	£25,506	£23,134

Key: ICER = incremental cost-effectiveness ratio, LY = life-year, Ph+ = Philadelphia chromosome positive, Ph- = Philadelphia chromosome negative, QALYs = quality-adjusted life years.

The company also highlights that the SMR preferred by the Appraisal Committee was generated from a cohort with only 11% of patients having had ALL with higher proportions of patients with acute myeloid leukaemia or chronic myeloid leukaemia. The company also states that the SMR value of 4

that was described as conservative may not be if there have been improvements in standard of care since the data was collected (between 1970 and 2002) and cite as an example, that 17 deaths were due to hepatitis C, and screening measures are now in place to reduce the number of such deaths.

Despite the comments made by the company, the ERG maintains the view that an SMR of 4 is a reasonable value to use within the modelling. In the discussion section of the Martin *et al*.[14] paper, the authors states that mortality rates '*remain four- to nine-fold higher than in the general population for at least 25 years thereafter*' The midpoint SMR estimated in Table 3 of this paper was 4.5. The company's comments relating to GvHD may be misleading as the mortality data reported in Martin *et al.*[14] were for patients who had not had a relapse of original disease five years after SCT, and thus the prominence of GvHD is less important (with only 9% of deaths attributable to this) compared with 11% of deaths being cardiovascular-related. The ERG has heard companies and clinical experts claim during NICE STAs that patients who have survived 5 years after SCT are functionally cured. The ERG notes that there is likely to be an impact on health due to the cumulative drug toxicities of previous treatments that could impact on health independent of ALL which would be expected to result in an increased SMR. The ERG acknowledges that treatments (for both ALL patients and the general population) will have improved over time, as highlighted by the company, although how this impacts on the SMR is unknown with the ERG using the value of 4.0 selected by another ERG in TA541. In this previous appraisal, the ERG considered this value to be '*conservative*'. However, to inform the Appraisal Committee, the ERG has run an additional scenario where an SMR of 2.20 was used instead of 4.0.

Whilst the population in Martin *et al.*[14] included only 11% of patients with ALL, the source preferred by the company, Maurer *et al.*,[15] was conducted in relapsed / refractory diffuse large B-cell lymphoma and thus 0% of this cohort had ALL.

It is also noted that [redacted]

2.3 Topic 3: Long-term quality of life for KTE-X19 treated patients relative to the general population

The company believes that the ERG's approach of applying a utility decrement is flawed, that the value chosen was disproportionate to the mortality risks, and that it fundamentally disagrees with mortality and health-related quality of life (HRQoL) being correlated and that the utility of people cured by a chimeric antigen receptor T cell receptor (CAR-T) therapy would have the same utility as the general population. The company also states that uncertainty in HRQoL could be resolved through data collection in the Cancer Drugs Fund (CDF). These points are summarised in turn.

The company states that short-term mortality risks which are largely ALL-specific are far less likely to impact on the long-term HRQoL of cured patients. It states that the ERG has used a post-cure utility decrement which was set to half the pre-cure utility decrement which would be disproportionate to the mortality risk pre- and post-cure. The company states that people treated with KTE-X19 would not be subject to GvHD (unless they had a subsequent allo-SCT) and would not have reduced HRQoL due to this. The company additional adds that some causes of mortality such as infection would not be associated with a chronic disutility. The company also states that the ERG multiplier used for HRQoL *"represented the mid-point between the utility value after the infusion and before relapse and the general population of a similar age"* and that "*a mid-point between the short-term disutility of R/R-ALL and general population utility is therefore disproportionate given the relative mortality risk post- vs. pre-cure timepoint and is not in alignment with the ERG's rationale";* this rationale is presumed to be for applying a utility multiplier for cured patients when there is an SMR above unity. The company appears to be stating (although the ERG is unsure of this) that if mortality and HRQoL are linked, that HRQoL decrements should be largest when the risk of mortality (particularly in the first year after treatment) is greatest.

In contrast to the views of the Appraisal Committee and the ERG, the company fundamentally disagrees that the higher long-term risk of mortality would be associated with poorer HRQoL. It states that infection would be a major contributor to mortality after SCT, which would not cause a chronic reduction in HRQoL. The company also notes that following the COVID-19 pandemic there is a large proportion of the population with weakened immune systems and that the general population utility estimates would include these people.

In Table 8 of the company's response to the ACD, the company provides a summary of utility assumption applied in previous relevant appraisals to show that there has potentially been a precedent for using general population mortality in patients considered functionally cured.

The ERG notes that the company's two descriptions of the ERG's adjustment to HRQoL are incorrect so this has been reproduced here for clarity. As described in Section 4.4.2.6 of the ERG report, "*The ERG assumes a multiplier (0.92) applied to general population utility values to adjust for lower HRQoL for cured patients after 3 years. This was calculated using the ratio between the utility value for post-infusion pre-relapse (0.82) and that for general population of similar age (0.89).*" Thus, a comparison was made between the patient without relapse after treatment and the general population and this was used in a multiplicative manner.

In relation to the perceived point that HRQoL multipliers would be lower when the risks of mortality are higher, the ERG notes that its multiplier is not used until 3 years after treatment at which point the company considers patients to be functionally cured; as such the impact of greater mortality in the first year of treatment is not relevant to this discussion.

With respect to the utility of the general population being lower post the COVID-19 pandemic the ERG notes that the values used in the company's model are taken from Ara and Brazier,[16] which was published considerably prior to the COVID-19 pandemic and also that whilst there will be a proportion of patients in the general population who have recovered from, or are living with, cancer this will be a significantly lower proportion than that within a R/R ALL cohort, which by definition would be 100% of those alive.

In Table 8 of the company's response to the ACD the company showed that in five of the other STAs of CAR-T infusions or treatments in R/R ALL, three appraisals applied the general population utility to cured patients; these were TA559, TA554, and TA450. The ERG regards this statement to be inaccurate. In TA554, the company applied the event-free survival utility value to the long-term survivors rather than using general population values. For TA559, the justification was that the SMR used to model excess mortality was equal to 1.0, and the ERG commented that "*if the survival of 'cured' patients remains affected by excess mortality this is also likely to be reflected in lower HRQoL than that of the general population for the period where excess mortality applies.*" The ERG applied general population utility only after progression-free survival and OS curves converged. Finally, the ERG for TA450 was unsure about the appropriateness of applying general population utility values and performed a scenario analysis where "*people alive after four years are assumed to have the same utility as the general population and are only at risk of all-cause mortality. All-cause mortality rates were based on UK general population mortality rates*."

The ERG did not identify any precedents where a general population utility was applied to a population whose SMR higher than unity. The ERG therefore maintains its logic that "*the assumption that patients are cured without residual comorbidities would not appear consistent with the assumption that patients*

have an increased risk of death compared to the age- and sex-matched population". The company's position of no utility decrement was not supported by the clinical experts consulted by the ERG who stated that having "*received at least two therapies prior to receiving KTE-X19 and subsequent therapies, and that cumulative drug toxicity on its own – let alone the disease itself – would impact the quality of their remaining lives.*" The ERG maintains its preference for a utility multiplier of 0.92.

Additionally, the fact [redacted]

2.4 Topic 4: Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19

In ZUMA-3, 14 of the 78 patients who received the infusion went on to receive subsequent allo-SCT. However, this was not accounted for either in the cost calculations or the QALY impacts for the KTE-X19 arm in the company's model. The ERG added the costs and QALYs losses associated with allo-SCT, an approach that was preferred by the NICE Appraisal Committee.

The company highlights again the sensitivity analyses where overall data were stratified by censoring at allo-SCT and considered this informative, despite lacking statistical power, as it showed no statistical difference between patients who received a transplant and those who did not. The company reiterates that the allo-SCTs performed in ZUMA-3 were pre-planned either due to high-risk prognostic factors and/or limited long-term data on KTE-X19 at the time of enrolment. Of the 14 people who received allo-SCT, [redacted] were in complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) adjudicated by central assessment, [redacted]. The company reports [redacted] which it states would not impact on the survival advantage of pre-planned allo-SCT. The company notes that the survival of patients who received allo-SCT in ZUMA-3 "*far exceeded*" the survival of patients who received SCT following comparator treatments "*despite their high-risk features*" which suggests the survival benefit was due to KTE-X19 and not allo-SCT. The company states that uncertainty regarding the rate of allo-SCT and OS could be addressed if KTE-X19 was in the CDF.

Whilst the company contends that use of allo-SCT in ZUMA-3 was pre-planned and that it would not be used in the UK clinical practice, the ERG notes that in only [redacted] of the 14 patients was the allo-SCT definitively pre-planned ([redacted] due to poor prognostic factors and [redacted] due to uncertainty about the

long-term benefits of KTE-X19) leaving the reasons for [redacted] allo-SCTs ([redacted]) unknown as [redacted]. The ERG also highlights that the issue is not the use of allo-SCT in practice, but whether patients who received allo-SCT in ZUMA-3 had a survival benefit due to this procedure. The company reiterates that [redacted] of the 14 patients receiving allo-SCT had achieved CR or CRi, however, as stated in the ERG report, this *"does not rule out the possibility of minimal residual disease (MRD) detection which would trigger the initiation of subsequent therapy."* Clinical advice to the ERG confirmed that they would consider allo-SCT for patients who had relapsed in ZUMA-3 and who were fit enough for this procedure, noting the mean age of patients in ZUMA-3. Additionally, the fact that [redacted] shows that the use of SCT will have impacted on the aggregated health of the ZUMA-3 patients.

With respect to the statistical analysis comparing the outcomes of patients who did, and did not, have an SCT, the ERG agrees that the study was not powered for this analysis and maintain the opinions expressed in the ERG report that *"the ERG remains uncertain of the imbalance in baseline characteristics between patients who received allo-SCT versus those who did not."*

The ERG maintains its view that *"the fact that allo-SCT was delivered to some ZUMA-3 patients means that they may have benefitted from it, costs were incurred, and patients' HRQoL was affected"* and that the costs and QALY implications should be considered in the model.

2.5 Topic 5: NHS Tariff for delivering CAR-T treatments

Since the company submission in November 2021, there has been uncertainty in the costs to the NHS of delivering CAR-T treatments. In the ACD, the Appraisal Committee used a value of £60,000 but stated that this value should be reviewed if new evidence became available. Since the ACD, NHS England has agreed a reduced tariff value of £41,101 which was used in the CDF re-appraisal of axicabtagene ciloleucel for treating diffuse large B-cell lymphoma after 2 or more systematic therapies [ID3980] for 100 days after infusion.[17] The company has used a value of £41,100 in its re-estimation of the ICERs presented in Table 1, having removed all other healthcare resource costs apart from the acquisition cost of KTE-X19, the costs of subsequent treatment and the cost of subsequent allo-SCT. However, the company believes that £41,100 is a substantial overestimate of the costs of providing KTE-X19 based on: the results of a prospective micro-costing exercise at one UK centre; that if patients die earlier than 100 days post CAR-T infusion, the costs may be lower; the value "*is far higher*" than the costs identified in a targeted literature review; and based on comparative costs of CAR-T and allo-SCT.

Table 4 shows the costs excluded by the company from its base case assuming they are covered by the tariff. However, the ERG was advised by NICE that the costs for "*bridging chemotherapy drugs and their administration, stem cell transplantation and intravenous immunoglobulin*" should not be excluded as "*these 3 costs are reimbursed separately by NHS England*". Therefore, the EAG included the costs associated with acquisition and administration costs of conditioning and bridging chemotherapies prior to infusion (which is an additional £3609). The EAG also applied a value of £41,101 for the tariff.

The ERG notes that the company excluded all costs associated with adverse events for KTE-X19 (or alternative treatment where a patient did not receive the infusion) assuming that these were included in the NHS tariff. The company also removed the costs of AEs associated with comparator drugs. The ERG amended the model so that only the costs associated with AEs occurring for patients after receiving KTE-X19 infusion are excluded. The AEs associated with comparator drugs remain costed as in the technical engagement.

Table 4: Costs excluded by the company assuming they are covered by the NHS tariff

Cost component	**Value**
Hospitalisation costs associated with delivering KTE-X19 infusion (CS, Section B.3.5.1.3)	[redacted]
Leukapheresis costs prior to infusion (CS, Section B.3.5.1.2)	£1953
Acquisition and administration costs of conditioning and bridging chemotherapies prior to infusion (CS, Section B.3.5.1.2)	£3609†
Management of AEs for all patients in KTE-X19 arm including those who did not receive the infusion (CS, Section B.3.5.4 and amended post technical engagement to include only events leading to ICU admissions)	[redacted]††
Monitoring costs for 100 days as described in (CS, Section B.3.5.2)*	£1478 for Ph- patients £1527 for Ph+ patients
Terminal care costs for those who die within 100 days (CS, Section B.3.5.5.1)*	£1545 for Ph- patients £1249 for Ph+ patients
Total*	[redacted] for Ph- patients [redacted] for Ph+ patients

CS - company submission

† Not excluded in the ERG base case

†† In the ERG base case, the costs of AEs are only excluded for patients who received a KTE-X19 infusion

*Differences between Ph- and Ph+ patients are due to the difference in survival estimates associated with the alternative treatments received if a patient does not receive a KTE-X19 infusion. (CS, Section B.3.3.2.1).

2.6 Implementation error with selection of survival modelling approach for event free survival and overall survival for patients receiving ponatinib

The ERG noted that the company's updated model following the ACD contained an implementation error in columns R and AN of the 'Survival_calculations' sheet, where spline models are selected erroneously rather than the parametric models. The ERG corrected this error.

3 Additional analyses undertaken by the ERG

3.1 Quantitative changes to the company's base case for the Ph- subgroup

Table 5 presents the results of the ERG's adjustments to the company's base case for the Ph- subgroup.

The company's base case ICER is £33,044 compared with blinatumomab, with inotuzumab being extendedly dominated; the ICERs of KTE-X19 compared with inotuzumab is £26,602. The largest change in the ICER occurs using an SMR of 4.00 instead of 1.09, which increases the ICER to £41,319 versus blinatumomab. Including allo-SCT associated costs and QALY loss for KTE-X19 patients increased the ICER by approximately £5000.

When including all the changes preferred by the ERG, the deterministic ICER increases to £54,118 for KTE-X19 versus blinatumomab (probabilistic ICER = £57,015). The deterministic ICERs of KTE-X19 versus inotuzumab was £41,151 (probabilistic ICER is £44,483). Using an SMR of 2.20 rather than 4.00 resulted in the ERG's preferred deterministic ICER becoming £47,466 compared with blinatumomab.

Table 5: Results of the ERG's exploratory analyses – Ph- subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population and naïve indirect comparison for inotuzumab and the NHS tariff for delivery of CAR-T therapy as described in Section 2.5							
Blinatumomab	4.58	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	12.64	[redacted]	[redacted]	8.06	[redacted]	[redacted]	£33,044
ICER of KTE-X19 versus inotuzumab is £26,602.							
ERG exploratory analysis 2: Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population with the inverse of HRs derived from MAIC to model inotuzumab							
Blinatumomab	4.58	[redacted]	[redacted]				
Inotuzumab	6.54	[redacted]	[redacted]				ED
KTE-X19	12.63	[redacted]	[redacted]	8.05	[redacted]	[redacted]	£33,107
ICER of KTE-X19 versus inotuzumab is £25,585.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for KTE-X19 patients							
Blinatumomab	4.58	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	12.64	[redacted]	[redacted]	8.06	[redacted]	[redacted]	£38,492
ICER of KTE-X19 versus inotuzumab is £33,362.							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
Blinatumomab	3.35	[redacted]	[redacted]				
Inotuzumab	4.80	[redacted]	[redacted]				ED
KTE-X19	8.82	[redacted]	[redacted]	5.47	[redacted]	[redacted]	£41,319
ICER of KTE-X19 versus inotuzumab is £32,616.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
Blinatumomab	4.58	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	12.64	[redacted]	[redacted]	8.06	[redacted]	[redacted]	£35,502
ICER of KTE-X19 versus inotuzumab is £28,406.							
ERG exploratory analysis 9: Amending the NHS tariff for CAR-T delivery costs as described in Section 2.5							
Blinatumomab	4.58	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	12.64	[redacted]	[redacted]	8.06	[redacted]	[redacted]	£34,057
ICER of KTE-X19 versus inotuzumab is £25,003.							
ERG base case (Exploratory analyses 2, 4-6, 9) – deterministic results							
Blinatumomab	3.35	[redacted]	[redacted]				
Inotuzumab	4.67	[redacted]	[redacted]				ED
KTE-X19	8.81	[redacted]	[redacted]	5.46	[redacted]	[redacted]	£53,540
ICER of KTE-X19 versus inotuzumab is £40,447.							
ERG base case (Exploratory analyses 2, 4-6, 9) – probabilistic results*							
Blinatumomab	3.46	[redacted]	[redacted]				
Inotuzumab	4.79	[redacted]	[redacted]				ED
KTE-X19	8.84	[redacted]	[redacted]	5.38	[redacted]	[redacted]	£56,573
ICER of KTE-X19 versus inotuzumab is £43,577.							
ERG scenario analysis (combining ERG base case + using an SMR of 2.2 instead of 4.0)							
Blinatumomab	3.91	[redacted]	[redacted]				
Inotuzumab	5.52	[redacted]	[redacted]				ED
KTE-X19	10.55	[redacted]	[redacted]	6.64	[redacted]	[redacted]	£47,466
ICER of KTE-X19 versus inotuzumab is £36,157.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported
AE - adverse event, ED - extendedly dominated, HR - hazard ratio, HRQoL - Health-related quality of life, MAIC - matching-adjusted indirect comparison, SMR - standardised mortality rate

3.2 Quantitative changes to the company's base case for the Ph+ subgroup

Table 6 presents the results of the ERG's adjustments to the company's base case for the Ph+ subgroup.

The company's base case ICER with the ERG correction (see Section 2.6) is £39,767 compared with ponatinib, with inotuzumab being extendedly dominated; the ICER of KTE-X19 compared with inotuzumab is £23,071. The largest change in the ICER occurs using an SMR of 4.00 instead of 1.09, which increases the ICER to £49,005 versus ponatinib. Including allo-SCT associated costs and QALY loss for KTE-X19 patients increased the ICER by approximately £5000.

When including all the changes preferred by the ERG, the deterministic ICER increases to £62,242 for KTE-X19 versus ponatinib (probabilistic ICER = £65,918). The deterministic ICER of KTE-X19 versus inotuzumab was £40,772 (probabilistic ICER is £43,697). Using an SMR of 2.20 rather than 4.00 resulted in the ERG's preferred deterministic ICER becoming £55,695

Table 6: Results of the ERG's exploratory analyses – Ph+ subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison and the NHS tariff for delivery of CAR-T therapy as described in Section 2.5							
Ponatinib	5.01	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.59	[redacted]	[redacted]	8.58	[redacted]	[redacted]	£38,302
ICER of KTE-X19 versus inotuzumab is £23,134.							
ERG exploratory analysis 0: Company base case + the error corrected per Section 2.6							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£39,767
ICER of KTE-X19 versus inotuzumab is £23,071.							
ERG exploratory analysis 2: Using the inverse of HRs derived from MAIC to model inotuzumab (in addition to exploratory analysis 0)							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	7.61	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.27	[redacted]	[redacted]	£39,582
ICER of KTE-X19 versus inotuzumab is £25,685.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for KTE-X19 patients (in addition to exploratory analysis 0)							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£44,997
ICER of KTE-X19 versus inotuzumab is £28,799.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients (in addition to exploratory analysis 0)							
Ponatinib	3.88	[redacted]	[redacted]				
Inotuzumab	4.80	[redacted]	[redacted]				ED
KTE-X19	9.49	[redacted]	[redacted]	5.61	[redacted]	[redacted]	£49,005
ICER of KTE-X19 versus inotuzumab is £28,351.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population (in addition to exploratory analysis 0)							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£42,530
ICER of KTE-X19 versus inotuzumab is £24,653.							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ERG exploratory analysis 9: Amending the NHS tariff for CAR-T delivery costs as described in Section 2.5 (in addition to exploratory analysis 0)							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£41,210
ICER of KTE-X19 versus inotuzumab is £22,155.							
ERG exploratory analysis 10: Assuming no adjunctive chemotherapy with ponatinib (in addition to exploratory analysis 0)							
Ponatinib	5.39	[redacted]	[redacted]				
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£40,950
ICER of KTE-X19 versus inotuzumab is £23,071.							
ERG base case (Exploratory analyses 0, 2, 4-6, 9, 10) – deterministic results							
Ponatinib	3.88	[redacted]	[redacted]				
Inotuzumab	5.42	[redacted]	[redacted]				ED
KTE-X19	9.52	[redacted]	[redacted]	5.64	[redacted]	[redacted]	£62,242
ICER of KTE-X19 versus inotuzumab is £40,772.							
ERG base case (Exploratory analyses 0, 2, 4-6, 9, 10) – probabilistic results*							
Ponatinib	3.96	[redacted]	[redacted]				
Inotuzumab	5.38	[redacted]	[redacted]				ED
KTE-X19	9.42	[redacted]	[redacted]	5.46	[redacted]	[redacted]	£65,918
ICER of KTE-X19 versus inotuzumab is £43,697.							
ERG scenario analysis (combining ERG base case + using an SMR of 2.2 instead of 4.0)							
Ponatinib	4.56	[redacted]	[redacted]				
Inotuzumab	6.41	[redacted]	[redacted]				ED
KTE-X19	11.40	[redacted]	[redacted]	6.84	[redacted]	[redacted]	£55,695
ICER of KTE-X19 versus inotuzumab is £36,397.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported
AE - adverse event, ED - extendedly dominated, HR - hazard ratio, HRQoL - Health-related quality of life, MAIC - matching-adjusted indirect comparison, SMR - standardised mortality rate

4 References

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Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal

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Impact of changing the SMR on the results for ERG deterministic base case results

As requested by NICE, the ERG reran the threshold analyses that was sent on the 8th of February using the list prices for blinatumomab, inotuzumab, ponatinib, and fludarabine 50mg. Table 1 shows the ICERs for the Ph- subgroup whereas Table 2 shows them for the Ph+ subgroup.

Table 1: The impact of varying the SMR applied for cured patients for the Ph- subgroup

SMR values	ICERs of KTE-X19 versus	
	Blinatumomab	Inotuzumab
4.0 (ERG base case)	£53,540	£40,447
3.5	£51,983	£39,355
3.0	£50,340	£38,197
2.5	£48,588	£36,956
2.2 (scenario suggested by the company)	£47,471	£36,160
2.0	£46,693	£35,605
1.5	£44,594	£34,099
1.09 (company base case)	£42,642	£32,690

Table 2: The impact of varying the SMR applied for cured patients for the Ph+ subgroup

SMR values	ICERs of KTE-X19 versus	
	Ponatinib	Inotuzumab
4.0 (ERG base case)	£62,242	£40,772
3.5	£60,576	£39,657
3.0	£58,809	£38,476
2.5	£56,915	£37,211
2.2 (scenario suggested by the company)	£55,701	£36,401
2.0	£54,853	£35,835
1.5	£52,556	£34,303
1.09 (company base case)	£50,405	£32,870