NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Pfizer (company) – includes new evidence
   - Leukaemia CARE
   - National Cancer Research Institute – Association of Cancer Physicians – Royal College of Physicians (joint response)
     - TYA UKALL2003 Relapse Outcomes

   No comment' response received from Department of Health

3. **Comments on the Appraisal Consultation Document from experts:**
   - Adele Fielding – Clinical Expert, nominated by Royal College of Pathologists

4. **Company new evidence appendix** – submitted by Pfizer

5. **Evidence Review Group critique of company new evidence -** prepared by Centre for Reviews and Dissemination and Centre for Health Economics York

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

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

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 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 determination (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, Social Services and Public Safety for Northern Ireland).

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient and professional	NCRI-ACP-RCP	The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. Why was Inotuzumab not approved when Blinatumomab was? Our experts are unclear why Inotuzumab has not reached the criteria for approval when Blinatumomab was recently approved by NICE. They question the difference in methodology used and composition of the reviewing panel. Inotuzumab appears to be at least as effective as Blinatumomab and possibly more effective in the face of frank bone marrow relapse (ie complete remission rate twice as high). Our experts question whether the comparator for the Inotuzumab cost effectiveness analysis have been Blinatumomab rather than FLAG-Ida.	Comments noted. The Institute recognises that guidance from other appraisals may differ since the evidence submitted may be different. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission, the ERG report and consultation responses. The committee concluded that because the evidence available for each appraisal is different, differences in modelling between the 2 appraisals is unavoidable (see FAD section 3.17).
2	Patient and professional	NCRI-ACP-RCP	Specific need in teenage and young adult (TYA) patients with ALL Our experts highlight the need for novel therapies in TYA ALL patients who relapse. Please see attached slides showing an analysis of outcomes following relapse in this group. The overall survival in patients who relapse on treatment is only 7% at 5 years, even though many of these patients received FLAG-Ida and an allogeneic haemopoietic stem cell transplant. This highlights the urgent need for agents such as Inotuzumab for these patients, with which patients are likely to achieve a deeper remission (ie MRD negative remission) prior to curative consolidation with an allograft or to allow entry into CAR T cell trials. Whilst the TYA group are no more important than older patients, should they achieve cure they will be expected to have a longer, healthy life subsequently. Our experts question whether this was taken into account in the cost effectiveness analysis.	Comment noted. The company did not present any subgroup analyses around patient characteristics. In addition, the marking authorisation for Inotuzumab ozogamicin is for adults only; please see FAD section 2 for more details.
3	Patient and professional	NCRI-ACP-RCP	The lack of access to inotuzumab in the UK would mean that patients who could be cured of ALL will die of their disease. This would not be the case in other developed countries and seems to be a highly undesirable situation. Given that Inotuzumab received marketing authorisation from the EMA last week, our experts question whether there is an opportunity to revisit pricing which could be taken into account in the evaluation of cost effectiveness	Comment noted. The Institute recognises that guidance from other countries may differ from its

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			of this agent.	own guidance, because of different criteria for making decisions. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission and the ERG report. Please see FAD section 3 for more details.
4	Patient and professional	Leukaemia CARE	We are writing on behalf of acute lymphoblastic leukaemia (ALL) patients in response to the recently published ACD for the appraisal of inotuzumab ozogamicin (ID 893). Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. It is often diagnosed as an emergency (64%), with 86% of patients starting treatment within a week of diagnosis. Whilst highly toxic chemotherapies have high response rates (80-90%), nearly half of patients will eventually relapse. In the relapsed or refractory setting, survival outcomes are poor, with a five-year survival rate for relapsed patients of less than 10%. This demonstrates the urgent need for effective salvage treatment options. In this setting, the most effective option for ALL patients is allogenic stem-cell transplantation (SCT). However, this is currently only an option for a small minority of patients. Last week (30th June 2017) the European Medicines Agency licensed inotuzumab ozogamicin as the first antibody-drug conjugate for the treatment of ALL. They found that inotuzumab ozogamicin has been shown to increase the proportion of patients who have complete remission and molecular remission and to delay the progression of disease. A further key benefit is it's potential to act as a "bridge" to transplant, increasing the number of people who are able to undergo SCT, the only curative option for these patients. This is something that is strongly welcomed by ALL patients, particularly in the relapsed/refractory setting. We hope that you will bear our comments in mind when considering your final recommendation and urge you to make inotuzumab ozogamicin available to all of those who could benefit from it.	Comments noted. The committee considered the innovativeness of inotuzumab ozogamicin, and acknowledged that people with B-cell acute lymphoblastic leukaemia would welcome a new treatment option. Please see FAD section 3.1 for more details.
5	Experts	On behalf of the Royal College of Pathologists and British Society for Haematology	I am commenting in the role of clinical expert. I attended the meeting. Naturally, I am generally disappointed with this decision on behalf of our patient population as I believe this agent has merit for the therapy of the relevant patient population and that this has been adequately demonstrated by the randomised controlled trial, published in the New England Journal of Medicine, which was presented in evidence. As discussed within the meeting, survival advantage can be very hard to demonstrate in this patient population since those patients whose disease did not respond within the control arm would have had access to several other active options which have recently become available including blinatumomab and chimeric antigen receptor T cells. My specific concern regarding this decision relates to: 1) Fairness. I have also participated in a consultation of another novel agent for the therapy of ALL -	Comments noted. The Institute recognises that guidance from other appraisals may differ since the evidence submitted may be different. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission,

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			blinatumomab. This was considered by a different committee. The agent was approved. As an academic who specialises in the therapy of ALL, if asked to comment on the relative merits of blinatumomab and inotuzumab, I absolutely would not be able to recommend one agent over the other except in very specific clinical circumstances. So I find it hard that two separate committees of NICE - without apparently having consulted each other and having used different input organisations for ERG have nonetheless gone ahead and made this decision for the community and for our patients. 2) Modelling. I am not an expert in the modelling of ICER but I am concerned that different assumptions were used for inotuzumab versus blinatumomab. I respectfully would request the committees review the modelling and assumptions on which this decision was based to ensure that they are completely congruous for both agents and that the identical baseline considerations and future projections have been taken into account.	the ERG report and consultation responses. The committee concluded that because the evidence available for each appraisal is different, differences in modelling between the 2 appraisals is unavoidable (see FAD section 3.17).
6	Others	NHS England	A “no comment” response received.	N/A
7	Company	Pfizer	Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee’s draft recommendation, and indeed believe that several assumptions which underpin the currently preferred ICER are clinically inappropriate and overly conservative with respect to the future benefits to patients; importantly, key modelling assumptions are also inconsistent with the precedent set by the recent appraisal for blinatumomab, which has the same treatment pathway as inotuzumab ozogamicin. We welcome NICE’s acknowledgement that inotuzumab ozogamicin is a clinically effective treatment option with an acceptable safety profile. As the committee have noted, the goal of intensive treatment for patients in the UK is to bridge to potentially curative therapy such as stem cell transplantation; after the study therapy in the INO-VATE RCT and prior to the start of any post induction therapy, around four-times as many patients in the inotuzumab arm reached a transplant than those receiving standard of care (43.3% versus 11.1%).1 This is unprecedented in these patients, whose life expectancy is a matter of months in current practice. However, despite this transformative clinical benefit, the ICER currently preferred by the committee is inconsistent with key assumptions that NICE accepted in the recent appraisal of blinatumomab, and resultantly does not fairly reflect the value for money inotuzumab can offer the NHS. Pfizer welcome the recommendation for blinatumomab as a step forwards for patient access, however we are concerned by the divergent committee conclusions with regard to preferred modelling assumptions with regard to the same patient pathway. As stated by the clinical expert at the committee meeting for inotuzumab, there are similarities between the medicines and the patients they treat. A key tenant of the Pfizer ACD response is a call for fairness in the methodological approach taken with inotuzumab ozogamicin in the context of the recent blinatumomab appraisal; it is nevertheless important to ensure that the clinical value of inotuzumab is not overshadowed by a technical dialogue. In our response below, we first present the ICER which represents the Committee’s preferred set of assumptions, as described in the ACD, noting the key differences with the company’s base case. The remainder of the document focusses on key assumptions which we consider inappropriate, providing relevant clinical and/or technical rationale in support of a more appropriate alternative. In the proposed revised base case, we have also included a Patient Access Scheme (PAS) (providing a [redacted] discount to the list price), which is currently under review by the Department of Health. We are confident that the most plausible ICER for inotuzumab ozogamicin falls well below the £50,000 per QALY threshold, noting that the committee has concluded inotuzumab ozogamicin meets the criteria to be considered as an end of life treatment. We believe that the information presented in this response should satisfy the Committee that inotuzumab ozogamicin represents a cost-effective use of NHS resources within its licensed indication, so that patients in England and Wales are given access to	Comments noted. The Institute recognises that guidance from other appraisals may differ since the evidence submitted may be different. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission, the ERG report and consultation responses. The committee concluded that because the evidence available for each appraisal is different, differences in modelling between the 2 appraisals is unavoidable (see FAD section 3.17).

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			this clinically effective, targeted medicine. Yours sincerely, [redacted] On behalf of Pfizer UK	
8	Company	Pfizer	**The Committee's preferred ICER** The ACD notes that the ICER which the committee considered most reflective of its preferred assumptions is one from the ERG's analysis, which is greater than £100,000 per QALY. There are key differences in assumptions between this ICER and the company's original base case ICER (set out in Table 31 within the ERG Report). Pfizer has considered the differences in assumptions between those which underpin the ERG's ICER (preferred by the committee) and the base case ICER in the original submission, and propose a revised estimate of cost-effectiveness in this response. The following aspects of the ERG's base case (presented in These four assumptions are detailed within sections 3 to 7 in this response. (Table 1 – not reported here) require thorough reconsideration by the committee: 1. The assumption applied to survival between haematopoietic stem cell transplant (HSCT) and the "cure point" - the point at which patients are assumed to be return to normal life expectancy *(scenarios 2 and 7 in the ERG Report Table 31)*. 2. The increased risk of mortality applied to patients in the longer term who pass the "cure point". *(scenario 8 in the ERG Report Table 31)*. 3. The exclusion of the costs of subsequent therapy from the RCT *(scenario 6 in the ERG Report Table 31)*. 4. The administration costs applied to both the intervention and control arm *(scenario 9 in the ERG Report Table 31).* These four assumptions are detailed within sections 3 to 7 in this response. (Table 1 – not reported here) We have made revisions to several other parameters to reflect the ERG's and the committee's preferences so as to minimize technical debate, whilst noting the majority of these have minimal impact on the ICER. These include: • Using the 3.5% discount rate for costs and QALYs • Age-adjusting utilities *(scenario 3 in the ERG Report Table 31)* • Applying chemotherapy costs in line with INO-*VATE (scenario 4 in the ERG Report Table 31)* • Pooled on treatment utilities *(scenario 5 in the ERG Report Table 31)*	Comments noted. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission, the ERG report and the consultation responses. Please see FAD section 3 for more details.

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			• Model fix identified during clarification questions *(scenario 1 in the ERG Report Table 31)*	
9	Company	Pfizer	**Recommendation of blinatumomab for previously treated PH-negative ALL** During the course of this appraisal, NICE issued final guidance for the appraisal of blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (ALL).[2] Pfizer welcomes NICE's recommendation for blinatumomab as it is important that ALL patients have access to new innovative treatments. As stated by the clinical expert at the committee meeting for inotuzumab, there are similarities between the medicines and the patients they treat. Given these similarities, there are a number of key modelling assumptions which NICE accepted in their preferred ICER in recommending blinatumomab that are thus applicable to this appraisal: • ***Survival between transplantation and the cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted treatments dependent parametric curves fit to the Kaplan-Meier data for patients pre-HSCT, post-HSCT and up until a cure point of 4 years post-HSCT. This is a clinically valid approach as it makes the best use of the available trial data. • ***Longer term survival post-cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted that once patients pass the a certain post-HSCT (in this appraisal named the "cure point"), the hazard rate for death is assumed to be that of the normal population, with a factor added to compensate for disease-related mortality that was derived from the gradient of the extrapolated parametric curve. This is a clinically valid approach as it makes use of the available trial data without relying on historical literature from patients using different treatment regimens to assume the impact to survival. • ***Health-related quality of life post cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted that patients who pass the cure point post-HSCT can expect a return to the health-related quality of life (utility) of the normal population. Pfizer is disappointed that the committee's preferred ICER for inotuzumab accepts a more conservative positon on all three of the above assumptions based on the fact that the assumptions selected in this appraisal are not grounded in a strong clinical rationale. Considerations of the precedent set in the blinatumomab appraisal around the above three assumptions are factored into the revised base case in this response, and referred back to in the following pages.	Comments noted. The Institute recognises that guidance from other appraisals may differ since the evidence submitted may be different. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission, the ERG report and consultation responses. The committee concluded that because the evidence available for each appraisal is different, differences in modelling between the 2 appraisals is unavoidable (see FAD section 3.17).
10	Company	Pfizer	**Survival between transplantation and the cure point** The company base case uses treatment-specific patient level data from the INO-VATE trial (fitted with parametric curves) pre-transplant, then post-transplant and up to the cure point. This approach is in line with that accepted by NICE in the recommendation of blinatumomab where treatment-specific parametrically-fit curves continue to be fit to the Kaplan-Meier data up to 4 years post-HSCT up to the cure point. However, the committee's preferred ICER in the inotuzumab appraisal ceases to use the treatment-specific patient level data past the point of transplant and instead chooses to pool survival from both arms, applying a covariate for MRD-negativity to account for survival differences. Using the treatment specific Kaplan-Meier data from patients post-HSCT to model the survival probabilities of	Comments noted. The committee did not agree with the company's overall survival extrapolation in the HSCT and post-HSCT state and therefore concluded that it was not appropriate for decision-making. Please see FAD sections 3.7 and 3.19 for more details.

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			patients post-HSCT is the best available data source. The ACD cites MRD-negativity as an assumed a driver of improved outcomes post-HSCT, but using the patient level data inherently takes into account any effect that MRD-negativity is having on patients' survival in either arm as well as the effect from any other known or unknown covariate that may be driving survival. Abandoning the treatment specific data as in the ERG's base case replaces treatment effects captured within the data with an assumption, and relies on this assumption perfectly modelling the assumed effect of MRD as well as any other specified covariates taken into account. Pfizer's basecase uses the treatment specific Kaplan-Meier data which inherently captures all covariates correctly without having to make assumptions and we believe is a more robust approach. In summary, Pfizer's concerns are two-fold: 1. The committee's preferred base case is inconsistent with the approach accepted for blinatumomab, wherein parametric curves are used to determine treatment specific survival post-HSCT up to the cure point. 2. Replacing treatment specific patient level Kaplan-Meier data from the RCT with an assumption relies on the effect of covariates such as MRD-negativity being perfectly reflected in the assumed model, and further assumes no other non-modelled covariates have an effect on survival. If it is deemed appropriate to assume that MRD-negativity is the *only* driver of treatment specific survival post-HSCT, then this is best modelled in an alternative way allowing for only this effect. In the committee's preferred ERG base case, survival between-HSCT and the cure point assumes the same underlying survival probabilities for each arm, but then differentiates within the model by a covariate for MRD-negativity along with other selected covariates within this model. A scenario is presented in this response where the model includes *only* the MRD covariate (no other covariates are included). Not only does this approach align with the assumption (if it is preferred) that MRD-negativity is the *only* driver of differences in survival post-HSCT, but this approach also results in the modelled data fitting the observed KM much better than the approach in the ERG base case (see Appendix C). If it assumed that more than just MRD is impacting survival post-HSCT, then it is recommended that continuing to use the treatment-specific patient level data during this period as the most robust approach (*i.e.* Pfizer's revised base case). Table 2 – not reported here	
11	Company	Pfizer	**Longer term survival post-cure point** Pfizer's base case assumed that after transplanted patients pass the cure point, their risk of mortality was similar to that of the general population. Conversely, the committee's preferred ICER included an elevated risk of mortality past this point, 4-times higher than that of the general population, a figure derived from a study by Martin et al. (2011).[4] Applying this estimate from Martin et al. to patients in this appraisal presents a number of issues. First, this study estimates mortality risk from a cohort in the United States who underwent transplants between 1980 and 2002. During this consultation on the ACD, we have sought further advice from several leading UK clinical experts on the degree to which HSCT practice and subsequent patient care differs from US practice in the 1980s and 1990s and UK practice in 2017. UK clinical expert feedback has indicated that the survival prospects and care pathway for patients transplanted is dramatically improved in comparison, and applying a risk of mortality from such a	Comments noted. The committee agreed with the clinical expert and ERG that post-HSCT patients would continue to have increased mortality compared with the general population. The committee concluded that a 4-fold increase in mortality for patients from 3 years after HSCT was its preferred assumption.

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			historical cohort can be misrepresentative of the outcomes expected for patients treated today. Indeed, an study analysing almost 1,500 transplanted US patients with ALL showed that during the period of 1987 to 2002, the survival probability for ALL patients 2-years post-transplant was between 23% and 28%, however in the period 2003 to 2006 the survival probability had almost doubled, to 41%.[5] Applying this improvement in outcomes to the 4-fold mortality risk figure cited in the ACD indicates this risk had fallen to between 2.2 and 2.7-fold (midpoint 2.5) higher than that of the general population by the end of 2006. This is still a conservative estimate of standard of care patients in today's practice, as transplanted patients in 2017 would pass the cure point in 2020, which is 14 years on from 2006. In the appraisal of blinatumomab, NICE accepted a risk of mortality past the cure point that was the general population mortality risk *added* to the risk derived from the extrapolated parametric curve for OS (a Gompertz curve fit to OS Kaplan-Meier). The factor by which this additive extrapolation elevated the risk of mortality beyond that of the general population is redacted; however applying this in our model sees the ICER fall below that in the original company's base case[1]. Pfizer has taken a more conservative approach in its revised base case than was accepted for blinatumomab, applying the estimate of a 2.5-fold risk of mortality above the general population as more relevant for today's standard of care patients than the historic 4-fold risk (noting this is still not reflective of 2017). The mortality risk (either the 4-fold from the historical cohort, or the 2.5-fold, a conservative reflects "today's" practice) is drawn from patients on standard of care therapy. This risk is not reflective of new anti-leukemic treatments, such as inotuzumab, and as such ignores potential benefits such as high rates of MRD-negativity, which the committee preferred to be incorporated into survival risk post-HSCT. The previously cited meta-analysis of 13,000 ALL patients (albeit not R/R ALL) identified an event-free survival HR of 0.28 (0.24, 0.33) for adults who are MRD-negative versus MRD-positive.[3] Applying this data to the 2.5-fold risk of morality for standard of care patients leads to an assumed increased risk of mortality for MRD-positive patients of 3.0x and for MRD-negative patients of 1.6x above the general population (calculations detailed in Appendix B). These estimates for mortality risk past the cure point are used in the revised basecase and equate to a 2.5-fold increase risk for standard of care patients and a 1.9 fold increase risk for inotuzumab patients. Table 3 – not reported here.	Please see FAD sections 3.9 and 3.20 for more details.
12	Company	Pfizer	**Cost of subsequent therapy** In the INO-VATE RCT, there was a difference between arms in the degree of subsequent therapy use, which can reasonably be expected to have impacted on the outcomes of patients. This impact is expected to act as a positive bias on the standard of care arm, because more patients received subsequent therapies that are associated with higher response rates than in the inotuzumab arm (in the standard of care arm [redacted] of standard of care patients subsequently received either blinatumomab or inotuzumab, whereas in the inotuzumab arm only [redacted] received subsequent blinatumomab).[1] As the Pfizer model uses patient level data from the trial, and thereby incorporates the benefits of these subsequent therapies within the base case, the cost of these subsequent treatments was also included. However,	Comments noted. The committee agreed that the cost of subsequent therapy based on the safety population could be included, but it was not appropriate to use the list prices for the calculation of the cost. Please see FAD section 3.21 for more detail.

[1] When applying the additive mortality approach, all patients in the standard of care die by 5 years. Comparatively, this is more favourable towards inotuzumab than when assuming the arms simply return to the mortality risk of the general population as per the Pfizer base case, hence why the ICER is lower in this scenario than the original base case.

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			the company's base case used the safety population (n=307) in the model rather than the ITT (n=326). The safety population has xx patients fewer than the ITT, as [redacted] patients were randomised to the standard of care arm in the INO-VATE RCT, but did not receive therapy. The company's submission (section 5.3.1) sets out rationale for excluding these from the base case, as these [redacted] would be categorised within the model as being in the no CR/CRi health state, and thus inclusion would have negatively impacted the standard of care arm. In the ACD, the committee preferred the ERG's scenario which excluded the cost of subsequent therapies from the model, as the ERG had highlighted the possibility of bias towards the inotuzumab arm in that the xx patients who did not have treatment in the INO-VATE trial and were excluded from the model may have been the patients who went on to have the subsequent innovative therapies. Table 15 in the company submission set out the subsequent therapy use for the ITT, but not broken down for the safety population. below now provides this breakdown; this shows that using the safety population does not result in subsequent treatment bias, as all of the subsequent blinatumomab and inotuzumab therapy use was within the safety population and not within the [redacted] untreated patients. Table 4 – not reported here	
13	Company	Pfizer	**Administration costs** The Pfizer base case applied an outpatient cost for the administration of inotuzumab, with inpatient stays captured as a result of treating adverse events. In the ACD, the committee preferred the ERG's scenario which stated inotuzumab would be administered in an inpatient setting, applying hospitalisation data from the INO-VATE trial as the cost. It is important to note that in the INO-VATE trial, hospitalisation is for a variety of reasons including underlying disease, comorbid conditions, and adverse events. Further, this cost differs between countries in the international trial due to differences in clinical practice. Using data which encompasses all such reasons and applying this as specifically an administration cost is inaccurate. Further, it risks double counting elsewhere in the model: for example, where inpatient stays related to adverse events are already costed. Since publication of the ACD, the company have sought guidance from several leading UK clinical experts on estimates for administration. Although an advantage of inotuzumab over current FLAG-base chemotherapy is that it can be administered in an outpatients setting, Pfizer's revised base case now includes inpatient stay for the first administration of the first cycle, following guidance from the clinical experts. However, it should be noted that the reason for this inpatient stay is likely to be more disease related (*i.e.* patients being unwell) rather than an administration requirement. The inclusion of this cost is therefore conservative. Pfizer noted that the clinical expert at the committee meeting stated that "several weeks" of inpatient stay is common for FLAG-based chemotherapy. Further, it is noted the ERG's Report which states that the company base case likely significantly underestimated costs in the standard of care arm (indeed, the ERG cited two studies reporting mean length of hospitalisation for PH-negative R/R ALL patients between 16.8 days and 26 days.[6,7] The clinical expert's estimate of 3 weeks was tested with the consulted experts recently consulted, who agreed it was reasonable to assume FLAG-based chemotherapy would frequently require around 3 weeks of inpatient admission. However, in the revised base case Pfizer uses a more conservative estimate of 2 weeks of inpatient stay as administration, noting that adverse events are costed separately so the use of an estimate of 3 weeks cost may risk double counting. In summary, Pfizer's revised base case ICER with the first administration of the first cycle for inotuzumab costed as an inpatient's stay, and FLAG-based chemotherapy costed as a 2-week inpatient stay.	Comments noted. The committee agreed that 1 inpatient day for inotuzumab ozogamicin is too low, and that it is likely that there is a difference in the number of inpatient days for inotuzumab ozogamicin and standard of care, but that the ratio is likely to be larger than the ratio used in the company's analysis (1/14). Please see FAD section 3.22 for more details.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Table 6 – not reported here	
14	Company	Pfizer	**Summary of analyses in the company's revised base case with the Patient Access Scheme** The company have submitted to the Department of Health for approval of a Patient Access Scheme (PAS), a simple discount which would reduce the price paid by the NHS in England, Wales and Northern Ireland to xxx less than the list price. The deterministic revised company base case is [redacted] per QALY with the PAS, discounted at 3.5% for costs and QALYs. The probabilistic ICER is [redacted] per QALY (the difference in the deterministic and probabilistic ICERs was previously explained in Section 5.8.1 of the company submission). When costs and QALYs are discounted at 1.5%, the deterministic ICER falls to [redacted] per QALY with the PAS, which is particularly relevant as the majority of inotuzumab's QALYs are accrued several years into the future. Indeed, the impact discounting has on the ICER is fully illustrated when no discount rates are applied: the deterministic ICER is almost halved, falling to [redacted] per QALY with the PAS. A summary of the revised base case with key assumptions included in the Pfizer base case are included in **Error! Reference source not found.**below and the individual change these cause in the ICER from the committee's currently preferred ERG base case. Details of further ICER combinations are presented in Appendix A. Table 7 – not reported here. We are confident that the most plausible ICER for inotuzumab ozogamicin falls below the £50,000 per QALY threshold, noting that the committee has concluded inotuzumab ozogamicin meets the criteria to be considered as an end of life treatment. We believe that the information presented in this response should satisfy the Committee that inotuzumab ozogamicin represents a cost-effective use of NHS resources.	Comments noted. Taking into consideration the deterministic and probabilistic ICERs, the committee concluded that the most plausible ICER including the patient access scheme for inotuzumab ozogamicin compared with standard care was substantially higher than £50,000 per QALY gained.). Please see FAD section 3.23 for more details.
15	Company	Pfizer	**Key scenario: 3 of cycles of inotuzumab if proceeding to HSCT** A scenario was presented in the company submission (Table 82) that explored the impact of costing only three cycles of inotuzumab in line with the draft SPC, noting that in the UK inotuzumab is expected to be used as a bridge to potentially curative therapy (such as HSCT), a point recently re-confirmed through clinical expert consultation. In line with the final EPAR and SPC (marketing authorisation received on 30 June 2017), for patients proceeding to HSCT the recommended duration of treatment is two cycles, with a third cycle considered for those patients who do not achieve CR/CRi and MRD-negativity after two cycles. Patients who do not achieve a CR/CRi within three cycles should discontinue treatment. Additional cycles of treatment (up to six) would only be given to patients who would not progress to HSCT, but as stated, this is not considered to be the population in the UK who would receive inotuzumab. As only a maximum of 3 cycles would thus be expected to be used in UK practice, this is scenario highly relevant for decision making. Indeed, costing a maximum of three cycles within the model (rather than six) does not result in bias towards inotuzumab as the efficacy remains unchanged: all inotuzumab patients who achieved CR/CRi and MRD-negativity (the typical pre-requisites for HSCT) did so within the first three cycles. Consequently, costing only three cycles of inotuzumab does not require any adjustment of the efficacy in the model. This scenario results is the base case ICER decreasing from [redacted] per QALY. Table 8 – not reported here.	Comment noted. The committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the company submission, the ERG report and the consultation responses.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Appendix A – not reported here.	

4th July 2017

Dear Professor Stevens,

Re: Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia ACD

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee's draft recommendation, and indeed believe that several assumptions which underpin the currently preferred ICER are clinically inappropriate and overly conservative with respect to the future benefits to patients; importantly, key modelling assumptions are also inconsistent with the precedent set by the recent appraisal for blinatumomab, which has the same treatment pathway as inotuzumab ozogamicin.

We welcome NICE's acknowledgement that inotuzumab ozogamicin is a clinically effective treatment option with an acceptable safety profile. As the committee have noted, the goal of intensive treatment for patients in the UK is to bridge to potentially curative therapy such as stem cell transplantation; after the study therapy in the INO-VATE RCT and prior to the start of any post induction therapy, around four-times as many patients in the inotuzumab arm reached a transplant than those receiving standard of care (43.3% versus 11.1%).[1] This is unprecedented in these patients, whose life expectancy is a matter of months in current practice.

However, despite this transformative clinical benefit, the ICER currently preferred by the committee is inconsistent with key assumptions that NICE accepted in the recent appraisal of blinatumomab, and resultantly does not fairly reflect the value for money inotuzumab can offer the NHS. Pfizer welcome the recommendation for blinatumomab as a step forwards for patient access, however we are concerned by the divergent committee conclusions with regard to preferred modelling assumptions with regard to the same patient pathway. As stated by the clinical expert at the committee meeting for inotuzumab, there are similarities between the medicines and the patients they treat. A key tenant of the Pfizer ACD response is a call for fairness in the methodological approach taken with inotuzumab ozogamicin in the context of the recent blinatumomab appraisal; it is nevertheless important to ensure that the clinical value of inotuzumab is not overshadowed by a technical dialogue.

In our response below, we first present the ICER which represents the Committee's preferred set of assumptions, as described in the ACD, noting the key differences with the company's base case. The remainder of the document focusses on key assumptions which we consider inappropriate, providing relevant clinical and/or technical rationale in support of a more appropriate alternative. In the proposed revised base case, we have also included a Patient Access Scheme (PAS) (providing a [redacted] discount to the list price), which is currently under review by the Department of Health. We are confident that the most plausible ICER for inotuzumab ozogamicin falls well below the £50,000 per QALY threshold, noting that the committee has concluded inotuzumab ozogamicin meets the criteria to be considered as an end of life treatment. We believe that the information presented in this response should satisfy the Committee that inotuzumab ozogamicin represents a cost-effective use of NHS resources within its licensed indication, so that patients in England and Wales are given access to this clinically effective, targeted medicine.

Yours sincerely,

[redacted]
On behalf of Pfizer UK

1. The Committee's preferred ICER

The ACD notes that the ICER which the committee considered most reflective of its preferred assumptions is one from the ERG's analysis, which is greater than £100,000 per QALY. There are key differences in assumptions between this ICER and the company's original base case ICER (set out in Table 31 within the ERG Report).

Pfizer has considered the differences in assumptions between those which underpin the ERG's ICER (preferred by the committee) and the base case ICER in the original submission, and propose a revised estimate of cost-effectiveness in this response. The following aspects of the ERG's base case (presented in These four assumptions are detailed within sections 3 to 7 in this response.

Table 1) require thorough reconsideration by the committee:

1. The assumption applied to survival between haematopoietic stem cell transplant (HSCT) and the "cure point" - the point at which patients are assumed to be return to normal life expectancy *(scenarios 2 and 7 in the ERG Report Table 31)*.
2. The increased risk of mortality applied to patients in the longer term who pass the "cure point". *(scenario 8 in the ERG Report Table 31)*.
3. The exclusion of the costs of subsequent therapy from the RCT *(scenario 6 in the ERG Report Table 31)*.
4. The administration costs applied to both the intervention and control arm *(scenario 9 in the ERG Report Table 31).*

These four assumptions are detailed within sections 3 to 7 in this response.

Table 1: Summary of the key four assumptions with which the company disagrees with the ERG's base case

	Assumption	Original company base case	ERG model which committee preferred
1	Survival between HSCT and the cure point	• Use parametric curves fit to treatment dependent Kaplan-Meier data from the RCT that take into account the treatment effect post-HSCT.	• Assume a pooled survival probability for both arms post-HSCT to determine survival post-HSCT up to the cure point, but allow covariate MRD to drive differences in curves via covariate analysis, along with other covariates kept within the model
2	Longer term survival post-cure point	• Assume general population mortality post cure point	• Assume a 4-fold increase in mortality compared with the general population post-cure point, taken from literature
3	Cost of subsequent therapy	• Use costs of subsequent therapies in line with what is used in the ITT in the trial	• Replacing the costs of the high cost subsequent therapies with the cost of chemotherapy
4	Administration costs	• Inotuzumab ozogamicin would need 3 outpatient visits per cycle • FLAG based chemotherapy requires 5 to 6 inpatient days for administration.	• Inotuzumab ozogamicin administration is costed using the total number of hospitalisation days from the RCT. Inpatient administration results in a 26 day hospital stay. • FLAG based chemotherapy uses a weighted average of NHS reference costs (average inpatient stay of 9.5 days)

We have made revisions to several other parameters to reflect the ERG's and the committee's preferences so as to minimize technical debate, whilst noting the majority of these have minimal impact on the ICER. These include:

- Using the 3.5% discount rate for costs and QALYs
- Age-adjusting utilities *(scenario 3 in the ERG Report Table 31)*
- Applying chemotherapy costs in line with INO-*VATE (scenario 4 in the ERG Report Table 31)*
- Pooled on treatment utilities *(scenario 5 in the ERG Report Table 31)*
- Model fix identified during clarification questions *(scenario 1 in the ERG Report Table 31)*

2. Recommendation of blinatumomab for previously treated PH-negative ALL

During the course of this appraisal, NICE issued final guidance for the appraisal of blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (ALL).[2] Pfizer welcomes NICE's recommendation for blinatumomab as it is important that ALL patients have access to new innovative treatments.

As stated by the clinical expert at the committee meeting for inotuzumab, there are similarities between the medicines and the patients they treat. Given these similarities, there are a number of key modelling assumptions which NICE accepted in their preferred ICER in recommending blinatumomab that are thus applicable to this appraisal:

- ***Survival between transplantation and the cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted treatments dependent parametric curves fit to the Kaplan-Meier data for patients pre-HSCT, post-HSCT and up until a cure point of 4 years post-HSCT. This is a clinically valid approach as it makes the best use of the available trial data.
- ***Longer term survival post-cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted that once patients pass the a certain post-HSCT (in this appraisal named the "cure point"), the hazard rate for death is assumed to be that of the normal population, with a factor added to compensate for disease-related mortality that was derived from the gradient of the extrapolated parametric curve. This is a clinically valid approach as it makes use of the available trial data without relying on historical literature from patients using different treatment regimens to assume the impact to survival.
- ***Health-related quality of life post cure point:*** In the preferred ICER for blinatumomab, the NICE committee accepted that patients who pass the cure point post-HSCT can expect a return to the health-related quality of life (utility) of the normal population.

Pfizer is disappointed that the committee's preferred ICER for inotuzumab accepts a more conservative positon on all three of the above assumptions based on the fact that the assumptions selected in this appraisal are not grounded in a strong clinical rationale. Considerations of the precedent set in the blinatumomab appraisal around the above three assumptions are factored into the revised base case in this response, and referred back to in the following pages.

3. Survival between transplantation and the cure point

The company base case uses treatment-specific patient level data from the INO-VATE trial (fitted with parametric curves) pre-transplant, then post-transplant and up to the cure point. This approach is in line with that accepted by NICE in the recommendation of blinatumomab where treatment-specific parametrically-fit curves continue to be fit to the Kaplan-Meier data up to 4 years post-HSCT up to the cure point. However, the committee's preferred ICER in the inotuzumab appraisal ceases to use the treatment-specific patient level data past the point of transplant and instead chooses to pool survival from both arms, applying a covariate for MRD-negativity to account for survival differences.

Using the treatment specific Kaplan-Meier data from patients post-HSCT to model the survival probabilities of patients post-HSCT is the best available data source. The ACD cites MRD-negativity as an assumed a driver of improved outcomes post-HSCT, but using the patient level data inherently takes into account any effect that MRD-negativity is having on patients' survival in either arm as well as the effect from any other known or unknown covariate that may be driving survival. Abandoning the treatment specific data as in the ERG's base case replaces treatment effects captured within the data with an assumption, and relies on this assumption perfectly modelling the assumed effect of MRD as well as any other specified covariates taken into account.

Pfizer's basecase uses the treatment specific Kaplan-Meier data which inherently captures all covariates correctly without having to make assumptions and we believe is a more robust approach.

In summary, Pfizer's concerns are two-fold:

1. The committee's preferred base case is inconsistent with the approach accepted for blinatumomab, wherein parametric curves are used to determine treatment specific survival post-HSCT up to the cure point.
2. Replacing treatment specific patient level Kaplan-Meier data from the RCT with an assumption relies on the effect of covariates such as MRD-negativity being perfectly reflected in the assumed model, and further assumes no other non-modelled covariates have an effect on survival.

If it is deemed appropriate to assume that MRD-negativity is the *only* driver of treatment specific survival post-HSCT, then this is best modelled in an alternative way allowing for only this effect. In the committee's preferred ERG base case, survival between-HSCT and the cure point assumes the same underlying survival probabilities for each arm, but then differentiates within the model by a covariate for MRD-negativity along with other selected covariates within this model. A scenario is presented in this response where the model includes *only* the MRD covariate (no other covariates are included). Not only does this approach align with the assumption (if it is preferred) that MRD-negativity is the *only* driver of differences in survival post-HSCT, but this approach also results in the modelled data fitting the observed KM much better than the approach in the ERG base case (see Appendix C). If it assumed that more than just MRD is impacting survival post-HSCT, then it is recommended that continuing to use the treatment-specific patient level data during this period as the most robust approach (*i.e.* Pfizer's revised base case).

Table 2. Summary of assumptions for long term survival post cure point

Pfizer original base case	***Preferred ERG base case***	***Pfizer's revised base case***
• Parametric curves fit to Kaplan-Meier data for survival post-HSCT	• Pool trial survival data post-HSCT, but allow covariate MRD to drive differences in curves via covariate analysis with other covariates kept within the model	• Parametric curves fit to Kaplan-Meier data for survival post-HSCT • Scenario: Assume same survival post-HSCT but allow *only* a covariate for MRD-negativity to impact

4. Longer term survival post-cure point

Pfizer's base case assumed that after transplanted patients pass the cure point, their risk of mortality was similar to that of the general population. Conversely, the committee's preferred ICER included an elevated risk of mortality past this point, 4-times higher than that of the general population, a figure derived from a study by Martin et al. (2011).[4]

Applying this estimate from Martin et al. to patients in this appraisal presents a number of issues. First, this study estimates mortality risk from a cohort in the United States who underwent transplants between 1980 and 2002. During this consultation on the ACD, we have sought further advice from several leading UK clinical experts on the degree to which HSCT practice and subsequent patient care differs from US practice in the 1980s and 1990s and UK practice in 2017. UK clinical expert feedback has indicated that the survival prospects and care pathway for patients transplanted is dramatically improved in comparison, and applying a risk of mortality from such a historical cohort can be misrepresentative of the outcomes expected for patients treated today. Indeed, an study analysing almost 1,500 transplanted US patients with ALL showed that during the period of 1987 to 2002, the survival probability for ALL patients 2-years post-transplant was between 23% and 28%, however in the period 2003 to 2006 the survival probability had almost doubled, to 41%.[5] Applying this improvement in outcomes to the 4-fold mortality risk figure cited in the ACD indicates this risk had fallen to between 2.2 and 2.7-fold (midpoint 2.5) higher than that of the general population by the end of 2006. This is still a conservative estimate of standard of care patients in today's practice, as transplanted patients in 2017 would pass the cure point in 2020, which is 14 years on from 2006.

In the appraisal of blinatumomab, NICE accepted a risk of mortality past the cure point that was the general population mortality risk *added* to the risk derived from the extrapolated parametric curve for OS (a Gompertz curve fit to OS Kaplan-Meier). The factor by which this additive extrapolation elevated the risk of mortality beyond that of the general population is redacted; however applying this in our model sees the ICER fall below that in the original company's base case[1]. Pfizer has taken a more conservative approach in its revised base case than was accepted for blinatumomab, applying the estimate of a 2.5-fold risk of mortality above the general population as more relevant for today's standard of care patients than the historic 4-fold risk (noting this is still not reflective of 2017).

The mortality risk (either the 4-fold from the historical cohort, or the 2.5-fold, a conservative reflects "today's" practice) is drawn from patients on standard of care therapy. This risk is not reflective of new anti-leukemic treatments, such as inotuzumab, and as such ignores potential benefits such as high rates of MRD-negativity, which the committee preferred to be incorporated into survival risk post-HSCT. The previously cited meta-analysis of 13,000 ALL patients (albeit not R/R ALL) identified an event-free survival HR of 0.28 (0.24, 0.33) for adults who are MRD-negative versus MRD-positive.[3] Applying this data to the 2.5-fold risk of morality for standard of care patients leads to an assumed increased risk of mortality for MRD-positive patients of 3.0x and for MRD-negative patients of 1.6x above the general population (calculations detailed in Appendix B). These estimates for mortality risk past the cure point are used in the revised basecase and equate to a 2.5-fold increase risk for standard of care patients and a 1.9 fold increase risk for inotuzumab patients.

[1] When applying the additive mortality approach, all patients in the standard of care die by 5 years. Comparatively, this is more favourable towards inotuzumab than when assuming the arms simply return to the mortality risk of the general population as per the Pfizer base case, hence why the ICER is lower in this scenario than the original base case.

Table 3. Summary of assumptions for long term survival post cure point

Pfizer original base case	*Preferred ERG base case*	*Pfizer's revised base case*
• Mortality risk is that of general population	• Mortality risk is 4x the general population for all patients	• Mortality risk is 2.5x general population for the standard of care, and 1.9x for inotuzumab

5. Cost of subsequent therapy

In the INO-VATE RCT, there was a difference between arms in the degree of subsequent therapy use, which can reasonably be expected to have impacted on the outcomes of patients. This impact is expected to act as a positive bias on the standard of care arm, because more patients received subsequent therapies that are associated with higher response rates than in the inotuzumab arm (in the standard of care arm [redacted] of standard of care patients subsequently received either blinatumomab or inotuzumab, whereas in the inotuzumab arm only [redacted] received subsequent blinatumomab).[1]

As the Pfizer model uses patient level data from the trial, and thereby incorporates the benefits of these subsequent therapies within the base case, the cost of these subsequent treatments was also included. However, the company's base case used the safety population (n=307) in the model rather than the ITT (n=326). The safety population has [redacted] patients fewer than the ITT, as [redacted] patients were randomised to the standard of care arm in the INO-VATE RCT, but did not receive therapy. The company's submission (section 5.3.1) sets out rationale for excluding these from the base case, as these [redacted] would be categorised within the model as being in the no CR/CRi health state, and thus inclusion would have negatively impacted the standard of care arm.

In the ACD, the committee preferred the ERG's scenario which excluded the cost of subsequent therapies from the model, as the ERG had highlighted the possibility of bias towards the inotuzumab arm in that the [redacted] patients who did not have treatment in the INO-VATE trial and were excluded from the model may have been the patients who went on to have the subsequent innovative therapies. Table 15 in the company submission set out the subsequent therapy use for the ITT, but not broken down for the safety population. Table 4. Subsequent induction therapies used in the INO-VATE 1022 trial (ITT population)[1]

Subsequent therapy	Inotuzumab ozogamicin	Standard of care	
		ITT	Safety
Blinatumomab	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
TKIs	[redacted]	[redacted]	[redacted]
Inotuzumab ozogamicin	[redacted]	[redacted]	[redacted]

Consequently, the revised base case includes the cost of subsequent therapy, as those going on to receive effective subsequent therapies such as inotuzumab and blinatumomab were patients from the safety population. It should be noted that including or excluding the additional [redacted] patients in the model has minimal impact on the ICER in the revised base case.

below now provides this breakdown; this shows that using the safety population does not result in subsequent treatment bias, as all of the subsequent blinatumomab and inotuzumab therapy use was within the safety population and not within the [redacted] untreated patients.

Table 4. Subsequent induction therapies used in the INO-VATE 1022 trial (ITT population)[1]

Subsequent therapy	Inotuzumab ozogamicin	Standard of care	
		ITT	Safety
Blinatumomab	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
TKIs	[redacted]	[redacted]	[redacted]

Inotuzumab ozogamicin	[redacted]	[redacted]	[redacted]

Consequently, the revised base case includes the cost of subsequent therapy, as those going on to receive effective subsequent therapies such as inotuzumab and blinatumomab were patients from the safety population. It should be noted that including or excluding the additional [redacted] patients in the model has minimal impact on the ICER in the revised base case.

Table 5. Summary of assumptions for subsequent therapy costs

Pfizer original base case	***Preferred ERG base case***	***Pfizer's revised base case***
• Include both cost and efficacy of subsequent therapies	• Replace cost of innovative therapies with cost of chemotherapy due to unknown use of innovative therapies in safety population	• Include both cost and efficacy of subsequent therapies as applicable to safety population

6. Administration costs

The Pfizer base case applied an outpatient cost for the administration of inotuzumab, with inpatient stays captured as a result of treating adverse events. In the ACD, the committee preferred the ERG's scenario which stated inotuzumab would be administered in an inpatient setting, applying hospitalisation data from the INO-VATE trial as the cost. It is important to note that in the INO-VATE trial, hospitalisation is for a variety of reasons including underlying disease, comorbid conditions, and adverse events. Further, this cost differs between countries in the international trial due to differences in clinical practice. Using data which encompasses all such reasons and applying this as specifically an administration cost is inaccurate. Further, it risks double counting elsewhere in the model: for example, where inpatient stays related to adverse events are already costed.

Since publication of the ACD, the company have sought guidance from several leading UK clinical experts on estimates for administration. Although an advantage of inotuzumab over current FLAG-base chemotherapy is that it can be administered in an outpatients setting, Pfizer's revised base case now includes inpatient stay for the first administration of the first cycle, following guidance from the clinical experts. However, it should be noted that the reason for this inpatient stay is likely to be more disease related (*i.e.* patients being unwell) rather than an administration requirement. The inclusion of this cost is therefore conservative.

Pfizer noted that the clinical expert at the committee meeting stated that "several weeks" of inpatient stay is common for FLAG-based chemotherapy. Further, it is noted the ERG's Report which states that the company base case likely significantly underestimated costs in the standard of care arm (indeed, the ERG cited two studies reporting mean length of hospitalisation for PH-negative R/R ALL patients between 16.8 days and 26 days.[6,7] The clinical expert's estimate of 3 weeks was tested with the consulted experts recently consulted, who agreed it was reasonable to assume FLAG-based chemotherapy would frequently require around 3 weeks of inpatient admission. However, in the revised base case Pfizer uses a more conservative estimate of 2 weeks of inpatient stay as administration, noting that adverse events are costed separately so the use of an estimate of 3 weeks cost may risk double counting.

In summary, Pfizer's revised base case ICER with the first administration of the first cycle for inotuzumab costed as an inpatient's stay, and FLAG-based chemotherapy costed as a 2-week inpatient stay.

Table 6. Summary of assumptions for administration costs

Pfizer original base case	*Preferred ERG base case*	*Pfizer's revised base case*
• Inotuzumab costed in outpatients setting	• [redacted] of inotuzumab administrations would be inpatient and such administrations result in 26 day hospital stay	• First administration of the first cycle of inotuzumab costed as inpatients setting
• FLAG costed for 6.2 days inpatient stay	• FLAG costed using NHS reference costs, averaging 9.5 inpatients stay	• FLAG costed for 14 days inpatient stay

7. Summary of analyses in the company's revised base case with the Patient Access Scheme

The company have submitted to the Department of Health for approval of a Patient Access Scheme (PAS), a simple discount which would reduce the price paid by the NHS in England, Wales and Northern Ireland to [redacted] less than the list price. The deterministic revised company base case is **£37,734 per QALY** with the PAS, discounted at 3.5% for costs and QALYs. The probabilistic ICER is £46,152 per QALY (the difference in the deterministic and probabilistic ICERs was previously explained in Section 5.8.1 of the company submission).

When costs and QALYs are discounted at 1.5%, the deterministic ICER falls to £28,179 per QALY with the PAS, which is particularly relevant as the majority of inotuzumab's QALYs are accrued several years into the future. Indeed, the impact discounting has on the ICER is fully illustrated when no discount rates are applied: the deterministic ICER is almost halved, falling to £21,932 per QALY with the PAS.

A summary of the revised base case with key assumptions included in the Pfizer base case are included in Table 7 below and the individual change these cause in the ICER from the committee's currently preferred ERG base case. Details of further ICER combinations are presented in Appendix A.

Table 7. Revised Pfizer base case with the PAS

Item	Revised Pfizer base case assumption	ICER with single change	ICER change from ERG base case (with PAS)
Committee preferred ERG parametric base case with a [redacted] PAS		£114,078* *list price* [redacted] *with PAS*	*£0*
(1) Survival between HSCT and the cure point	• (i) Use parametric curves fit to Kaplan-Meier data for survival post-HSCT	[redacted]	[redacted]
	• (ii) Scenario: Assume same survival post-HSCT but allow *only* a covariate for MRD-negativity to drive any differences	[redacted]	[redacted]
(2) Longer term survival post-cure point	• Mortality risk 3.0x general population for MRD+ and 1.6x for MRD- patients ➢ *equates to mortality risk of 2.5x general pop for SoC, and 1.9x for inotuzumab*	[redacted]	[redacted]
(3) Cost of subsequent therapy	• Include both cost and efficacy of subsequent therapies as applicable to safety population	[redacted]	[redacted]
(4) Administration costs	• First administration of inotuzumab in first cycle costed as inpatients setting • FLAG costed for 14 days inpatient stay	[redacted]	[redacted]
(5) Utilities for patients post-cure point	• Apply normal population utilities for disease-free patients, as was accepted for blinatumomab	[redacted]	[redacted]
Pfizer revised base case	**1(i) + 2 + 3 + 4 + 5**	**£37,734**	
Post-HSCT survival scenario analysis	**1(ii) + 2 + 3 + 4 + 5**	**£42,523**	

We are confident that the most plausible ICER for inotuzumab ozogamicin falls below the £50,000 per QALY threshold, noting that the committee has concluded inotuzumab ozogamicin meets the criteria to be considered as an end of life treatment. We believe that the information presented in this response should satisfy the Committee that inotuzumab ozogamicin represents a cost-effective use of NHS resources.

Key scenario: 3 of cycles of inotuzumab if proceeding to HSCT

A scenario was presented in the company submission (Table 82) that explored the impact of costing only three cycles of inotuzumab in line with the draft SPC, noting that in the UK inotuzumab is expected to be used as a bridge to potentially curative therapy (such as HSCT), a point recently re-confirmed through clinical expert consultation. In line with the final EPAR and SPC (marketing authorisation received on 30 June 2017), for patients proceeding to HSCT the recommended duration of treatment is two cycles, with a third cycle considered for those patients who do not achieve CR/CRi and MRD-negativity after two cycles. Patients who do not achieve a CR/CRi within three cycles should discontinue treatment. Additional cycles of treatment (up to six) would only be given to patients who would not progress to HSCT, but as stated, this is not considered to be the population in the UK who would receive inotuzumab.

As only a maximum of 3 cycles would thus be expected to be used in UK practice, this is scenario highly relevant for decision making. Indeed, costing a maximum of three cycles within the model (rather than six) does not result in bias towards inotuzumab as the efficacy remains unchanged: all inotuzumab patients who achieved CR/CRi and MRD-negativity (the typical pre-requisites for HSCT) did so within the first three cycles. Consequently, costing only three cycles of inotuzumab does not require any adjustment of the efficacy in the model. This scenario results is the base case ICER decreasing from £37,734 per QALY to [redacted] per QALY.

Table 8. Revised Pfizer base case with the PAS and the 3 cycle scenario analysis

Item	Revised Pfizer base case assumption	ICER with change (with PAS)
(6) Max 3 cycles of inotuzumab as per SPC	• Cost inotuzumab for only 3 cycles, in line with SPC	[redacted] with sole change from ERG base
Pfizer revised base case with 3 cycle scenario analysis – survival (i)	**1(i) + 2 + 3 + 4 + 5 + 6**	[redacted]
Pfizer revised base case with 3 cycle scenario analysis – survival (ii)	1(ii) + 2 + 3 + 4 + 5 + 6	[redacted]

References

1. Pfizer Inc. An Open-Label, Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigator's Choice in Adult Patients with Relapsed or Refractory CD22-Positive Acute Lymphoblastic Leukemia (ALL). INO-VATE (B1931022) CSR.
2. National Institute for Health and Care Excellence. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. 2017. Available at: https://www.nice.org.uk/guidance/ta450
3. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, Wood BL, Kelloff GJ, Jessup JM, Radich JP. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017
4. Martin PJ, Counts GW, Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol 2010;28:1011-6. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2009.25.6693
5. Karanes C, Nelson GO, Chitphakdithai P, Agura E, Ballen KK, Bolan CD, Porter DL, Uberti JP, King RJ, Confer DL. Twenty years of unrelated donor hematopoietic cell transplantation for adult recipients facilitated by the National Marrow Donor Program. Biol Blood Marrow Transplant. 2008 Sep;14(9 Suppl):8-15
6. Boluda B, Rodríguez-Veiga R, Martínez-Cuadrón D, Lorenzo I, Sanz G, Sanz J, et al. Time and cost of hospitalisation for salvage therapy among adults with Philadelphia (Ph)-negative B-cell relapsed/refractory (R/R) acute lymphoblastic leukaemia (ALL) in Spain. In: ISPOR 19th Annual European Congress. Vienna, Austria; 2016.
7. Dombret H, Thomas X, Chevallier P, Nivot E, Reitan J, Barber B, et al. Healthcare burden and reimbursement of hospitalization during chemotherapy for adults with Ph-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia in France: a retrospective chart review. J Med Econ 2016;19:1034-9.

Appendix A: Deterministic ICERs for other combination of assumptions

Further combinations of assumptions in the selected ICER from Table 7, including reverting to the ERG's original base case for preferred survival assumptions.

Table 9. Further combinations of assumptions with the revised deterministic base case at [redacted] PAS

Item	Pfizer revised base case assumptions	ICER with changes
Pfizer revised base case for assumptions (2+3+4+5) but ERG assumptions for: • post HSCT survival (1): pooled with MRD-covariate along with other covariates kept in the model, as per ERG base case • post-cure (2) risk applied to morality, based on MRD	2 + 3 + 4 + 5	£52,672
	2 + 3 + 4 + 5 + 6 *(3 cycles)*	[redacted]
Pfizer revised base case for assumptions (3+4+5) but ERG assumptions for: • post HSCT survival (1): pooled with MRD-covariate along with other covariates kept in the model, as per ERG base case • post-cure point survival (2) where a 2.5x increased risk vs general population is applied (as per section 4) as opposed to 4x, as per ERG base case	3 + 4 + 5	£55,535
	3 + 4 + 5 + 6 *(3 cycles)*	[redacted]
Pfizer revised base case for assumptions (1+3+4+5) but ERG assumptions for: • post-cure point survival (2) where a 2.5x increased risk vs general population is applied to both MRD+ and MRD- patients alike (as per section 4) as opposed to 4x from the ERG base case	1(i) + 3 + 4 + 5	[redacted]
	1(i) + 3 + 4 + 5 + 6 *(3 cycles)*	[redacted]
Pfizer revised base case without blinatumomab utilities applied to patients disease-free post cure point	1(i) + 2 + 3 + 4	[redacted]
	1(ii) + 2 + 3 + 4	[redacted]

One Birch Court,
Blackpole East
Worcester, WR3 8SG
[redacted]

[redacted]

4th July 2017

Dear NICE Technology Appraisal Committee C,

Re: Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]

We are writing on behalf of acute lymphoblastic leukaemia (ALL) patients in response to the recently published ACD for the appraisal of inotuzumab ozogamicin (ID 893).

Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. It is often diagnosed as an emergency (64%), with 86% of patients starting treatment within a week of diagnosis. Whilst highly toxic chemotherapies have high response rates (80-90%), nearly half of patients will eventually relapse.

In the relapsed or refractory setting, survival outcomes are poor, with a five-year survival rate for relapsed patients of less than 10%. This demonstrates the urgent need for effective salvage treatment options. In this setting, the most effective option for ALL patients is allogenic stem-cell transplantation (SCT). However, this is currently only an option for a small minority of patients.

Last week (30th June 2017) the European Medicines Agency licensed inotuzumab ozogamicin as the first antibody-drug conjugate for the treatment of ALL. They found that inotuzumab ozogamicin has been shown to increase the proportion of patients who have complete remission and molecular remission and to delay the progression of disease. A further key benefit is it's potential to act as a "bridge" to transplant, increasing the number of people who are able to undergo SCT, the only curative option for these patients. This is something that is strongly welcomed by ALL patients, particularly in the relapsed/refractory setting.

We hope that you will bear our comments in mind when considering your final recommendation and urge you to make inotuzumab ozogamicin available to all of those who could benefit from it.

Yours Sincerely,

[redacted]

[redacted]
Leukaemia CARE

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From The Registrar
[redacted]

7 July 2017

Dear Sir or Madam

Re: ACD - Consultees & Commentators: Leukaemia (acute lymphoblastic, B-cell, relapsed, refractory) - inotuzumab ozogamicin ID893

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 33,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

Why was Inotuzumab not approved when Blinatumomab was?

Our experts are unclear why Inotuzumab has not reached the criteria for approval when Blinatumomab was recently approved by NICE. They question the difference in methodology used and composition of the reviewing panel. Inotuzumab appears to be at least as effective as Blinatumomab and possibly more effective in the face of frank bone marrow relapse (ie complete remission rate twice as high). Our experts question whether the comparator for the Inotuzumab cost effectiveness analysis have been Blinatumomab rather than FLAG-Ida.

Specific need in teenage and young adult (TYA) patients with ALL

Our experts highlight the need for novel therapies in TYA ALL patients who relapse. Please see attached slides showing an analysis of outcomes following relapse in this group. The overall survival in patients who relapse on treatment is only 7% at 5 years, even though many of these patients received FLAG-Ida and an allogeneic haemopoietic stem cell transplant. This highlights the urgent need for agents such as Inotuzumab for these patients, with which patients are likely to achieve a deeper remission (ie MRD negative remission) prior to curative consolidation with an allograft or to allow entry into CAR T cell trials. Whilst the TYA group are no more important than older patients, should they achieve cure they will be expected to have a longer, healthy life subsequently. Our experts question whether this was taken into account in the cost effectiveness analysis.

The lack of access to inotuzumab in the UK would mean that patients who could be cured of ALL will die of their disease. This would not be the case in other developed countries and seems to be a highly undesirable situation. Given that Inotuzumab received marketing authorisation from the EMA last week, our experts question whether there is an opportunity to revisit pricing which could be taken into account in the evaluation of cost effectiveness of this agent.

Yours faithfully

TYA UKALL2003 Relapse Outcomes

Incidence of Relapse

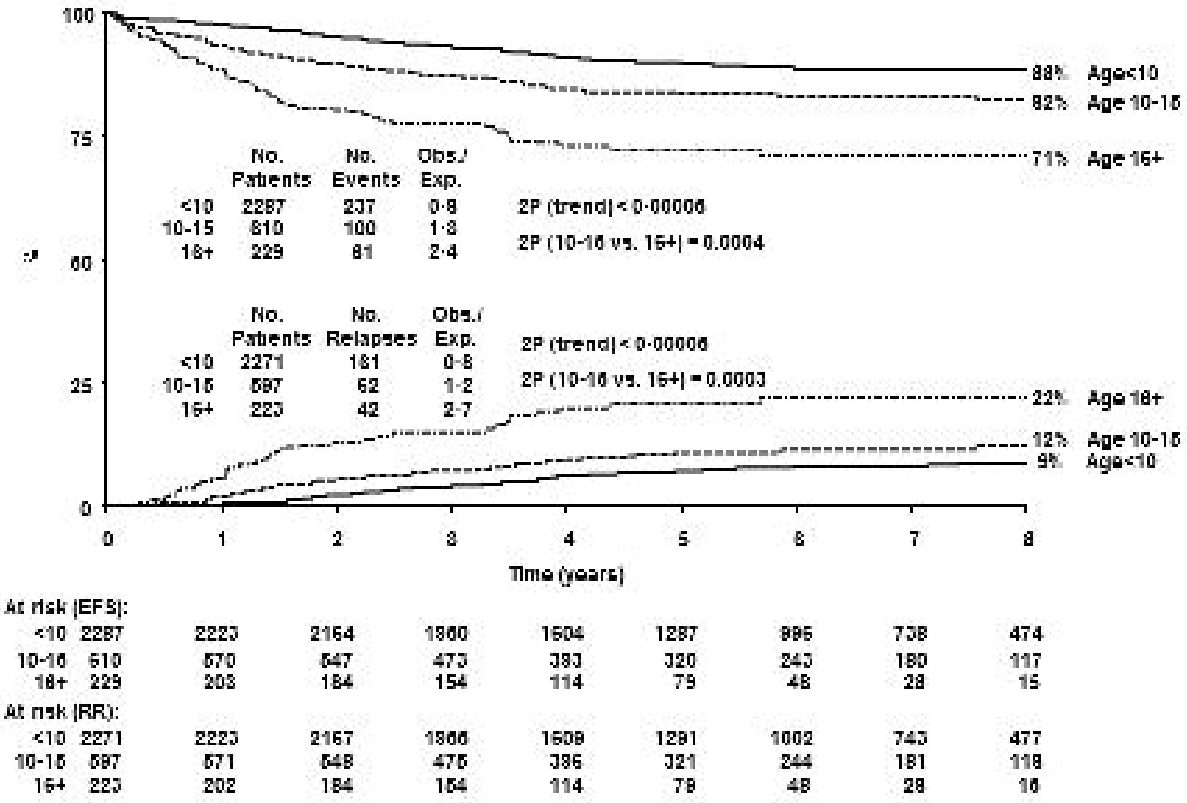
229 patients recruited overall

RR 8.8% at 5 years

Median follow up 4 years 10 months

Median FU trial overall 5 years 10 months

Figure 2a: EFS and RR by age group



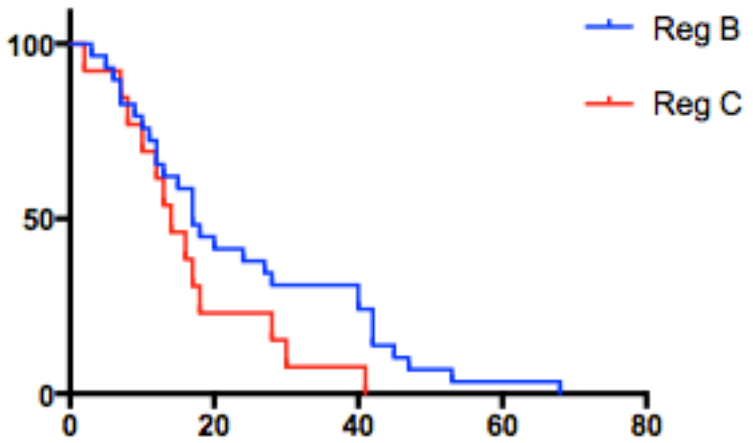
Presenting Features of Those Who Relapsed at Initial Diagnosis

	Patients who subsequently relapsed (n=42)	All recruited patients (n=229)
Wcc	21.8 (0.5-800)	-
CNS Involvement	1 (2.4%)	3 (1.3%)
Immunophenotype T/B	12 (28.6%)/30 (71.4%)	63 (27.6%)/165 (72.4%)
Cytogenetic risk group Good Intermediate Poor	 4 (9.5%) 13 (31.5%) 6 (14.3%)	 37 (25.3%) 90 (61.6%) 10 (6.9%)
MRD risk group Low Intermediate High	 2 (0.5%) 12 (28.6%) 28 (66.7%)	 54 (23.6%) 60 (26.2%) 109 (47.6%)

Clinical Features at Relapse

		All	B Cell	T Cell
Time to relapse	≤ 24 months	28	17	11
	>24 months	14	13	1
Site of relapse	BM	30	23	8
	BM+CNS	4	3	3
	BM + other	1	1	0
	Isolated CNS	6	5	1

The median time from the start of treatment to relapse was 17 months (17.5 months for B-ALL and 14 months for T-ALL, *P*=.1).



Time to relapse for Reg B and Reg C
p=0.01

First Line Salvage Therapy

	All	B Cell	T Cell
R3	9	6	3
Fludara/Ara-C based	17	13	4
Clo/Cy/Etop	3	3	0
Nelarabine based	1	0	1
Other	7	6	1
None	5	2	3

Other includes (1 patient each treated with, single agent Clofarabine,,1 MARALL, 1 Blinatumamb, IT + HD MTX, UKALL2011 induction, UKALL12 induction, HyperCVAD)

Salvage chemotherapy with curative intent was attempted in 37/42 (88.1%) patients

Response to First Line Salvage Therapy

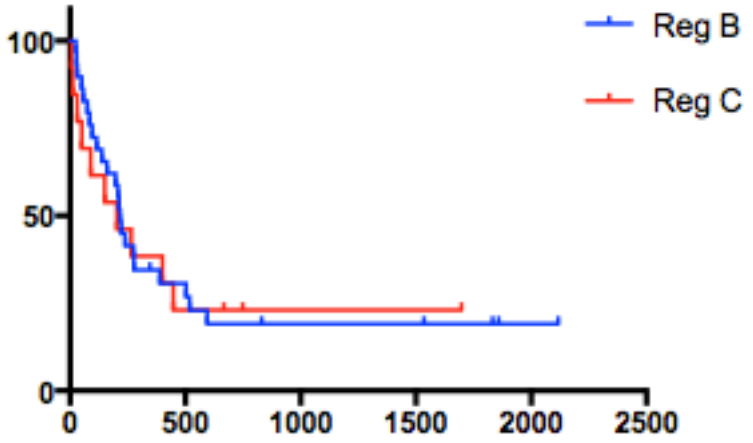
	All	B Cell	T Cell
Response to 1st			
CR2	20	17	3
Refractory	14	9	5 (inc 1 PR)
NRM	2	1	1
UK	2	1	1
CR2 ever			
All	22/37(59.5%)	18/28 (64.3%)	4/10 (40%)
Relapsed ≤24 months	11/23 (47.8%)	8/15 (53.3%)	3/8 (37.5%)
Relapsed >24 months	11/14 (78.6%)	9/13 (69.2%)	1/1 (100%)
Allograftin CR2	21	17	4

CR2 achieved in 20/37 (54%) patients 17/30 (57%) B cell and 3/12 (25%) T cell
CR2 more likely to be achieved if relapse >24 months

Survival from Relapse

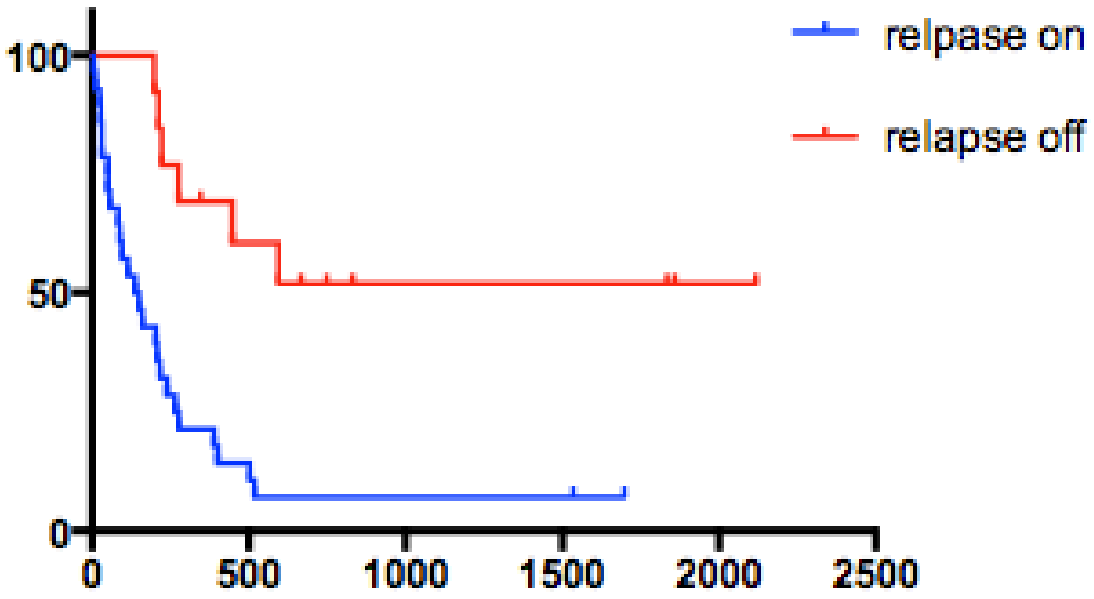
At a median post relapse follow up of
50 months (range 11-69 months)
9 patients are alive, 8 in CR, 1 on Rx

5 year OS 20.4% (95% CI; 9.7-33.8%)



OS survival from relapse Reg B and Reg C

Survival from Relapse



All patients relapse on v off treatment p=0.0004

Survival from Relapse

Treatment Phase	B-cell	T-cell	All	Survival
Induction	0	0	0	N/A
Consolidation	1	0	1	0% (0/1))
IM1	0	1	1	0% (0/1)
DI1	1	1	2	0% (0/2)
IM2	2	2	4	25% (1/4)
DI2	0	2	2	0% (0/2)
Maintenance	13	6	19	5% (1/19)
Off treatment	12	1	13	54% (7/13)

2/29 (7%) patients relapsing on treatment survived,
7/13 (54%) patients relapsing off treatment survived

Summary

- RR at 8 years in TYA patients on UKALL2003 22%
- Relapse not adequately predictable by current strategies
- No clear/consensus approach to relapse
- Although CR2 achieved in 54%
- 5 year OS from relapse 20.4% (95% CI; 9.7-33.8%)
  - 7% patients with on treatment relapse surviving
  - 54% patients with off treatment relapse surviving

Single Technology Appraisal (STA): **Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia [ID893]**

Appraisal consultation document

Dr Adele Fielding on behalf of the Royal College of Pathologists and British Society for Haematology

Thank you for asking me to comment on the ACD for Leukaemia (acute lymphoblastic, B-cell, relapsed, refractory) - inotuzumab ozogamicin [893]

I am commenting in the role of clinical expert. I attended the meeting.

Naturally, I am generally disappointed with this decision on behalf of our patient population as I believe this agent has merit for the therapy of the relevant patient population and that this has been adequately demonstrated by the randomised controlled trial, published in the New England Journal of Medicine, which was presented in evidence. As discussed within the meeting, survival advantage can be very hard to demonstrate in this patient population since those patients whose disease did not respond within the control arm would have had access to several other active options which have recently become available including blinatumomab and chimeric antigen receptor T cells.

My specific concern regarding this decision relates to:

1) Fairness. I have also participated in a consultation of another novel agent for the therapy of ALL - blinatumomab. This was considered by a different committee. The agent was approved. As an academic who specialises in the therapy of ALL, if asked to comment on the relative merits of blinatumomab and inotuzumab, I absolutely would not be able to recommend one agent over the other except in very specific clinical circumstances. So I find it hard that two separate committees of NICE - without apparently having consulted each other and having used different input organisations for ERG have nonetheless gone ahead and made this decision for the community and for our patients.

2) Modelling. I am not an expert in the modelling of ICER but I am concerned that different assumptions were used for inotuzumab versus blinatumomab. I respectfully would request the committees review the modelling and assumptions on which this decision was based to ensure that they are completely congruous for both agents and that the identical baseline considerations and future projections have been taken into account.

Appendix B: **New analyses/evidence:** Calculating assumed risk of mortality in MRD-negative and MRD-positive patients, using estimates from the literature

The risk of mortality for standard of care patients is assumed to be 2.49. This is calculated by taking the midpoint of the 23% and 28% estimates of 2-year survival post-transplant for standard of care ALL patients from 1987 to 2002 (=25.5%) and calculating how much less this is that the estimate of 41%, which reflects improved practice between 2003 and 2006 (=0.622). Applied to the committee preferred estimate of a 4.0x mortality risk produces a morality risk of 2.49 (i.e. reflective of practice in 2006).

From the figure of 2.49, the absolute risk of mortality above the general population is calculated (general population risk of morality = 1, therefore absolute risk above this = 1.49). As this estimate reflects a standard of care cohort, the proportions of MRD-negative and positive from the standard of care cohort are used, along with the hazard ratio for event-free survival derived from the literature of 0.28 for MRD-negative vs MRD-positive patients, to calculate the risk of mortality in MRD-positive and MRD-negative patients. The calculation is performed on the absolute risk above the general population (i.e. the risk above a value of 1) to avoid a result that could estimate survival below the of the general population (i.e. <1)

These risk equate to 2.49 for the average patient in the standard of care arm, and also reflect an HR of 0.28 in the absolute risk above the general population, between MRD- and MRD+ patients (Table 1).

Table 1. Within the estimate of a 2.49x risk of mortality for the standard of care, what is the risk for MRD-negative and positive patients, considering an HR of 0.28 between these?

Risk of mortality x general population (GP) for SoC	**2.49**
Absolute risk above general population (GP) for SoC	1.49
MRD-negative in SoC	36%
MRD-positive in SoC	64%
HR for MRD-negative vs MRD-positive	**0.28**
Absolute risk of mortality above GP for MRD-	0.57
Absolute risk of mortality above GP for MRD+	2.02
Risk of mortality x GP for MRD- patients	**1.57**
Risk of mortality x GP for MRD+ patients	**3.02**

For completeness, these calculations are also conducted using the original estimate of 4.0x the risk of mortality for standard of care patients (Table 2), although these figures are not used in the revise basecase.

Table 2. Within the estimate of a 4.0x risk of mortality for the standard of care, what is the risk for MRD-negative and positive patients, considering an HR of 0.28 between these?

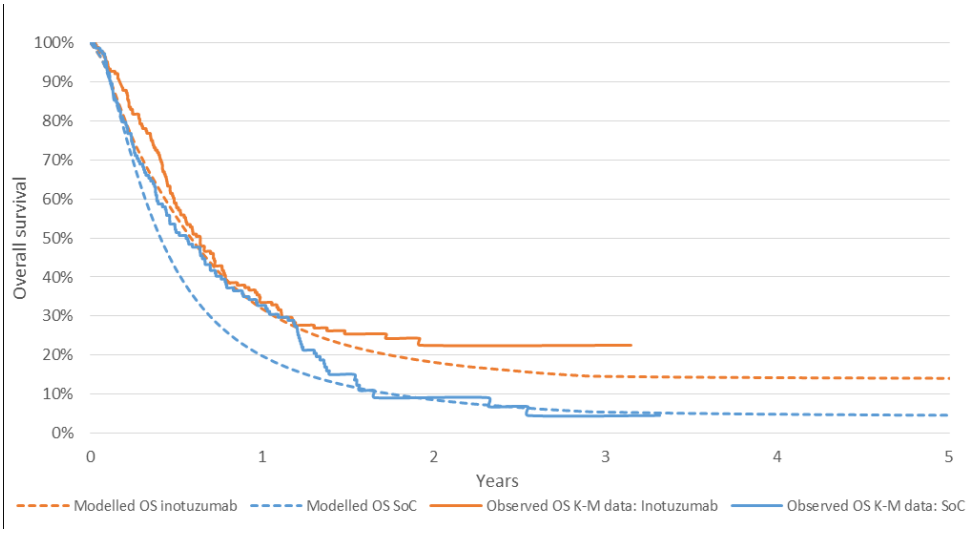
Risk of mortality x general population (GP) for SoC	**4.00**
Absolute risk above general population (GP) for SoC	3.00
MRD-negative in SoC	36%
MRD-positive in SoC	64%
HR for MRD-negative vs MRD-positive	**0.28**
Absolute risk of mortality above GP for MRD-	1.14
Absolute risk of mortality above GP for MRD+	4.07
Risk of mortality x GP for MRD- patients	**2.14**
Risk of mortality x GP for MRD+ patients	**5.07**

Appendix C: **New analyses/evidence:** Survival between HSCT and the cure point - a visual inspection

Below is displayed the model output for overall survival (dashed lines) versus overall survival Kaplan-Meier data from the INO-VATE 1022 trial. It should be recalled that because of the use of the cure point after 3 years whereby the survival curves plateau, the majority of QALYs in both arms are driven by the tails of the curves, rather than the start of the curves. As such, fitting the tails of the curves accurately is more important in terms of the eventual ICER than fitting the start of the curves.

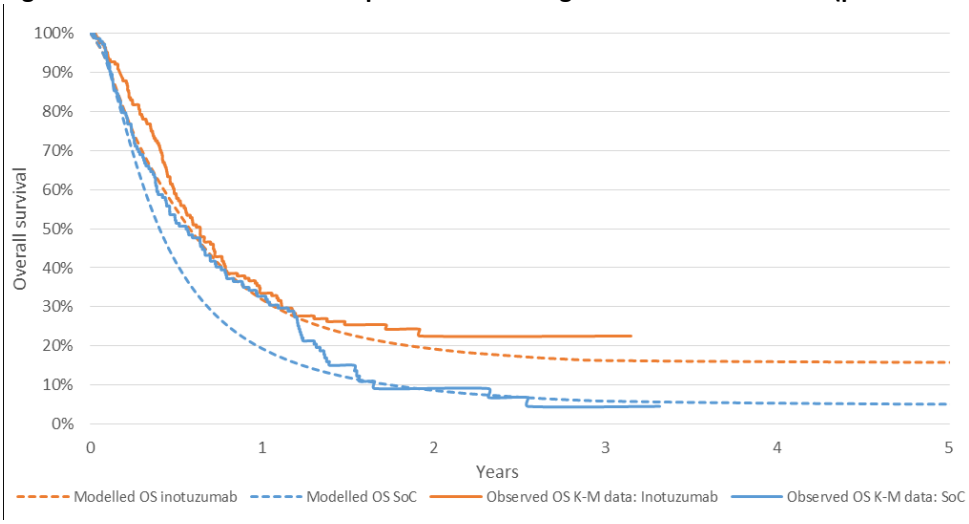
The only assumption difference between the two models is that of survival between HSCT and the cure-point. Figure 1 is the ERG's base case whereby survival between HSCT and the cure point assumes the same underlying survival probabilities for each arm, but is then differentiated within the model by a covariate for MRD-negativity along with other selected covariates kept within the model. Figure 2 is an alternative approach, based upon the assumption that *only* MRD-status drives differences in survival post-HSCT; figure 2 includes *only* MRD as a covariate in the model.[1]

Figure 1. Modelled survival vs Kaplan-Meier – using ERG base (pooled survival split by MRD)



[1] It should be noted that if it assumed that more than just MRD is impacting survival post-HSCT, then we believe that continuing to use the treatment-specific patient level data during this period is the most robust approach (*i.e.* Pfizer's revised base case).

Figure 2. Modelled survival vs Kaplan-Meier – using Pfizer revised scenario (pooled survival MRD)



As can be seen, the modelled data is similar for the standard of care arm in both scenarios, however the revised analysis (Figure 2) has a better fit to the tail of the inotuzumab curve (although still is conservative with respect to the inotuzumab observed Kaplan-Meier). In the ERG base case (Figure 1), the modelled inotuzumab arm underestimates the survival benefit more, when compared to the Kaplan-Meier. As such, Figure 2 (scenario 1ii in Table 7) is a better fit to the data than Figure 1 (the ERG basecase), although both appear conservative with respect to the observed inotuzumab data.

New analyses/evidence: Longer term survival post-cure point

Applying this estimate from Martin et al. to patients in this appraisal presents a number of issues. First, this study estimates mortality risk from a cohort in the United States who underwent transplants between 1980 and 2002. During this consultation on the ACD, we have sought further advice from several leading UK clinical experts on the degree to which HSCT practice and subsequent patient care differs from US practice in the 1980s and 1990s and UK practice in 2017. UK clinical expert feedback has indicated that the survival prospects and care pathway for patients transplanted is dramatically improved in comparison, and applying a risk of mortality from such a historical cohort can be misrepresentative of the outcomes expected for patients treated today. Indeed, an study analysing almost 1,500 transplanted US patients with ALL showed that during the period of 1987 to 2002, the survival probability for ALL patients 2-years post-transplant was between 23% and 28%, however in the period 2003 to 2006 the survival probability had almost doubled, to 41%.[5] Applying this improvement in outcomes to the 4-fold mortality risk figure cited in the ACD indicates this risk had fallen to between 2.2 and 2.7-fold (midpoint 2.5) higher than that of the general population by the end of 2006. This is still a conservative estimate of standard of care patients in today's practice, as transplanted patients in 2017 would pass the cure point in 2020, which is 14 years on from 2006.

In the appraisal of blinatumomab, NICE accepted a risk of mortality past the cure point that was the general population mortality risk *added* to the risk derived from the extrapolated parametric curve for OS (a Gompertz curve fit to OS Kaplan-Meier). The factor by which this additive extrapolation elevated the risk of mortality beyond that of the general population is redacted; however applying this in our model sees the ICER fall below that in the original company's base case[2]. Pfizer has taken a more conservative approach in its revised base case than was accepted for blinatumomab, applying the estimate of a 2.5-fold risk of mortality above the general population as more relevant for today's standard of care patients than the historic 4-fold risk (noting this is still not reflective of 2017).

The mortality risk (either the 4-fold from the historical cohort, or the 2.5-fold, a conservative reflects "today's" practice) is drawn from patients on standard of care therapy. This risk is not reflective of new anti-leukemic treatments, such as inotuzumab, and as such ignores potential benefits such as high rates of MRD-negativity, which the committee preferred to be incorporated into survival risk post-HSCT. The previously cited meta-analysis of 13,000 ALL patients (albeit not R/R ALL) identified an event-free survival HR of 0.28 (0.24, 0.33) for adults who are MRD-negative versus MRD-positive.[3] Applying this data to the 2.5-fold risk of morality for standard of care patients leads to an assumed increased risk of mortality for MRD-positive patients of 3.0x and for MRD-negative patients of 1.6x above the general population (calculations detailed in Appendix B). These estimates for mortality risk past the cure point are used in the revised basecase and equate to a 2.5-fold increase risk for standard of care patients and a 1.9 fold increase risk for inotuzumab patients.

[2] When applying the additive mortality approach, all patients in the standard of care die by 5 years. Comparatively, this is more favourable towards inotuzumab than when assuming the arms simply return to the mortality risk of the general population as per the Pfizer base case, hence why the ICER is lower in this scenario than the original base case.

New analyses/evidence: Administration costs

Since publication of the ACD, the company have sought guidance from several leading UK clinical experts on estimates for administration. Although an advantage of inotuzumab over current FLAG-base chemotherapy is that it can be administered in an outpatients setting, Pfizer's revised base case now includes inpatient stay for the first administration of the first cycle, following guidance from the clinical experts. However, it should be noted that the reason for this inpatient stay is likely to be more disease related (*i.e.* patients being unwell) rather than an administration requirement. The inclusion of this cost is therefore conservative.

Pfizer noted that the clinical expert at the committee meeting stated that "several weeks" of inpatient stay is common for FLAG-based chemotherapy. Further, it is noted the ERG's Report which states that the company base case likely significantly underestimated costs in the standard of care arm (indeed, the ERG cited two studies reporting mean length of hospitalisation for PH-negative R/R ALL patients between 16.8 days and 26 days.[6,7] The clinical expert's estimate of 3 weeks was tested with the consulted experts recently consulted, who agreed it was reasonable to assume FLAG-based chemotherapy would frequently require around 3 weeks of inpatient admission. However, in the revised base case Pfizer uses a more conservative estimate of 2 weeks of inpatient stay as administration, noting that adverse events are costed separately so the use of an estimate of 3 weeks cost may risk double counting.

In summary, Pfizer's revised base case ICER with the first administration of the first cycle for inotuzumab costed as an inpatient's stay, and FLAG-based chemotherapy costed as a 2-week inpatient stay.

New analyses/evidence: Patient Access Scheme

The company have submitted to the Department of Health for approval of a Patient Access Scheme (PAS), a simple discount which would reduce the price paid by the NHS in England, Wales and Northern Ireland to [redacted] less than the list price.

CONFIDENTIAL UNTIL PUBLISHED

Evidence Review Group's response to ACD comments Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD
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Date completed	10/07/2017

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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1 Summary

The ERG received the response to the ACD consultation on 5th July 2017. The company response included a 15 page document and an updated model. The company response to the ACD provides new data on the rate of subsequent therapies in the safety population of INO-VATE. It also includes a new revised base case that rejects some of the committee's preferred assumptions, introduces an additional treatment effect on survival post "cure point" mediated through MRD negativity, includes increased utility values for patients who remain progression free after the "cure point" and altered administration costs. Finally it also includes new scenario analyses for modelling survival post-HSCT and for the number of cycles of inotuzumab that would be administered.

This report consists of:

1. A critique of the company response to ACD
2. Verification of the numbers provided in the company response
3. The results of additional ERG analyses requested by NICE

Table 1 summarises the ERG response to the company's revised base case, and signposts to the relevant sections of this report. The ERG welcomes the new information presented by the company on the rates of subsequent therapies in the safety population. The ERG does not accept any of the other changes made by the company.

Table 1: Summary of ERG critique of company revised base case.

Item	Revised Pfizer base case assumption	ERG critique	Signpost
(1) Survival between HSCT and the cure point	• (i) Use parametric curves fit to Kaplan-Meier data for survival post-HSCT	No new information has been presented. This analysis was not accepted in the first committee meeting. The post-HSCT survival data are based on a small, post-randomisation sub population and so methods such as this that attribute all survival gains to treatment received are inappropriate. The original ERG report detailed the lack of face validity of these parametric models (ERG report p82-84).	Section 2.2
	• (ii) Scenario: Assume same survival post-HSCT but allow *only* a covariate for MRD-negativity to drive any differences	Any analysis based on the 'HSCT and post HSCT' sub population is highly uncertain, but one that adjusts for a greater number of observed confounders could be regarded as preferable to one that adjusts only for rates of MRD	Section 2.2

		negativity. This new scenario analysis can be regarded as inferior to the original company analysis that adjusted for MRD negativity and other covariates.	
(2) Longer term survival post-cure point	• Mortality risk 3.0x general population for MRD+ and 1.6x for MRD- patients ➢ *equates to mortality risk of 2.5x general pop for SoC, and 1.9x for inotuzumab*	The choice of new references and the new analyses are fundamentally flawed. The introduction of a new treatment effect is not supported by the evidence.	Section 2.3
(3) Cost of subsequent therapy	• Include both cost and efficacy of subsequent therapies as applicable to safety population	The new information on the rates of subsequent therapy in the safety population is welcomed. It is now appropriate to include the costs of subsequent therapy as observed in the trial. However, the use of list prices will substantially overestimate the costs of these subsequent therapies to the NHS	Section 2.4
(4) Administration costs	• First administration of inotuzumab in first cycle costed as inpatients setting • FLAG costed for 14 days inpatient stay	No new information has been presented. The company now assumes a stay of 1 day for an inpatient stay associated with inotuzumab and 14 days for FLAG. No explanation or justification is provided for the differential length of stay.	Section 2.5
(5) Utilities for patients post-cure point	• Apply normal population utilities for disease-free patients, as was accepted for blinatumomab	The original utility values based on a relevant published study are preferable to this new assumption which lacks supporting evidence.	Section 2.1

2 Critique of company response to ACD

The company structured their response around three areas:

- A comparison against the NICE final guidance for blinatumomab
- Four 'key assumptions' underpinning the Committee's preferred ICER
    i. Survival between HSCT and the cure point
    ii. Longer-term survival post cure point
    iii. Cost of subsequent therapy
    iv. Administration costs
- An additional scenario regarding the number of cycles of inotuzumab

Sections 2.1 to 2.6 provide the ERG critique of each element of the company response.

2.1 Comparison with blinatumomab

The ERG does not believe that the comparison against the NICE final guidance for blinatumomab is helpful as it fails to adequately explore the reasons why the two appraisals might differ. Blinatumomab was not listed as a comparator in the scope for the inotuzumab appraisal. The company chose not to make a comparison against blinatumomab in their original submission given that it was in the process of being appraised by NICE. During the course of the appraisal of inotuzumab, NICE issued the final guidance for blinatumomab (1).

The company argue that blinatumomab and inotuzumab are similar, and therefore assumptions accepted by NICE in their preferred ICER for blinatumomab might apply to the appraisal of inotuzumab. The ERG does not agree with this premise. Blinatumomab and inotuzumab do overlap in terms of the target patient population, although blinatumomab is licenced only for Philadelphia chromosome negative (Ph-) patients with B-cell acute lymphoblastic leukaemia (ALL), while inotuzumab is licensed for both Ph- and Philadelphia chromosome positive (Ph+). However, they are different products, with a different mechanism of action, different method of administration, different prices and a different underlying evidence base, all of which may reasonably lead to differences between the appraisals. Appendix A provides a table highlighting differences between the two products and the supporting trial data used in the respective NICE appraisals.

The company response to the ACD focuses on three aspects of the preferred ICER for blinatumomab:

1. Survival between transplantation and the cure point
2. Longer term survival post-cure point
3. Health-related quality of life post cure point

The first two aspects relate to two of the four 'key assumptions' identified in the company response to ACD, and as such are considered in more detail in Sections 2.2 and 2.3. Here we provide a brief overview and response to the comments raised by the company with respect to the recommendation for blinatumomab.

The company response notes that, with respect to survival between HSCT and the "cure point",

"In the preferred ICER for blinatumomab, the NICE committee accepted treatments dependent parametric curves fit to the Kaplan-Meier data for patients pre-HSCT, post-HSCT and up until a cure point of 4 years post-HSCT. This is a clinically valid approach as it makes the best use of the available trial data." Response to ACD p3

The ERG note that in the blinatumomab appraisal these treatment dependent parametric curves were fit to each arm of the randomised trial, constituting a randomised comparison between arms. In contrast, the parametric survival curves for the inotuzumab appraisal were fit to three separate sub populations of the INO-VATE 1022 trial. Furthermore, the resulting parametric curves did not provide an appropriate basis for extrapolation and significantly underestimated survival with standard of care (ERG report p82-84). Crucially, the 'HSCT & post-HSCT' sub population is a small, post-randomisation subset in which the baseline was reset to time of HSCT rather than entry to trial. As noted in the original ERG report, separate parametric curves fit to the 'HSCT & post-HSCT' subgroup do not constitute a randomised comparison and results should be interpreted with extreme caution. This issue is covered in more detail in Section 2.2.

The company response notes that, on longer-term survival "post-cure point",

"In the preferred ICER for blinatumomab, the NICE committee accepted that once patients pass the a certain post-HSCT (in this appraisal named the "cure point"), the hazard rate for death is assumed to be that of the normal population, with a factor added to compensate for disease-related mortality that was derived from the gradient of the extrapolated parametric curve. This is a clinically valid approach as it makes use of the available trial data without relying on historical literature from patients using different treatment regimens to assume the impact to survival." Response to ACD p3

The ERG notes that in the appraisal for blinatumomab it was assumed that the hazard rate for death would be higher than the general population once patients pass the "cure point", which is consistent with the assumption made in the inotuzumab appraisal. The ERG also note that the supporting data from the TOWER trial data do not extend beyond 2 years, and as such the mortality post-cure point is not based on observed patient data, but an assumption regarding the extrapolation of trial data. The issue of the magnitude by which mortality may exceed that of the general population post "cure point" is addressed further in Section 2.3.

The company response notes that, that for health-related quality of life post "cure point",

"In the preferred ICER for blinatumomab, the NICE committee accepted that patients who pass the cure point post-HSCT can expect a return to the health-related quality of life (utility) of the normal population." Response to ACD p3

The ERG cannot find reference to committee discussion of this issue in the FAD for blinatumomab. The ERG for the blinatumomab appraisal (Warwick Evidence) did accept this assumption in their critique of Amgen's submission for blinatumomab, and so the company response may have misattributed this to the committee discussions.

The company response to ACD does not contain any new information on health related quality of life. In the updated model supplied with the company's response to ACD they have revised the utility values assigned to patients post-cure upward to that of the general population. In both the ERG and original company base case those utility values had been derived from a review of the literature that had identified a suitable study that looked at the quality of life of patients following receipt of HSCT. (2). The impact of the change in the company's revised base case is to increase the starting value to 0.88 for patients who remain progression free post HSCT from the previous starting value of 0.74 for 3-5 years post-HSCT and 0.76 for 5 years post-HSCT, thus introducing a 0.14 and 0.12 increment in utilities for 3-5 years and beyond 5 year post-HSCT respectfully. The ERG is of the opinion that utility values based on a relevant published study are preferable to an assumption without supporting evidence, and so do not accept this revision.

2.2 The assumption applied to survival between HSCT and the "cure point"

The company response to the ACD has not provided any new evidence compared to that provided in the original submission, but does present a new scenario analysis for modelling survival post-HSCT. The ERG believes that the arguments presented by the company in their response to the ACD are flawed as they fail to recognise the non-randomised nature of the data.

As noted in the original ERG report, the key concern is that the 'HSCT and post HSCT' sub population is a small, post-randomisation subset of the trial population. This means that the fitting of treatment-specific parametric curves does not constitute a randomised comparison, and will be subject to confounding by both observed and unobserved covariates. The original ERG report also noted that the separate parametric curves fit to the 'HSCT and post HSCT' sub population lacked face validity and were not a suitable basis for extrapolation (ERG report p82-84).

The role of MRD negativity as a driver of outcomes post-HSCT was suggested by the company in their original appraisal. In the ERG report it was noted that this may be more clinically justifiable, and produce more externally valid results, compared to extrapolating treatment-specific parametric curves that attribute all differences in survival post HSCT to a treatment benefit from inotuzumab (ERG report p87-88). However, the ERG noted that estimating the impact of MRD negativity on survival using the small 'HSCT and post HSCT' sub population was highly uncertain and should be interpreted with caution. The company response to ACD considers whether MRD negativity may be the only driver of treatment-specific survival post-HSCT. The current evidence does not provide robust support for any difference in survival post-HSCT between inotuzumab and standard of care. The role of MRD negativity as a prognostic factor is also unproven for patients receiving second salvage treatment and beyond (3) (33% of patients in INOVATE 1022 were on second salvage-

treatment phase) and following receipt of non-chemotherapy induction regimens (4) (also noted in clinical expert statement submitted by Professor Adele Fielding).

The company ACD response states that,

"Pfizer's basecase uses the treatment-specific Kaplan-Meier data which inherently captures all covariates correctly without having to make assumptions and we believe is a more robust approach" Response to ACD p4.

This is incorrect and fails to recognise the observational nature of the comparison being made. This interpretation can only be applied to a randomised comparison, which any analysis of the 'HSCT and post HSCT' sub population is not.

The company present a new scenario analysis in which parametric curves are fit to the pooled Kaplan-Meier overall survival data from the 'HSCT and post HSCT' sub population, and where MRD negativity is the only covariate. Any analysis based on the 'HSCT and post HSCT' sub population is highly uncertain, but one that adjusts for a greater number of observed confounders could be regarded as preferable to one that adjusts only for rates of MRD negativity post induction therapy. As such, the ERG regards the new scenario analysis presented by the company as inferior to the original company analysis that adjusted for MRD negativity and other covariates. As the company do not use this scenario analysis in their revised base case, it is not considered further in this report.

2.3 The increased risk of mortality applied to patients who pass the "cure point"

The company response expresses concern about the magnitude by which mortality in survivors of HSCT post "cure point" might exceed that of the general population. The ERG considers that the choice of new references and the new analyses presented by the company are fundamentally flawed. The company revised base case incorporates an additional treatment effect on survival by differentiating the risk of mortality post "cure point" according to rates of MRD negativity. The ERG considers that the introduction of this new treatment effect is inappropriate and not supported by any evidence.

Using the company base case "cure point", the key parameter of interest is the magnitude of the increased risk of mortality in 3 year survivors of HSCT and beyond, compared to the general population. The ERG base case included an estimate for this increased mortality rate based on patients who had survived for five years or more following HSCT from Martin et al.(5) In recognition that survival post HSCT may have improved over time, the ERG selected the lower bound from the quoted range of four- to nine-fold higher than in the general population.

In their response to ACD comments the company present some information on cumulative survival at 2 years post HSCT, and compare how this differs for patients receiving HSCT in the period 1987-2002 compared to those receiving HSCT in the period 2003-2006 based on a study by Karanes et al. (6). These cumulative survival probabilities are not informative because they do not indicate anything about the hazard of death compared to the general population. Furthermore, survival at 2 years post HSCT in the company model is still governed by parametric curves fit to the INO-VATE 1022 trial data, as those patients have yet to reach the "cure point" at three years. The method by which the company has used estimates of two year cumulative survival to make adjustments to the estimated increased risk of mortality in patients who pass the "cure point" lacks a coherent logic and is mathematically incorrect. A comparison of the hazard for mortality at 24 months (or the rate of change of the survival curve or interval survival probability) would have been preferable, but this is not available in the reference used by the company.

The company also seek to introduce a further treatment effect from inotuzumab post HSCT in the form of reduced mortality post "cure point", driven by rates of MRD negativity. Given that the existence of any treatment-specific differences in survival post HSCT is highly uncertain, the ERG believes it is inappropriate to further exaggerate the differences with an additional post "cure point" difference in survival. The reference the company use to support their approach looks at the role of MRD negativity in predicting survival post induction therapy.(4) The information required is the role of MRD negativity in predicting survival in long term survivors of HSCT, for which the ERG is not aware of any evidence. The incorrect application of the hazard estimated for the role of MRD negativity post induction therapy in Berry et al. double counts survival benefits from the point of induction therapy already captured in the economic analysis, and extrapolates additional benefits that are not supported by existing evidence.

2.4 The exclusion of costs of subsequent therapy

The company have provided new information on the rates of subsequent therapy in the safety population. The ERG welcomes this data, and agrees that it is now appropriate to include the costs of subsequent therapy as observed in the trial. However, the ERG notes that the use of list prices will substantially overestimate the costs of these subsequent therapies to the NHS. It may also be appropriate to exclude the costs of second line inotuzumab from this comparison, as this implies a sequencing decision about whether to have inotuzumab first, or standard of care followed by inotuzumab, which is not current NHS practice and is out of the scope of this appraisal.

2.5 The administration costs

The company response to the ACD does not contain any new information regarding administration costs. The company have misunderstood and misrepresented the ERG analysis, which applies a

duration of stay of 9.47 days for both inotuzumab and standard of care based on NHS Reference Costs, and not a duration of 26 days for inotuzumab (Response to ACD Table 6, p9). The company revised base case recognises that length of stay in hospital for patients during admission of therapy is not simply due to the practicality of administering any treatment, and assumes a duration of 1 day for an inpatient stay associated with inotuzumab, and a duration of 14 days for an inpatient stay associated with standard of care. The company response to ACD does not note this differential duration of stay, nor provide any justification for it. The ERG also note that the company revised base case applies the unit cost per bed day from the company's original base case, and not the ERG base case.

2.6 Company response 'Key scenario': 3 cycles of inotuzumab

The company claim that all patients who "achieved CR/CRi and MRD negativity" did so within the first three cycles (Response to ACD p11). The information required is whether all patients who achieved CR/CRi and/or received HSCT had *no more than* 3 cycles of inotuzumab. This information is not available. The ERG note that 128 patients (78%) of patients who received inotuzumab achieved CR/CRi and/or received HSCT (120 patients achieved CR/CRi and 8 patients received HSCT without achieving CR/CRi). The median number of treatment cycles in the INO-VATE 1022 trial was 3.0, indicating that 23% of patients achieving CR/CRi and 28% of patients achieving CR/CRi or receiving HSCT had three cycles or more of inotuzumab. The ERG also note that the median time from randomisation to achieving CR/CRi for patients receiving inotuzumab was reported to be [redacted], and that the time required to receive three cycles of inotuzumab is 2.5 months. [redacted]. The ERG therefore concludes that costing only three cycles of inotuzumab cannot be regarded as consistent with the efficacy in the model.

3 Verification of numbers provided in company response

The full set of verified numbers is provided in Appendix B. The company have incorporated the new information on the rates of subsequent therapies from the safety population in all calculations. This means that the starting point for the differences shown from the committee preferred parametric base case is an incremental cost effectiveness ratio (ICER) of £113,378 rather than £114,078. Based on incorporating the rates of subsequent therapies from the safety population in all calculations, the ERG was able to verify the numbers provided in the company response.

4 Results of additional ERG analyses requested by NICE

The ERG ran a number of additional scenarios requested by NICE. These were to:

- Run the ERG parametric base case and the company revised base case with the PAS and increasing the "cure point" post HSCT from three years to four years.
- Run the ERG base case assuming normal population utility values (0.88) in those surviving past the cure point instead of utilising values from Kurosawa (0.74 and 0.76)
- Run the ERG base case assuming 26 days of inpatient stay for patients admitted while receiving standard of care (and retaining 9.5 days of inpatient stay as per NHS Reference costs for patients admitted while receiving inotuzumab.

The results are shown in Table 2.

Table 2: Results of the additional analyses requested by NICE

Requested Scenarios	Description	ICER ERG base case with PAS	Change from ERG base case with PAS	ICER Pfizer revised base-case with PAS
Base case with PAS	Base case with PAS and rate of subsequent therapy based on safety population.	[redacted]	-	£42,523
(1) 4 year cure point	Patients 4 years post-HSCT are assumed "cured"	[redacted]	[redacted]	[redacted]
(2) Utilities from general population	Apply normal general population utility values patient who remain progression free after HSCT past the "cure point".	[redacted]	[redacted]	
(3) Increased SoC inpatient stay	26 inpatient days in hospital for SoC and 9.5 for inotuzumab.	[redacted]	[redacted]	
(4) Subsequent therapies costed with list prices	Includes the cost (using list prices) of subsequent therapies applicable to the safety population.	[redacted]	[redacted]	
(1) + (2)	"Cure point" at 4 years and utilities from the general population for progression free post "cure point"	[redacted]	[redacted]	
(3) + (4)	Increased SoC inpatient stay and subsequent therapies costed at list price	[redacted]	[redacted]	

5 Appendix A

Table 3 provides a highlight of some of the differences between blinatumomab and inotuzumab and their associated trial data.

Table 3. Comparison between blinatumomab (TOWER) and inotuzumab (INO-VATE 1022)

	Blinatumomab (TOWER trial)	Inotuzumab (INO-VATE 1022 trial)
Marketing authorisation	Adults with Ph- R/R B-cell ALL	Adults R/R B-cell ALL, regardless of Ph chromosome subtype
Mechanism of action	Blinatumomab is a T-cell engager antibody targeting CD19 and the CD3/T cell receptor. When blinatumomab binds to both the cancer cell and T-cell, the T-cell is recruited and activated to destroy the cancer cell.	Inotuzumab is an antibody-drug conjugate that consists of a derivative of calicheamicin attached to an engineered humanised monoclonal immunoglobulin G4 antibody, which targets CD22.
Administration	Continuous intravenous infusion for up to 96 hours at a dosage of 9 µg/day (starting dose; days 1–7) or 28 µg/day (subsequent doses). Each cycle of treatment is 28 days of continuous infusion. Patients may receive 2 cycles of treatment, separated by a 14 day treatment-free interval. Patients who achieve complete remission may receive up to 3 additional cycles of consolidation treatment. Hospitalisation is recommended for initiation at a minimum for the first 9 days of the first cycle and the first 2 days of subsequent cycles.	Intravenous infusion over 1-hour at a starting dose of 1.8mg/m^2. Cycle 1 lasts for 21 days but may be extended to 28 days. Each subsequent cycle lasts for 28 days.
Trial population	Adults with Ph- R/R B-cell ALL - Untreated first relapse with first remission duration <12 months - Untreated second or greater relapse - Relapse after allo-SCT	Adults with Ph- or Ph+ R/R CD22 positive B-cell ALL due to receive either salvage 1 or salvage 2 therapy
Baseline characteristics	Mean age: 41 (median 37) Prior allo-SCT: 34.5% Refractory to primary or salvage therapy (salvage status 1): 42% Salvage status 2: 34% Salvage status >2: 24% In first relapse with first remission duration <12 months: 28% In untreated 2nd or greater relapse: 12% Relapse after allo-SCT: 18%	Mean age: 46 (median 47) Prior HSCT: 17% Salvage phase 1: 66% Salvage phase 2: 33% Duration of first remission <12 months: 63% Duration of first remission ≥12 months: 37%
Trial comparator	FLAG +/- IDA based regimen High dose methotrexate based regimen Clofarabine based regimen	FLAG Cytarabine plus mitoxantrone HiDAC

	HiDAC based regimen	
Trial results	OS: 7.7m (95% CI 5.6-9.6) vs 4.0m (95% CI 2.9-5.3) CR: 33.6% (95% CI 28.0-39.5) vs 15.7% (95% CI 10.0-23.0) CR/CRh/CRi: 43.9% (95% CI 37.9-50.0) vs 24.6% (95% CI 17.6-32.8) DoR: 7.3m vs 4.6m MRD remission among responders: 76.3% vs 48.5% Allo-SCT: 24.0% vs 23.9%	OS: 7.7m (95% CI 6.0-9.2) vs 6.7m (95% CI 4.9-8.3) RMST analysis: 13.9m vs 9.9m CR: [redacted] CR/CRi: 73.2% (95% CI 65.7-79.8) vs 30.9% (95% CI 23.9-38.6) Median DoR: [redacted] MRD negativity among responders: [redacted] HSCT: [redacted]
AEs	Any grade 3 AE: 37% vs 30% Any grade 4 AE: 31% vs 44% Any grade 5/fatal AE: 19% vs 17% Grade ≥3 AE of interest that was higher in blin group than SOC: cytokine release syndrome (13 pts (5%) vs 0)	Grade 3-4 AE: [redacted] Grade 5/fatal AE: [redacted] AE of interest that was higher in ino group than SOC: VOD [redacted]

6 Appendix B

The ERG note that the numbers in Tables 7, 8 and 9 of the company response to ACD all contain the new information on the rate of subsequent therapies as determined for the safety population. The use of the rate of subsequent therapies from the safety population makes only a small difference to the ICER, and the ERG is happy to accept this change. For completeness Table 4, Table 5 and Table 6 provide the ICERs without this additional change.

Table 4: ERG verified numbers provided in company response to ACD Table 7.

Item	Revised Pfizer base case assumption	ICER with single change	ICER change from ERG base case with PAS	ICER with subsequent therapies as per ITT population
Committee preferred ERG parametric base case with a [redacted] PAS		£113,378 *list price* [redacted] *with PAS*	*£0*	£114,078 *list price* [redacted] *with PAS*
(1) Survival between HSCT and the cure point	(i) Use parametric curves fit to Kaplan-Meier data for survival post-HSCT	[redacted]	[redacted]	[redacted]
	(ii) Scenario: Assume same survival post-HSCT but allow *only* a covariate for MRD-negativity to drive any differences	[redacted]	[redacted]	[redacted]
(2) Longer term survival post-cure point	• Mortality risk 3.0x general population for MRD+ and 1.6x for MRD- patients ➢ *equates to mortality risk of 2.5x general pop for SoC, and 1.9x for inotuzumab*	[redacted]	[redacted]	[redacted]
(3) Cost of subsequent therapy	Include both cost and efficacy of subsequent therapies as applicable to safety population	[redacted]	[redacted]	[redacted]
(4) Administration costs	• First administration of inotuzumab in first cycle costed as inpatients setting • FLAG costed for 14 days inpatient stay	[redacted]	[redacted]	[redacted]
(5) Utilities for patients post-cure point	Apply normal population utilities for disease-free patients, as was accepted for blinatumomab	[redacted]	[redacted]	[redacted]
Pfizer revised base case	**1(i) + 2 + 3 + 4 + 5**	**£37,734**	[redacted]	[redacted]

Post-HSCT survival scenario analysis	**1(ii) + 2 + 3 + 4 + 5**	**£42,523**	[redacted]	[redacted]

Table 5: ERG verified numbers provided in company response to ACD Table 8

Item	Revised Pfizer base case assumption	ICER with change (with PAS)	Subsequent therapies ITT population
(6) Max 3 cycles of inotuzumab as per SPC	Cost inotuzumab for only 3 cycles, in line with SPC	[redacted] with sole change from ERG base	[redacted]
Pfizer revised base case with 3 cycle scenario analysis – survival (i)	**1(i) + 2 + 3 + 4 + 5 + 6**	[redacted]	[redacted]
Pfizer revised base case with 3 cycle scenario analysis – survival (ii)	1(ii) + 2 + 3 + 4 + 5 + 6	[redacted]	[redacted]

Table 6: ERG verified of numbers provided in company response to ACD Table 9

Item	Pfizer revised base case assumptions	ICER with changes	Subsequent therapies IIT population**
Pfizer revised base case for assumptions (2+3+4+5) but ERG assumptions for: • post HSCT survival (1): pooled with MRD-covariate along with other covariates kept in the model, as per ERG base case • post-cure (2) risk applied to morality, based on MRD	2 + 3 + 4 + 5	£52,672	[redacted]
	2 + 3 + 4 + 5 + 6 *(3 cycles)*	[redacted]	[redacted]
Pfizer revised base case for assumptions (3+4+5) but ERG assumptions for: • post HSCT survival (1): pooled with MRD-covariate along with other covariates kept in the model, as per ERG base case • post-cure point survival (2) where a 2.5x increased risk vs general population is applied (as per section 4) as opposed to 4x, as per ERG base case	3 + 4 + 5	£55,535	[redacted]
	3 + 4 + 5 + 6 *(3 cycles)*	[redacted]	[redacted]

Pfizer revised base case for assumptions (1+3+4+5) but ERG assumptions for: • post-cure point survival (2) where a 2.5x increased risk vs general population is applied to both MRD+ and MRD- patients alike (as per section 4) as opposed to 4x from the ERG base case	1(i) + 3 + 4 + 5	[redacted]	[redacted]
	1(i) + 3 + 4 + 5 + 6 *(3 cycles)*	[redacted]	[redacted]
Pfizer revised base case without blinatumomab utilities applied to patients disease-free post cure point	1(i) + 2 + 3 + 4	[redacted]	[redacted]
	1(ii) + 2 + 3 + 4	[redacted]	[redacted]

7 References

1. National Institute for Health and Care Excellence (NICE). Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia [TA450]. London: NICE; 2017.

2. Kurosawa S, Yamaguchi H, Yamaguchi T, Fukunaga K, Yui S, Wakita S, et al. Decision analysis of postremission therapy in cytogenetically intermediate-risk acute myeloid leukemia: the impact of FLT3 internal tandem duplication, nucleophosmin, and CCAAT/enhancer binding protein alpha. Biol Blood Marrow Transplant. 2016;22(6):1125-32.

3. Jabbour E, Short NJ, Jorgensen JL, Yilmaz M, Ravandi F, Wang SA, et al. Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory b-cell acute lymphoblastic leukemia. Cancer. 2017;123(2):294-302.

4. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. JAMA Oncol. 2017:e170580.

5. Martin PJ, Counts GW, Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, et al. Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol. 2010;28(6):1011-6.

6. Karanes C, Nelson GO, Chitphakdithai P, Agura E, Ballen KK, Bolan CD, et al. Twenty years of unrelated donor hematopoietic cell transplantation for adult recipients facilitated by the National Marrow Donor Program. Biol Blood Marrow Transplant. 2008;14(9 Suppl):8-15.