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)
   - Leukaemia CARE
   - National Cancer Research Institute – Association of Cancer Physicians – Royal College of Physicians – Royal College of Pathologists and British Society of Haematologists – joint response

   Department of Health and Social Care submitted a "no comment" response

3. **Comments on the Appraisal Consultation Document from experts:**
   - Professor Adele Fielding – clinical expert, nominated by The Royal College of Pathologists – endorsed by NCRI-ACP-RCP
   - Professor David Marks – clinical expert, nominated by Pfizer

   There were no comments received through the NICE website

4. **Unpublished data from the inotuzumab compassionate use program submitted by the clinical experts**

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 second 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	We are concerned that the cost effectiveness calculations in this technology appraisal are based on 2 incorrect assumptions that negatively impact on the ICER; a) the number of in patient days required for administration of Inotuzumab compared to standard of care and b) the number of cycles to be used. These are not reasonable assumptions and do not provide sound guidance for the NHS. **<u>In-patient bed days</u>** In section 3.13 of the ACD, the rationale for the assumption that 9.5 in patient days would be required for both inotuzumab and FLAG is made. Although challenged as described in section 3.22, the ICER still incorporates this incorrect assumption which is not reflective of clinical practice. The number of days an individual patient is hospitalised is dependent on the need for a) management of disease related complications, b) the administration of the therapy to be given and c) management of complications of the therapy. a) The time taken to control disease related complications is dependent on the speed of disease control. As described in section 3.4 of the ACD, inotuzumab is more likely to achieve a complete haematological response than standard of care 80.7% vs 29.4%, p<0.0001). Whilst it is impossible to define the exact number of bed days required solely for management of complications of disease, it will clearly be shorter for inotuzumab compared to standard of care given this considerable difference in remission rates. b) FLAG is an intensive chemotherapy given over 5 days and necessitates hospital admission due to duration/timings of the infusions, management of immediate side effects eg nausea and vomiting and the need for supportive care eg prevention, monitoring and treatment of tumour lysis syndrome. Inotuzumab is given as an infusion on days 1, 8 and 15 in a 4 week cycle and can be administered as an out-patient. c) FLAG is associated with profound suppression of bone marrow function resulting in	Comment noted. Following the submission of observational data on the average number of inpatient days with inotuzumab ozogamicin and FLAG-IDA the committee concluded that there is a substantial difference in the average length of stay between the two treatments. Please see section 3.29 of FAD2.

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			prolonged neutropenia with a risk of sepsis, which may be life-threatening. Patients also require regular red cell and platelet transfusions. The majority of patients need to stay in hospital until count recovery, which generally takes 4-6 weeks. As described in section 3.5 of the ACD, inotuzumab has a favourable toxicity profile which rarely necessitates hospital readmission. Indeed, the risk of neutropenic fever is halved in patients receiving inotuzumab compared to those receiving standard of care (26.8% vs 53.8%). Professor Fielding has provided the committee with real-life data from Bristol and UCLH showing the combined effect of the 3 factors described above on duration of in-patient stay. [redacted] It should be noted that these data are from a time when clinicians were unfamiliar with inotuzumab, were cautious and more likely to keep patients in hospital longer than necessary; any future comparison of in-patient days required between inotuzumab and FLAG Ida is therefore likely to be even more favourable. Thus it is not reasonable for the cost effectiveness model to be based on an assumption that the in-patient stay for inotuzumab vs standard of care is the same ie 9.5 days, as in reality, the number of bed days required for patients receiving inotuzumab is less than 25% of that needed for FLAG-Ida.	
2	Patient and professional	NCRI-ACP-RCP	**<u>Number of cycles of Inotuzumab</u>** In section 3.30, the ACD summarises the view of the clinical community that given the NHS has limited resource, there is a rationale to restrict the use of Inotuzumab to patients who will have an allogeneic haematopoietic stem cell transplant if adequate disease control is gained. Section 3.4 of the ACD highlights data from the INO-VATE 1022 trial showing that patients with relapsed or refractory ALL are more likely to proceed to transplant (ie be well enough and have adequate disease control) if they are treated with Inotuzumab rather than standard of care (41% vs 11%, p<0.001). The trial also showed that 73% of patients who achieved a remission (ie a pre-requisite of transplant) did so after 1 cycle of Inotuzumab. The ACD agrees in section 3.30 that using Inotuzumab as a bridge to transplant would require a median of 2 cycles for most patients, with a maximum of 3 cycles. However, the committee have decided to calculate the ICER for 6 cycles of Inotuzumab since the 'model should be consistent and that benefit and cost should not be uncoupled'.	Comment noted. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles). The committee were not presented with any statistically valid analyses by the company which showed the clinical effectiveness of inotuzumab up to a maximum of 3 cycles. Any analyses the company did provide broke trial randomisation. Therefore the committee agreed that the

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			This is not reasonable as the ICER is based on a two to three fold higher cost of drug than is proposed by the clinical community. **The clinical community would absolutely support the use of Inotuzumab only as a bridge to transplant and only to a maximum of 3 cycles.** If the concern of the committee is that there will be a drift to an increasing number of cycles of Inotuzumab being given, then reassurance can be readily given by 1. The NICE recommendations being clear that Inotuzumab is available only a) to patients who are eligible for allogeneic HSCT should their disease remit and b) to a maximum no of cycles of 3 2. NHS England can enforce these stipulations by the effective mechanisms it already has in place to do so	sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be uncoupled. See section 3.27 of the FAD2
3	Patient and professional	NCRI-ACP-RCP	The restriction of use of Inotuzumab as described above would direct resource effectively to those most likely to be cured of ALL and without which many will succumb to their disease. **The calculation of an ICER using incorrect assumptions of duration of hospital stays and a two to threefold higher use of drugs is not reasonable and does not provide sound guidance to the NHS.**	Comment noted. Following the submission of observational data on the average number of inpatient days with inotuzumab ozogamicin and FLAG-IDA the committee concluded that there is a substantial difference in the average length of stay between the two treatments. Please see section 3.29 of FAD2.
4	Experts	On behalf of the Royal College of Pathologists and British Society for Haematology	**The committee concluded that it preferred the ERG's analysis with the administration cost of inotuzumab ozogamicin based on INO-VATE 1022 and an average length of stay of 9.5 days in both arms.** As a clinical expert, I strongly and profoundly disagree that patients have the same length of stay for inotuzumab ozogamicin (IO) as for FLAG-based regimens. In my experience of providing FLAG-based regimens to patients over many years, I typically find that patients are admitted for the entire duration of their chemotherapy, neutropaenic period and recovery. In fact, I usually personally counsel patients to expect a 4-6 week stay, in total. Even the MacMillan patient information sheet about FLAG-Ida (link below) informs patients they will be treated for 7 days then 'rest in hospital' for 3-4 weeks until recovery. I have absolutely no idea how the figure of 9.5 days for FLAG has been derived, as it bears no relationship to our experience of clinical	Comment noted. Following the submission of observational data on the average number of inpatient days with inotuzumab ozogamicin and FLAG-IDA the committee concluded that there is a substantial difference in the average length of stay between the two treatments. Please see section 3.29 of FAD2.

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			reality in the UK. My view on this should not be heard as if I am some kind of campaigning outlier – the committee could ask any clinician in the UK who regularly uses this regimen and would hear the same response, which is why that sort of information is given to patients UK-wide. If there is going to be a guess or an estimate on this point, surely, this must be based in clinical reality? We have been invited to submit 'real world' data collected from two centres, UCLH and Bristol, comparing length of stay for inotuzumab provided to patients on the compassionate use program with patients treated in our institutions receiving FLAG-based regimen. I sincerely hope these data will be taken into account in revising the model. https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/combinationregimen/flag-ida.aspx **The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial.** I do not agree that the cycle number of 6 used for the calculation. It neither accurately reflects the data from INOVATE study *or* the benefit accruing from fewer than 6 cycles. As stated in the New England Journal of Medicine paper *"Patients in the inotuzumab ozogamicin group received treatment for a median of 3 cycles (range, 1 to 6)" - so* most patients DID NOT receive 6 cycles of IO therapy. In fact, only 45 of 164 (27%) patients in this trial received more than 3 cycles of IO. I am also concerned that, having been granted an appeal with 'incorrect cycle number' as a basis, that mine and others significant and well-justified concerns have been completely ignored. I am absolutely not satisfied that there is any scientific rationale for the choice of 6 cycles in the ICER calculation and indeed this totally contradicts NICE's own stated aim of the modelling which was to reflect the data in the INOVATE study. It is also clear that the main benefit to IO - namely the achievement of complete remission, which is a prerequisite for allogeneic bone marrow transplant, typically accrued after 1 cycle. This is also clearly reported in the paper *"most patients who achieved complete remission or complete remission with incomplete hematologic recovery did so at the end of cycle 1 (64 of 88 patients [73%] in the inotuzumab ozogamicin group)".* Furthermore, I would like to remind the committee that the SPC for IO recommends a maximum	Comment noted. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles). The committee were not presented with any statistically valid analyses by the company which showed the clinical effectiveness of inotuzumab up to a maximum of 3 cycles. Any analyses the company did provide broke trial randomisation. Therefore the committee agreed that the sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be

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			of 3 cycles. I believe we are doing UK patients with ALL a disservice if we persist in evaluating the cost of this agent in such a rigid and uncompromising manner	uncoupled. See section 3.27 of the FAD2.
5	Clinical expert	On behalf of the Royal College of Pathologists and British Society for Haematology	First it is agreed that the post HSCT utility be between 0.76 and 0.88. In my expert opinion the fairest number to adopt is a midway point of 0.82. As stated on May 26 the way the UK does allografts with alemtuzumab, results in less extensive chronic GVHD which is the main cause of a reduced QOL. The data from Seattle (utility 0.76) describe a population with very severe chronic GVHD.	Comment noted. The results of the economic analyses between the values from Kurasowa at al 2016 (0.76) and those of the general population (0.88). Please see section 3.25 of the FAD2.
6	Clinical expert	On behalf of the Royal College of Pathologists and British Society for Haematology	Second we have agreed to use real (robust) clinical data for hospitalisation. The paper from the UCL and Bristol groups, which Professor Fielding and I have personally been involved shows the hospitalisation days for Inotuzumab (patients treated on compassionate use) are far fewer than the hospitalisation days for FLAG-Ida, the SOC comparator. These data will be submitted shortly to NICE and it is hoped that they are accepted and used to modify the ICER. The previous use of NHS reference costs in calculating bed days cannot be justified: they relate to reimbursement and do not constitute 'evidence'	Comment noted. These data have been accepted by the committee for inclusion in the economic modelling. See section 3.29 of the FAD2.
7	Clinical expert	On behalf of the Royal College of Pathologists and British Society for Haematology	The ACD is incorrect in 2 important areas: The committee has again reverted to using data from the Martin paper which reflects 25 years of transplantation prior to the publication year of 2010 and has 'insisted' on using a 4 fold increase in mortality. On April 26th I informed the committee what has changed or was different since the time of the Martin paper: 1. Less chronic GVHD (by using alemtuzumab) 2. Better prevention of infection including in patients with chronic GVHD 3. Better diagnosis and treatment of secondary malignancy due to better knowledge of risk factors and the institution of long term follow up clinics in the UK 4. The LTFUs also better address long term health issues such as excessive weight, metabolic syndrome and cardiovascular risk. This is routine now and the UK has some	Comment noted. The committee accepted that transplant care had improved but it had not been presented with any new evidence to suggest that mortality from 3 years post-HSCT was lower than that presented in Martin et al. 2010. See section 3.26 of the FAD2.

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			leaders in the field such as John Snowden The committee asked me my opinion and I estimated that a threefold increase in mortality over the general population was a reasonable estimate. For the committee to use old, out of date evidence would be wrong and unfair	
8	Clinical expert	On behalf of the Royal College of Pathologists and British Society for Haematology	Finally the committee very surprisingly is insisting on using 6 cycles as the standard because the efficacy data from Inovate are derived from patients who received this amount of Inotuzumab. The committee are not addressing the upheld appeal point Inotuzumab has the capacity to get nearly half the treated patients who achieve CR to transplant which offers them a chance of cure. Nearly all the patients on the final plateau of the OS curve have been transplanted. All the efficacy (ie prolonged survival) of this transplanted group comes from patients who received 1-3 cycles of inotuzumab. Pfizer provided evidence at the post appeal hearing that the patients who had 4-6 cycles and had a transplant had very poor survival No patient in the UK will receive more than 3 cycles of inotuzumab but the great majority will receive 2 cycles. For these reasons we insist that the committee and the ERG base its calculations and conclusions on between 2 and 3 cycles. To not do this would be wrong, unfair and would not be addressing the upheld appeal point If all these matters are addressed and used for the economic model then a substantially lower ICER will be produced.	Comment noted. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles). The committee were not presented with any statistically valid analyses by the company which showed the clinical effectiveness of inotuzumab up to a maximum of 3 cycles. Any analyses the company did provide broke trial randomisation. Therefore the committee agreed that the sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be uncoupled. See section 3.27 of the FAD2.
9	Patient and professional	Leukaemia Care	It is disappointing that committee have been unable to make recommendations on using inotuzumab ozogamicin for treatment of relapsed/refractory ALL. This decision adds yet another delay to patients gaining access to a treatment that is potentially lifesaving. These patients have a high unmet need and currently face a poor prognosis (a 5-year survival rate of less than 10%). As a proven bridge towards stem cell transplant, inotuzumab ozogamicin has the potential to	Comment noted. The committee has now recommended inotuzumab ozogamicin within its marketing authorisation. See section 1 of the FAD2.

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			significantly improve survival for relapsed or refractory ALL patients, who may otherwise have limited options. It is our submission that it would be in the best interest of patients in England for NICE to recommend the use of inotuzumab ozogamicin.	
10	Patient and professional	Leukaemia Care	As per 3.30 of the ACD, the committee concluded that the number of inotuzumab cycles should reflect the number given in the INO-VATE 1022 trial. This committee's recommendation is not reflective of UK clinical practice and appears to contradict the successful appeal by ourselves (and the Joint Appellant) last year. It is irrational, perverse and disproportionate. We repeat our submission that the recommendation should be restricted to patients where there is an intent to proceed to stem cell transplantation, with the modelling capped at a maximum of 3 cycles. Should the committee uphold their assumption in the Final Appraisal Determination (FAD), it is our intention to appeal, as this recommendation is unreasonable in light of the evidence submitted to NICE, because it is not reflective of UK clinical practice.	Comment noted. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles). The committee were not presented with any statistically valid analyses by the company which showed the clinical effectiveness of inotuzumab up to a maximum of 3 cycles. Any analyses the company did provide broke trial randomisation. Therefore the committee agreed that the sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be uncoupled. See section 3.27 of the FAD2.
11	Patient and professional	Leukaemia Care	Additionally, we also have concerns in relation to the health-related quality of life utilities post-cure point. As per the inotuzumab ACD at 3.17, "The committee understood that the populations considered in both appraisals were similar, but it concluded that because the evidence available for each appraisal is different, differences in modelling are unavoidable." Although the appeal panel determined that the committee are not bound by the modelling and interpretation of a separate appraisal, the appeal panel found that the committee should give	Comment noted. At the third meeting and at ACD2 consultation stage, the committee heard from the clinical experts that although many patients who have had a transplant and who did not experience complications should be expected to return

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			reasons for the departure from the post-cure point assumptions previously approved by NICE in the blinatumomab appraisal. In our opinion, the reasons listed in the ACD (3.17, 3.20, 3.27, 3.27 etc) do not address the rationale for a difference in the health-related quality of life post-cure point between the two appraisals. There is no clinical basis for assuming a difference in health-related quality of life post-cure point between patients who receive blinatumomab (then proceed to transplant) and inotuzumab ozogamicin (then proceed to transplant). As such, we request further reasons for the committee's insistence on this clinically implausible difference.	to full health, a number of patients will have longer term health problems related to the transplant. They suggested that the utility values are likely to be between 0.76 and 0.88. Please see section 3.33 of the FAD which presents the results of the economic analyses between the values from Kurasowa et al 2016 (0.76) and those of the general population (0.88).
12	Company	Pfizer	**1. New ICER with the committee's preferred assumptions** The committee have requested new analyses from the company to inform the fourth committee meeting, based upon its revised preferences: (a) Utility values for all patients 5 years post-HSCT between 0.76 and 0.88 (b) A 4-fold increase in mortality for patients 3 years post-HSCT and beyond (c) The same number of treatment cycles for inotuzumab ozogamicin as given in INO-VATE 1022 (up to 6 cycles) (d) The cost of subsequent therapy from the safety population using the generic price for imatinib and list price for blinatumomab (e) Robust clinical data to inform the number of inpatient days for inotuzumab and standard chemotherapy (FLAG) Applying the committee's preferences for (a-e), using the means from the new UK real-world inpatient stay data that was requested by the committee from clinical experts, the ICER is	Comment noted. See section 1 of the FAD2 for the updated recommendations.

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			£33,749 to £37,497 per QALY with inotuzumab's PAS (the range reflective of the 0.76 to 0.88 utility range).[1] Four scenarios are presented alongside this new basecase below, detailed further in the following pages.	
13	Company	Pfizer	**2. Robust clinical data to inform the number of inpatient days** The committee's preferred assumptions in the ACD2 include: "using robust clinical data to inform the number of inpatient days for inotuzumab and the standard of care". In order to ensure that the available evidence was captured, a systematic literature review (SLR) was presented in section 5.5.1 and Appendix 9.1 of the company's evidence submission to identify healthcare resource utilisation related to R/R ALL. This SLR has now been updated during the ACD2 consultation to search specifically for hospitalisation data related to either inotuzumab or FLAG based chemotherapy that has been published more recently; this update did not identify any relevant new data (see Appendix 1). The committee had requested UK clinical experts provide NICE with real-world hospitalisation data for both inotuzumab and FLAG based chemotherapy. The KOL's data are included in Appendix 2, and summarised in **Error! Reference source not found.**.[1] The data is from [redacted] Two studies that reported hospitalisation for chemotherapy patients were noted in the ERG Report, one French (Dombret, 2016) and one Spanish (Boluda, 2016). These studies were published after our initial SLR, but would not have met our SLR inclusion criteria as they did not contain UK data. For comparison however, the hospitalisation reported in the French and Spanish studies are presented in **Error! Reference source not found.** alongside the UK data. The data for chemotherapy [redacted] The other source of data that included UK patients was the INO-VATE trial, however there were only 9 patients across the two arms recruited from the UK (n=4 for inotuzumab and n=5 for chemotherapy); these are too small to provide meaningful estimates so have not been analysed. The UK real-world data is thus the most relevant data for decision making. The INO-VATE mean hospitalisation data had been previously used to inform the ERG's basecase and the committee's original decision, but there are a important limitations with using these data rather over the real-world data beyond just the sample size:	Comment noted. Following the submission of observational data on the average number of inpatient days with inotuzumab ozogamicin and FLAG-IDA the committee concluded that there is a substantial difference in the average length of stay between the two treatments. Please see section 3.29 of FAD2.

[1] In order to implement the committee's preference for utilities (a), the model was adjusted so that a single utility value is able to be applied to all patients past 5 years post-HSCT. Previously the model had split utility into different values depending on whether patients had progressed or not in the longer term. For transparency, a log of all model changes accompanies this response (see Appendix 4).

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			• The trial treated with inotuzumab for a mean of 2.8 cycles whereas the UK data shows a mean of [redacted] per patient [redacted]. Relatedly, hospitalisation related to treatment with inotuzumab can be expected to be considerably [redacted] in the NHS than in the trial. • The mean estimate for hospitalisation which informed the ERG's basecase was the mean calculated *only* from patients who had been hospitalised, however [redacted] patients in the inotuzumab arm and [redacted] patients in the standard of care arm were not hospitalised at all (Pfizer, data on file). Excluding those patients with 0 days of hospitalisation upward biased the ICER. • FLAG is an established therapy whereas inotuzumab is a new therapy. It is expected there would initially be more hospitalisation with the new therapy as clinicians familiarise with it, such as during the trial, but once familiar it is expected real-world hospitalisation with inotuzumab would reduce as it is administered in an outpatient setting. The UK real-world data is the most robust clinical data to inform for UK decision-making. Using these means for inpatient stay ([redacted] days), combined with the committee's preferences for *a-d* as set out in Section 1, the ICER is £33,749 to £37,497 per QALY (the range reflecting the preferred utilities).[2] Inotuzumab is also cost-effective when the French or Spanish data is considered to inform the number of inpatient days for FLAG. If the median inpatient days are used for inotuzumab rather than the mean, as advised by the clinical experts of the real-world dataset as best representing the inotuzumab's patient experiences due to the skew in the data, the ICER reduces (scenario 1 in **Error! Reference source not found.**). It is important to note that the model was originally set up costing inpatient days associated with adverse events separately from those related to administration. However, the new real-world data is for all-cause hospitalisation meaning there is now double counting of adverse event hospitalisations in the revised analyses which bias against inotuzumab. AE costs are driven in the majority by the cost of treating veno-occlusive disease (VOD) with defibrotide. The company's evidence submission sets out that the model considered approximately £54,710 in	

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			costs per patient related specifically to hospitalisation for VOD (section 5.5.5 in the company's evidence submission). If these VOD hospitalisation costs are now removed, the ICER reduces (scenario 2 in **Error! Reference source not found.**). It should also be noted this was a originally conservative assumption to cost defibrotide for every patient with VOD as it would not be given to all patients in practice, as assumed in the model's costings.	
14	Company	Pfizer	**3. Number of cycles of treatment** In the ACD2, the committee acknowledged inotuzumab would be expected to be used in patients proceeding to HSCT for a maximum of 3 cycles (in accordance with the SPC), but have requested cost-effectiveness analyses with INO-VATE trial treatment regimen (up to 6 cycles) so as to not de-couple cost and efficacy. The ICER with the committee's preference for 6 cycles is presented in the new basecase in Table 1, Section 1. The appeal panel advised that: *"the appraisal committee should reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional 3rd, if needed, and a costing model based on appropriate stopping rules may be considered."* As such, a 6 cycle analysis using the INO-VATE trial treatment schedule does not meet the appeal criteria. We believe the previously presented scenario that caps cost at 3 cycles is relevant to meeting the appeal panel's criteria as the evidence supports that efficacy need not be adjusted in such a scenario, thereby meaning that the decoupling of cost should not be a concern when interpreting this analysis. As has been discussed previously in this appraisal, CR/CRi and MRD-negativity with inotuzumab are achieved within 3 cycles in the trial; capping treatment at 3 cycles would thus achieve similar rates as observed in the trial where up to 6 cycles was used. New data is now presented in **Error! Reference source not found.** (Appendix 3) that shows [redacted] This supports that when cost is capped at 3 cycles, the efficacy associated with inotuzumab need not be adjusted in order to interpret the ICER appropriately. ICERs with different considerations of a cost cap are provided in **Error! Reference source not found.** as scenario 3 (a cost cap at 3 cycles) and scenario 4 (the cost using average treatment duration from of [redacted] cycles from the new UK real-world data). From these scenarios, it is clear to see that, in the context of UK practice, it is highly likely that the ICER reduces significantly versus using the trial treatment duration.	Comment noted. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles). The committee were not presented with any statistically valid analyses by the company which showed the clinical effectiveness of inotuzumab up to a maximum of 3 cycles. Any analyses the company did provide broke trial randomisation. Therefore the committee agreed that the sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be uncoupled. See section 3.27 of the FAD2.

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Worldwide Biopharmaceutical Businesses

ID893 Appraisal of inotuzumab ozogamicin
15th June 2018

Dear Professor O'Brien,

Thank you for the opportunity to comment on the second Appraisal Consultation Document (ACD2) for inotuzumab ozogamicin ("inotuzumab"). In response to the committee's request, we have provided revised analyses that use the committee's preferences from the ACD2 ahead of the fourth appraisal committee meeting.

When the committee's revised preferences from the ACD2 are considered with the new clinical expert inpatient stay data requested by the committee, the ICER lays between £33,749 to £37,497 per QALY with the PAS (the range corresponding to the committee's preferred range for utility estimates 5-years post-HSCT). This ICER is based upon treating with inotuzumab for up to 6 cycles, hence inotuzumab is highly cost-effective in the whole population: both those in whom the intent is to proceed to HSCT (who would receive a maximum of 3 cycles, the expected use in UK practice) and those who treated beyond 3 cycles in the trial.

The new clinical expert's data also contains real-world NHS treatment duration for inotuzumab. If these data are accounted for in the calculation of the treatment cost for inotuzumab then the ICER becomes [redacted]. When the median rather than the mean for inotuzumab inpatient days is used [redacted], or when adverse event hospitalisation is no longer double counted, or when the risk to longer term mortality is lower than that reported in Martin et al. (as advised by the clinical experts, quoted in the ACD2), the ICER for inotuzumab versus standard of care chemotherapy reduces, and can plausibly fall below [redacted] per QALY considering these collectively.

Inotuzumab is a clinically effective treatment that allows significantly more patients to reach potentially curative therapy than with the current standard of care and in this response to the ACD2 the case for cost-effectiveness is compelling. Based on this, we believe it is critically important that inotuzumab is made available on the NHS to patients in England and Wales without further delay.

Yours sincerely,

[redacted]

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Registered Office: Ramsgate Road
Sandwich, Kent CT13 9NJ, UK

1. New ICER with the committee's preferred assumptions

The committee have requested new analyses from the company to inform the fourth committee meeting, based upon its revised preferences:

(a) Utility values for all patients 5 years post-HSCT between 0.76 and 0.88
(b) A 4-fold increase in mortality for patients 3 years post-HSCT and beyond
(c) The same number of treatment cycles for inotuzumab ozogamicin as given in INO-VATE 1022 (up to 6 cycles)
(d) The cost of subsequent therapy from the safety population using the generic price for imatinib and list price for blinatumomab
(e) Robust clinical data to inform the number of inpatient days for inotuzumab and standard chemotherapy (FLAG)

Applying the committee's preferences for (a-e), using the means from the new UK real-world inpatient stay data that was requested by the committee from clinical experts, the ICER is £33,749 to £37,497 per QALY with inotuzumab's PAS (the range reflective of the 0.76 to 0.88 utility range).[1] Four scenarios are presented alongside this new basecase below, detailed further in the following pages.

Table 1. ICERs for the committee's preferred assumptions and four scenarios

	Utility 0.88 for (a)	**Utility 0.76 for (a)**
New basecase: Committee's preferences for (a-e) with UK KOL real-world mean data used to inform inpatient stays	£33,749	£37,497
Scenarios		
➢ *Scenario 1:* New basecase, but using the median to inform inotuzumab inpatient days	[redacted]	[redacted]
➢ *Scenario 2:* New basecase, but removing double counting of VOD hospitalisation	[redacted]	[redacted]
➢ *Scenario 3:* New basecase, but 3 cycle cost cap	[redacted]	[redacted]
➢ *Scenario 4:* New basecase, but UK real-world treatment duration used to inform treatment cost	[redacted]	[redacted]

See Section 2 for detail on scenarios 1 and 2, and Section 3 for scenarios 3 and 4.

[1] In order to implement the committee's preference for utilities (a), the model was adjusted so that a single utility value is able to be applied to all patients past 5 years post-HSCT. Previously the model had split utility into different values depending on whether patients had progressed or not in the longer term. For transparency, a log of all model changes accompanies this response (see Appendix 4).

2. Robust clinical data to inform the number of inpatient days

The committee's preferred assumptions in the ACD2 include: "using robust clinical data to inform the number of inpatient days for inotuzumab and the standard of care". In order to ensure that the available evidence was captured, a systematic literature review (SLR) was presented in section 5.5.1 and Appendix 9.1 of the company's evidence submission to identify healthcare resource utilisation related to R/R ALL. This SLR has now been updated during the ACD2 consultation to search specifically for hospitalisation data related to either inotuzumab or FLAG based chemotherapy that has been published more recently; this update did not identify any relevant new data (see Appendix 1).

The committee had requested UK clinical experts provide NICE with real-world hospitalisation data for both inotuzumab and FLAG based chemotherapy. The KOL's data are included in Appendix 2, and summarised in Table 2.[1] The data is from [redacted]

Two studies that reported hospitalisation for chemotherapy patients were noted in the ERG Report, one French (Dombret, 2016) and one Spanish (Boluda, 2016). These studies were published after our initial SLR, but would not have met our SLR inclusion criteria as they did not contain UK data. For comparison however, the hospitalisation reported in the French and Spanish studies are presented in Table 2 alongside the UK data. The data for chemotherapy [redacted]

The other source of data that included UK patients was the INO-VATE trial, however there were only 9 patients across the two arms recruited from the UK (n=4 for inotuzumab and n=5 for chemotherapy); these are too small to provide meaningful estimates so have not been analysed. The UK real-world data is thus the most relevant data for decision making. The INO-VATE mean hospitalisation data had been previously used to inform the ERG's basecase and the committee's original decision, but there are a important limitations with using these data rather over the real-world data beyond just the sample size:

- The trial treated with inotuzumab for a mean of 2.8 cycles whereas the UK data shows a mean of [redacted] per patient ([redacted]). Relatedly, hospitalisation related to treatment with inotuzumab can be expected to be considerably [redacted] in the NHS than in the trial.
- The mean estimate for hospitalisation which informed the ERG's basecase was the mean calculated *only* from patients who had been hospitalised, however [redacted] patients in the inotuzumab arm and [redacted] patients in the standard of care arm were not hospitalised at all (Pfizer, data on file). Excluding those patients with 0 days of hospitalisation upward biased the ICER.
- FLAG is an established therapy whereas inotuzumab is a new therapy. It is expected there would initially be more hospitalisation with the new therapy as clinicians familiarise with it, such as during the trial, but once familiar it is expected real-world hospitalisation with inotuzumab would reduce as it is administered in an outpatient setting.

Table 2. Real-world resource utilisation for inotuzumab and chemotherapy in R/R B-cell ALL during the treatment period

Reference	Population	Average number of hospitalisations and length of each stay	Average length of hospitalisation per patient
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Boluda 2016	Spanish, n=32 Ph- B-cell ALL, R/R most commonly FLAG-Ida	42 inpatient stays in 31 patients • Inpatient stays per patient = 1.4 23 day cases in 31 patients • Day case, mean per patient = 0.7 52 outpatient visit in 31 patients • Outpatient, mean per patient = 1.7	36 days mean (inpatient only)
Dombret 2016	French, n=32 Ph- B-cell ALL, R/R Chemotherapy	71 inpatient stays in 32 patients • Inpatient stays per patient = 2.2, mean of 16.8 days per stay 70 day cases in 32 patients • Day case, mean per patient = 2.1 6 outpatient visit in 32 patients • Outpatient, mean per patient = 0.2	37 days mean (inpatient only) 40 days mean (total time spent in hospital)*

**Dombret report that, in total, 46% of the 87 day treatment period was spent in hospital*

The UK real-world data is the most robust clinical data to inform for UK decision-making. Using these means for inpatient stay ([redacted] days), combined with the committee's preferences for *a-d* as set out in Section 1, the ICER is £33,749 to £37,497 per QALY (the range reflecting the preferred utilities).[2] Inotuzumab is also cost-effective when the French or Spanish data is considered to inform the number of inpatient days for FLAG. If the median inpatient days are used for inotuzumab rather than the mean, as advised by the clinical experts of the real-world dataset as best representing the inotuzumab's patient experiences due to the skew in the data, the ICER reduces (scenario 1 in Table 1).

It is important to note that the model was originally set up costing inpatient days associated with adverse events separately from those related to administration. However, the new real-world data is for all-cause hospitalisation meaning there is now double counting of adverse event hospitalisations in the revised analyses which bias against inotuzumab. AE costs are driven in the majority by the cost of treating veno-occlusive disease (VOD) with defibrotide. The company's evidence submission sets out that the model considered approximately £54,710 in costs per patient related specifically to hospitalisation for VOD (section 5.5.5 in the company's evidence submission). If these VOD hospitalisation costs are now removed, the ICER reduces (scenario 2 in Table 1). It should also be noted this was a originally conservative assumption to cost defibrotide for every patient with VOD as it would not be given to all patients in practice, as assumed in the model's costings.

[2] The ICERs also include outpatient costs for inotuzumab as it is expected to be administered in an outpatient setting. The UK real-world data shows treatment for a mean of [redacted] cycles per patient (costed at 3 administrations per cycle).

3. Number of cycles of treatment

In the ACD2, the committee acknowledged inotuzumab would be expected to be used in patients proceeding to HSCT for a maximum of 3 cycles (in accordance with the SPC), but have requested cost-effectiveness analyses with INO-VATE trial treatment regimen (up to 6 cycles) so as to not de-couple cost and efficacy. The ICER with the committee's preference for 6 cycles is presented in the new basecase in Table 1, Section 1.

The appeal panel advised that: *"the appraisal committee should reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional 3rd, if needed, and a costing model based on appropriate stopping rules may be considered."* As such, a 6 cycle analysis using the INO-VATE trial treatment schedule does not meet the appeal criteria.

We believe the previously presented scenario that caps cost at 3 cycles is relevant to meeting the appeal panel's criteria as the evidence supports that efficacy need not be adjusted in such a scenario, thereby meaning that the decoupling of cost should not be a concern when interpreting this analysis. As has been discussed previously in this appraisal, CR/CRi and MRD-negativity with inotuzumab are achieved within 3 cycles in the trial; capping treatment at 3 cycles would thus achieve similar rates as observed in the trial where up to 6 cycles was used. New data is now presented in **Error! Reference source not found.** (Appendix 3) that shows [redacted] This supports that when cost is capped at 3 cycles, the efficacy associated with inotuzumab need not be adjusted in order to interpret the ICER appropriately.

ICERs with different considerations of a cost cap are provided in Table 1 as scenario 3 (a cost cap at 3 cycles) and scenario 4 (the cost using average treatment duration from of [redacted] cycles from the new UK real-world data). From these scenarios, it is clear to see that, in the context of UK practice, it is highly likely that the ICER reduces significantly versus using the trial treatment duration.

References

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.

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.

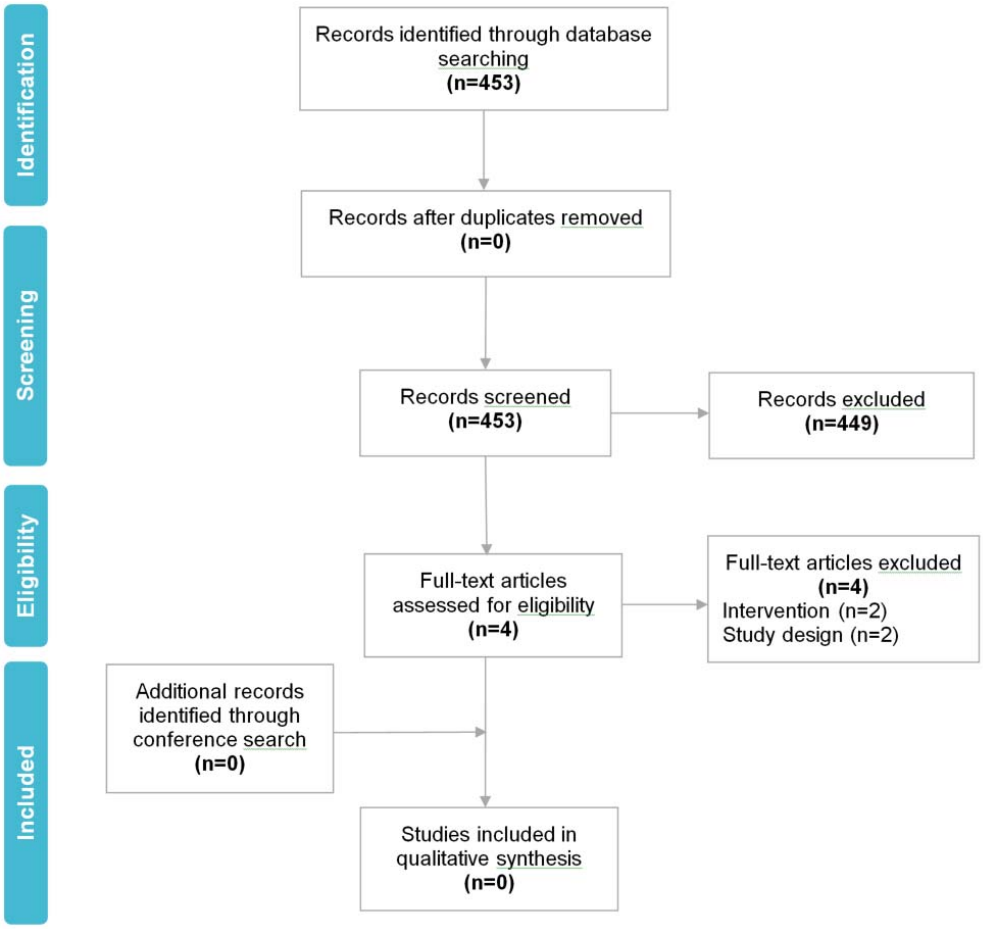
[redacted]

Pfizer *unpublished*. INO-VATE 1022 Clincial Study Report. Data on file.

Appendix 1: Systematic literature review update.

In the SLR update, the same search terms as Appendix 9 in the company submission were used. Databases searched included Medline & EMBASE, Medline-in-process, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect, Health Technology Assessment Database, NHS EED, Economic Evaluation Database. ISPOR EU 2016 and 2017 conferences were also searched. In this update, inclusion criteria were specific to the interventions of interest, inotuzumab and FLAG based chemotherapy, and searched for relevant hospitalisation data. No published UK data to inform the length of inpatient stay with either of the interventions were identified in this update.

Figure 1. PRISMA for search update



Appendix 2: Clinical expert's UK real-world inpatient stay data

These data are unpublished and are data the clinical experts have provided to NICE.

[redacted]

Appendix 3: New data illustrating OS post-HSCT relative to treatment cycles

Error! Reference source not found. presents OS in those patients who had HSCT and who received 3 or fewer cycles versus those receiving greater than 3 cycles.

[redacted]

As 93% of inotuzumab's QALYs in the model are generated from the post-HSCT state (taken from the model *Results* sheet, Q25/Q26), the data presented in Figure 2 for the post-HSCT are not re-presented for the pre-HSCT states as those states do not drive the results.

Appendix 4: Model change log

Due to potential confusion between the company and the ERG with the post-appeal model (model dated 8th March 2018) and the ERG's resulting preference to revert instead to the post-ACD1 model prior to the most recent committee meeting (model dated 4th July 2017), we have applied model changes directly to that post-ACD1 model and have not used the post-appeal model. Changes made to the post-ACD1 model are documented in a separate Excel file titled *Model Change Log* so edits can be checked by the ERG.

Notes on model calculations behind two scenarios included above in Table 1:

Scenario 2, Table 1: To run the scenario that removes the hospitlisation costs from defibrotide, cell D131 on the *Costs* sheet was reduced by £54,711 (the difference between cells D130 and D132 in the *Costs* sheet in the model = 28.48 days at £1921 per day, page 232 of company submission). The quoted estimates for AE-related costs in the model (£13,725 and £1,899) are from cell DP9 in the *INO OS* sheet and cell FE9 in the *SoC OS* sheet.

Scenario 4, Table 1: To run the scenario that uses an average of [redacted] cycles as opposed to 2.8 mean cycles of cost, the total cost of inotuzumab needs to be [redacted] than 2.8. To implement this simplistically in the model, the price of inotuzumab was [redacted]. Cell D146 on the *Dashboard* sheet was used to run this scenario.

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

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Consultation on the appraisal consultation document – deadline for comments **5pm on Friday 15 June 108** please return via NICE DOCS

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

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	It is disappointing that committee have been unable to make recommendations on using inotuzumab ozogamicin for treatment of relapsed/refractory ALL. This decision adds yet another delay to patients gaining access to a treatment that is potentially lifesaving. These patients have a high unmet need and currently face a poor prognosis (a 5-year survival rate of less than 10%). As a proven bridge towards stem cell transplant, inotuzumab ozogamicin has the potential to significantly improve survival for relapsed or refractory ALL patients, who may otherwise have limited options. It is our submission that it would be in the best interest of patients in England for NICE to recommend the use of inotuzumab ozogamicin.
2	As per 3.30 of the ACD, the committee concluded that the number of inotuzumab cycles should reflect the number given in the INO-VATE 1022 trial. This committee's recommendation is not reflective of UK clinical practice and appears to contradict the successful appeal by ourselves (and the Joint Appellant) last year. It is irrational, perverse and disproportionate. We repeat our submission that the recommendation should be restricted to patients where there is an intent to proceed to stem cell transplantation, with the modelling capped at a maximum of 3 cycles.

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	Should the committee uphold their assumption in the Final Appraisal Determination (FAD), it is our intention to appeal, as this recommendation is unreasonable in light of the evidence submitted to NICE, because it is not reflective of UK clinical practice.
3	Additionally, we also have concerns in relation to the health-related quality of life utilities post-cure point. As per the inotuzumab ACD at 3.17, "The committee understood that the populations considered in both appraisals were similar, but it concluded that because the evidence available for each appraisal is different, differences in modelling are unavoidable." Although the appeal panel determined that the committee are not bound by the modelling and interpretation of a separate appraisal, the appeal panel found that the committee should give reasons for the departure from the post-cure point assumptions previously approved by NICE in the blinatumomab appraisal. In our opinion, the reasons listed in the ACD (3.17, 3.20, 3.27, 3.27 etc) do not address the rationale for a difference in the health-related quality of life post-cure point between the two appraisals. There is no clinical basis for assuming a difference in health-related quality of life post-cure point between patients who receive blinatumomab (then proceed to transplant) and inotuzumab ozogamicin (then proceed to transplant). As such, we request further reasons for the committee's insistence on this clinically implausible difference.

Insert extra rows as needed

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

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCPath-BSH
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted], RCP registrar

Comment number	Comments

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

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The NCRI-ACP-RCP-RCPath-BSH is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by Professor Adele Fielding. We have also liaised with our experts and would like to make the following comments.
	We are concerned that the cost effectiveness calculations in this technology appraisal are based on 2 incorrect assumptions that negatively impact on the ICER; a) the number of in patient days required for administration of Inotuzumab compared to standard of care and b) the number of cycles to be used. These are not reasonable assumptions and do not provide sound guidance for the NHS.
2	**In-patient bed days** In section 3.13 of the ACD, the rationale for the assumption that 9.5 in patient days would be required for both inotuzumab and FLAG is made. Although challenged as described in section 3.22, the ICER still incorporates this incorrect assumption which is not reflective of clinical practice. The number of days an individual patient is hospitalised is dependent on the need for a) management of disease related complications, b) the administration of the therapy to be given and c) management of complications of the therapy. a) The time taken to control disease related complications is dependent on the speed of disease control. As described in section 3.4 of the ACD, inotuzumab is more likely to achieve a complete haematological response than standard of care 80.7% vs 29.4%, p<0.0001). Whilst it is impossible to define the exact number of bed days required solely for management of complications of disease, it will clearly be shorter for inotuzumab compared to standard of care given this considerable difference in remission rates. b) FLAG is an intensive chemotherapy given over 5 days and necessitates hospital admission due to duration/timings of the infusions, management of immediate side effects eg nausea and vomiting and the need for supportive care eg prevention, monitoring and treatment of tumour lysis syndrome. Inotuzumab is given as an infusion on days 1, 8 and 15 in a 4 week cycle and can be administered as an out-patient. c) FLAG is associated with profound suppression of bone marrow function resulting in prolonged neutropenia with a risk of sepsis, which may be life-threatening. Patients also require regular red cell and platelet transfusions. The majority of patients need to stay in hospital until count recovery, which generally takes 4-6 weeks. As described in section 3.5 of the ACD, inotuzumab has a favourable toxicity profile which rarely necessitates hospital readmission. Indeed, the risk of neutropenic fever is halved in patients receiving inotuzumab compared to those receiving standard of care (26.8% vs 53.8%). Professor Fielding has provided the committee with real-life data from Bristol and UCLH showing the combined effect of the 3 factors described above on duration of in-patient stay. [redacted] It should be noted that these data are from a time when clinicians were unfamiliar with inotuzumab, were cautious and more likely to keep patients in hospital longer than necessary; any future comparison of in-patient days required between inotuzumab and FLAG Ida is therefore likely to be even more favourable. Thus it is not reasonable for the cost effectiveness model to be based on an assumption that the in-patient stay for inotuzumab vs standard of care is the same ie 9.5 days, as in reality, the number of bed days required for patients receiving inotuzumab is less than 25% of that needed for FLAG-Ida.

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

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3	**Number of cycles of Inotuzumab** In section 3.30, the ACD summarises the view of the clinical community that given the NHS has limited resource, there is a rationale to restrict the use of Inotuzumab to patients who will have an allogeneic haematopoietic stem cell transplant if adequate disease control is gained. Section 3.4 of the ACD highlights data from the INO-VATE 1022 trial showing that patients with relapsed or refractory ALL are more likely to proceed to transplant (ie be well enough and have adequate disease control) if they are treated with Inotuzumab rather than standard of care (41% vs 11%, p<0.001). The trial also showed that 73% of patients who achieved a remission (ie a pre-requisite of transplant) did so after 1 cycle of Inotuzumab. The ACD agrees in section 3.30 that using Inotuzumab as a bridge to transplant would require a median of 2 cycles for most patients, with a maximum of 3 cycles. However, the committee have decided to calculate the ICER for 6 cycles of Inotuzumab since the 'model should be consistent and that benefit and cost should not be uncoupled'. This is not reasonable as the ICER is based on a two to three fold higher cost of drug than is proposed by the clinical community. **The clinical community would absolutely support the use of Inotuzumab only as a bridge to transplant and only to a maximum of 3 cycles.** If the concern of the committee is that there will be a drift to an increasing number of cycles of Inotuzumab being given, then reassurance can be readily given by 1. The NICE recommendations being clear that Inotuzumab is available only a) to patients who are eligible for allogeneic HSCT should their disease remit and b) to a maximum no of cycles of 3 2. NHS England can enforce these stipulations by the effective mechanisms it already has in place to do so
4	The restriction of use of Inotuzumab as described above would direct resource effectively to those most likely to be cured of ALL and without which many will succumb to their disease. **The calculation of an ICER using incorrect assumptions of duration of hospital stays and a two to threefold higher use of drugs is not reasonable and does not provide sound guidance to the NHS.**

Insert extra rows as needed

Dear Professor OBrien and Committee,

Thank you for giving us the opportunity to respond to the ACD2 of May 2018, ID893 Inotuzumab.

I believe that the constructive and board ranging discussion we heard at the meeting following the appeal took into account all the issues that were raised in the appeal. On seeing the ACD2, I now have concerns that, despite the issues being heard and discussed broadly, they were then not taken into account in the re-analysis of the cost:benefit analysis of this agent.

The two specific concerns that I wish to raise are as follows. In bold, I reproduce the text from the ACD which gives rise to my concerns, and below, I share my rationale for those concerns.

The committee concluded that it preferred the ERG's analysis with the administration cost of inotuzumab ozogamicin based on INO-VATE 1022 and an average length of stay of 9.5 days in both arms.

As a clinical expert, I strongly and profoundly disagree that patients have the same length of stay for inotuzumab ozogamicin (IO) as for FLAG-based regimens. In my experience of providing FLAG-based regimens to patients over many years, I typically find that patients are admitted for the entire duration of their chemotherapy, neutropaenic period and recovery. In fact, I usually personally counsel patients to expect a 4-6 week stay, in total. Even the MacMillan patient information sheet about FLAG-Ida (link below) informs patients they will be treated for 7 days then 'rest in hospital' for 3-4 weeks until recovery. I have absolutely no idea how the figure of 9.5 days for FLAG has been derived, as it bears no relationship to our experience of clinical reality in the UK. My view on this should not be heard as if I am some kind of campaigning outlier – the committee could ask any clinician in the UK who regularly uses this regimen and would hear the same response, which is why that sort of information is given to patients UK-wide. If there is going to be a guess or an estimate on this point, surely, this must be based in clinical reality? We have been invited to submit 'real world' data collected from two centres, UCLH and Bristol, comparing length of stay for inotuzumab provided to patients on the compassionate use program with patients treated in our institutions receiving FLAG-based regimen. I sincerely hope these data will be taken into account in revising the model.

https://www.macmillan.org.uk/cancerinformation/cancertreatment/treatmenttypes/chemotherapy/combinationregimen/flag-ida.aspx

The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial.

I do not agree that the cycle number of 6 used for the calculation. It neither accurately reflects the data from INOVATE study *or* the benefit accruing from fewer than 6 cycles. As stated in the New England Journal of Medicine paper *"Patients in the inotuzumab ozogamicin group received treatment for a median of 3 cycles (range, 1 to 6)" - so* most patients DID NOT receive 6 cycles of IO therapy. In fact, only 45 of 164 (27%) patients in this trial received more than 3 cycles of IO. I am also concerned that, having been granted an appeal with 'incorrect cycle number' as a basis, that mine and others significant and well-justified concerns have been completely ignored. I am absolutely not satisfied that there is any scientific rationale for the choice of 6 cycles in the ICER calculation and indeed this totally contradicts NICE's own stated aim of the modelling which was to reflect the data in the INOVATE study.

It is also clear that the main benefit to IO - namely the achievement of complete remission, which is a prerequisite for allogeneic bone marrow transplant, typically accrued after 1 cycle. This is also clearly reported in the paper *"most patients who achieved complete remission or complete remission with incomplete hematologic recovery did so at the end of cycle 1 (64 of 88 patients [73%] in the inotuzumab ozogamicin group)".*

Furthermore, I would like to remind the committee that the SPC for IO recommends a maximum of 3 cycles.

I believe we are doing UK patients with ALL a disservice if we persist in evaluating the cost of this agent in such a rigid and uncompromising manner

Yours sincerely,

Adele Fielding MBBS PhD FRCP FRCPath

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments **5pm on Friday 15 June 108** please return via NICE DOCS

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Royal College of Pathologists**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Not applicable**]
Name of commentator person completing form:	[**Professor David I. Marks**]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	I have carefully read the Inotuzumab ACD2 May 32 page document and have a number of comments to make, and I strongly disagree with the conclusions of the committee on several matters The committee meeting on April 26 was well chaired, diligently discussed the appeal points, and carefully listened to the 2 clinical experts about the evidence. What I felt we had agreed is that we needed to go beyond the published evidence especially when the evidence was inadequate or not up to date. The 32 page document has not done this and at times reveals an intellectual rigidity that does not serve the interests of patients well
1	First it is agreed that the post HSCT utility be between 0.76 and 0.88. In my expert opinion the fairest number to adopt is a midway point of 0.82. As stated on May 26 the way the UK does allografts with alemtuzumab, results in less extensive chronic GVHD which is the main cause of a reduced QOL. The data from Seattle (utility 0.76) describe a population with very severe chronic GVHD.
2	Second we have agreed to use real (robust) clinical data for hospitalisation. The paper from the UCL and Bristol groups, which Professor Fielding and I have personally been involved shows the hospitalisation days for Inotuzumab (patients treated on compassionate use) are far fewer than the hospitalisation days for FLAG-Ida, the SOC comparator. These data will be submitted shortly to NICE and it is hoped that they are accepted and used to modify the ICER. The previous use of NHS reference costs in calculating bed days cannot be justified: they relate to reimbursement and do not constitute 'evidence'

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

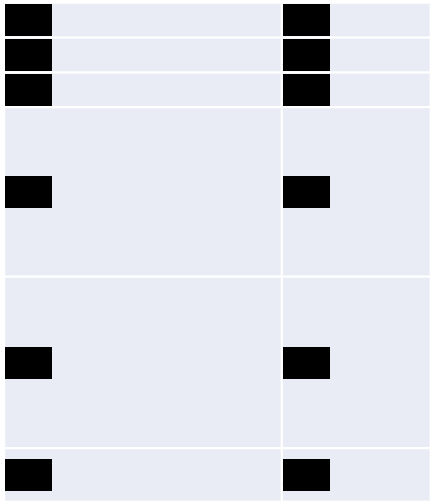
NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments **5pm on Friday 15 June 108** please return via NICE DOCS

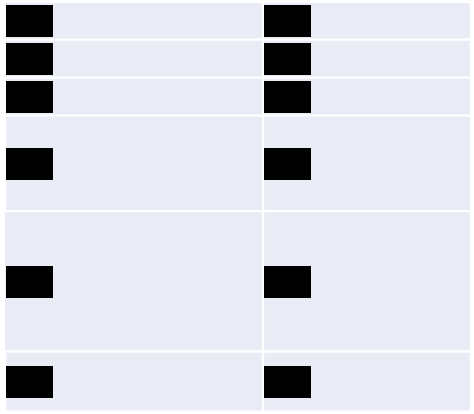
3	The ACD is incorrect in 2 important areas: The committee has again reverted to using data from the Martin paper which reflects 25 years of transplantation prior to the publication year of 2010 and has 'insisted' on using a 4 fold increase in mortality. On April 26th I informed the committee what has changed or was different since the time of the Martin paper: 1. Less chronic GVHD (by using alemtuzumab) 2. Better prevention of infection including in patients with chronic GVHD 3. Better diagnosis and treatment of secondary malignancy due to better knowledge of risk factors and the institution of long term follow up clinics in the UK 4. The LTFUs also better address long term health issues such as excessive weight, metabolic syndrome and cardiovascular risk. This is routine now and the UK has some leaders in the field such as John Snowden The committee asked me my opinion and I estimated that a threefold increase in mortality over the general population was a reasonable estimate. For the committee to use old, out of date evidence would be wrong and unfair
4	Finally the committee very surprisingly is insisting on using 6 cycles as the standard because the efficacy data from Inovate are derived from patients who received this amount of Inotuzumab. The committee are not addressing the upheld appeal point Inotuzumab has the capacity to get nearly half the treated patients who achieve CR to transplant which offers them a chance of cure. Nearly all the patients on the final plateau of the OS curve have been transplanted. All the efficacy (ie prolonged survival) of this transplanted group comes from patients who received 1-3 cycles of inotuzumab. Pfizer provided evidence at the post appeal hearing that the patients who had 4-6 cycles and had a transplant had very poor survival No patient in the UK will receive more than 3 cycles of inotuzumab but the great majority will receive 2 cycles. For these reasons we insist that the committee and the ERG base its calculations and conclusions on between 2 and 3 cycles. To not do this would be wrong, unfair and would not be addressing the upheld appeal point
5	If all these matters are addressed and used for the economic model then a substantially lower ICER will be produced.

Insert extra rows as needed

FLAG-Ida:
Inpatient stay data



Inotuzumab:
Inpatient stay data

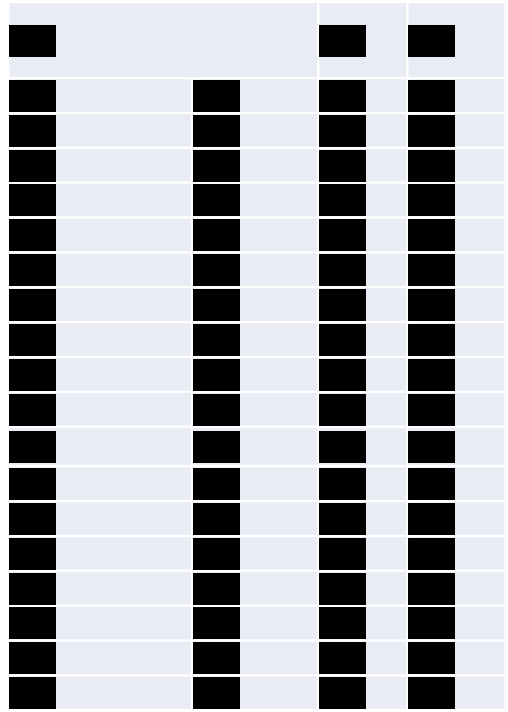


Frequency distribution of inpatient days per cycle
FLAG-Ida versus Inotuzumab

Number of cycles

Number of inpatient days

Data taken from IO compassionate use program



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Evidence Review Group's response to ACD2 comments Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

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Date completed	25/06/2018

Note on the text

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All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 Summary

Following the third appraisal committee meeting, the Committee was unable to make a recommendation on inotuzumab ozogamicin as an option for treating relapsed or refractory B-cell ALL. The Committee recommended that NICE request further cost-effectiveness analyses from the company to reflect the Committee's preferred assumptions and new data on the length of inpatient stay for patients admitted while receiving inotuzumab or standard care.

Inotuzumab is less costly in terms of inpatient admissions compared to standard of care as a proportion of cycles can be delivered on an outpatient basis. This has been reflected in the cost-effectiveness analyses seen by the Committee throughout the appraisal. However, the question of whether there are further cost savings from a reduction in the length of stay among patients who are admitted has remained uncertain, and the cost-effectiveness results are sensitive to the assumed difference in length of stay per hospitalisation. The Committee previously saw ICERs for inotuzumab versus standard of care that reflect a lower number of inpatient admissions with inotuzumab, but that assumed the same number of bed days per hospitalisation. These were [redacted] per QALY for a utility value of 0.76 five years post HSCT, and [redacted] per QALY for a utility value of 0.88 years post HSCT. Including the observational data provided by clinical experts on length of stay per hospitalisation provides ICERs of [redacted] per QALY for inotuzumab compared to standard of care (utility value of 0.76 five years post HSCT) and [redacted] per QALY (utility value of 0.88 five years post HSCT). These ICERs should be interpreted with caution as, while based on real world data, they infer a treatment benefit on the basis of a small sample of unadjusted observational data. Alternative published estimates for length of stay per hospitalisation with FLAG-IDA increase the ICER to above £50,000 per QALY.

The ERG received the response to the second ACD consultation on 18th June 2018. The clinical experts provided real world data on the length of stay for patients who received inotuzumab or standard of care on an inpatient basis. The company response included a 10 page document and an updated model and cost-effectiveness analysis.

This report consists of:

- A review of the Committee's requests, real world evidence on length of stay, and its role in the cost-effectiveness analysis
- A review of the company response to ACD2
- Verification of ICERs provided in the company response
- The results of the cost-effectiveness analysis for alternative number of bed days per hospitalisation

2 Committee's requests in ACD2

The Committee requested an additional sensitivity analysis on the utility values for patients who survive five years beyond haematopoietic stem cell transplant (HSCT). The Committee requested that the utility value be altered between that provided by a published study that assessed health related quality of life five years after HSCT (0.76) and the UK general population health related quality of life at the average age of patients that would receive inotuzumab (0.88).

The Committee maintained a preference for the assumption that patients who survive ALL and HSCT may continue to experience worse health than the general population, with a 4-fold increase in mortality compared with the general population for patients three years post-HSCT and beyond.

The Committee also maintained a preference for basing the number of treatment cycles on the INO-VATE 1022 trials from which the efficacy data are derived (up to 6 cycles, mean [redacted] cycles).

The Committee maintained their request that the cost of subsequent therapy be based on those received in the safety population that the efficacy data are derived from, using the generic price for imatinib and the list price for blinatumomab (while recognising that a patient access scheme is in place that provides a discount on the list price).

At the third Committee meeting the clinical experts indicated that they may be able to provide some real world evidence on the length of inpatient stay for patients admitted while receiving inotuzumab or standard of care. The Committee requested that this data be incorporated in the cost-effectiveness analysis.

2.1 Number of inpatient days

The cost-effectiveness analysis calculates an administration cost for inotuzumab and standard of care based on the proportion that receive each cycle of treatment whilst an inpatient or on an outpatient basis. The following equation shows the basis on which inpatient administration costs are calculated:

$$Number\ of\ cycles\ delivered\ as\ an\ inpatient\ x\ cost\ per\ bed\ day\ x\ number\ of\ bed\ days$$

The number of patients who have an inpatient admission while receiving a cycle of inotuzumab is taken from the INO-VATE 1022 trial ([redacted] of all cycles delivered), and the model assumed that all cycles of standard of care (100%) are delivered on an inpatient basis. The cost per bed day is estimated from NHS reference costs. In order to differentiate the cost per inpatient admission for inotuzumab from that for standard of care, the model can include different estimates for the average number of bed days per inpatient admission, i.e. the average length of stay. There is little evidence to

inform this length of stay for standard of care, and no published data on average length of stay with inotuzumab. Average length of stay for FLAG is thought to be about 3-4 weeks in routine clinical practice, and the first ERG report identified a French case study (*Dombret et al. Journal of Medical Economics 2016*) and Spanish case study (*Boluda et al, ISPOR 19th Annual European Conference 2016*) that provided estimates of 16.8 and 26 days respectively for FLAG-IDA (*ERG report Section 5.2.5.2, page 101*). The company were unable to provide information on the length of stay from the INO-VATE 1022 trial. At the third Committee meeting, the clinical experts indicated that they could provide an estimate this length of stay based on patients that they had observed within their practice.

The clinical experts presented the real world data in the form of a slide. The data include [redacted]. These data represent approximately [redacted]. The [redacted] means that the estimates are highly uncertain. The data are observational and unadjusted, and so the difference in length of stay between FLAG-IDA and inotuzumab may be explained by factors other than choice of treatment.

While UK standard of care is FLAG-IDA, this differs from the standard of care provided in the INO-VATE 1022 trial (65% FLAG, 23% CM, 12% HIDAC), and FLAG-IDA may be associated with slightly increased toxicity and increased length of stay compared to FLAG. As inotuzumab is not yet recommended by NICE, the patients that have received inotuzumab in practice represent a selected sample that includes patients treated under the compassionate use programme. The clinical experts assert that these patients may be sicker than the average patient who would receive inotuzumab. It is notable that the patients in the real world evidence [redacted]

[redacted]. Based on the limited information available, it would appear that this real world sample may not be representative of the patients who were included in the INO-VATE 1022 trial from which the efficacy data are generated.

Among patients who received FLAG-IDA as an inpatient, the mean length of stay was [redacted]. The graph for inotuzumab shows that [redacted]

The number required for the model is the average length of stay among those with bed days, which requires that the mean be calculated for [redacted] during which patients were admitted for at least one night. The average number of bed days per patient admitted while receiving a cycle of inotuzumab is [redacted]

[redacted]

The data provided by the clinical experts produce a [redacted]. Comparing these data to the other available sources for length of stay with FLAG-IDA, and based on what information is known about the real world sample of patients, it is possible that this real world evidence [redacted]

[redacted]

[redacted]

3 Company response to ACD2

The company present updated cost-effectiveness analyses that include the real world evidence on length of stay from the clinical experts. The company report two sets of results, one for a utility value of 0.88 five years post HSCT and one for a utility value of 0.76 five years post HSCT, as per the Committee request. In addition to the requested analyses, the company present four further scenario analyses:

1. Using the median instead of the mean to inform inpatient days
2. Removing the costs of veno-occlusive disease on the assumption that this is reflected in the real world inpatient stay data
3. Capping the number of cycles of inotuzumab at three
4. Using the number of cycles of inotuzumab from the real world clinical expert data

3.1 Updated cost-effectiveness analyses per Committee requests

The company response appears to misunderstand the manner by which the company model estimates the administration costs and which data that are included in the company model. The company response asserts that the ERG base case was based on the mean hospitalisation data from INO-VATE 1022, and that this was incorrectly calculated. As explained earlier, the company post ACD model estimates the number of inpatient admissions based on data from INO-VATE 1022, which accurately captures the fact that a proportion of patients treated with inotuzumab did not have any hospitalisation. No information on length of stay per hospitalisation or per patient was provided from INO-VATE 1022. As explained in Section 2.1, the model calculates the cost of administration based on the following equation:

$$Number\ of\ cycles\ delivered\ as\ an\ inpatient\ x\ cost\ per\ bed\ day\ x\ number\ of\ bed\ days$$

The real world data and the estimates from Boluda and Dombret are required to inform the number of bed days per hospitalisation and not the average length of hospitalisation per patient.

The company provided a new revised model alongside their response to the second appraisal committee determination. As no revision to the model structure was requested by the Committee, this model should in principle be identical to the revised model presented post ACD. The ERG prefer to

maintain consistency by using the same model that generated the ICERs that informed earlier Committee meetings, as this ensures that model errors are not introduced unnecessarily.

Using the post-ACD model that produced the ICERs previously seen by the Committee, and implementing the Committee's preferred analysis from the ACD2 using a utility value of 0.76 and using the mean number of bed days reported by the clinical experts ([redacted]) produces an ICER of [redacted] per QALY with inotuzumab compared to standard of care. This differs to the ICER presented by the company in their response to the ACD3 ([redacted]), which indicates that the revised model includes additional changes beyond those requested by the Committee. A technical appendix is provided to guide the company in confirming the ERG application of the Committee's preferred assumptions in the company's post-ACD model.

Table 1 shows the cost-effectiveness results for alternative assumptions about the number of bed days per hospitalisation with inotuzumab and FLAG. If the model is updated to include [redacted] mean number of bed days per inpatient administration of inotuzumab, the ICER increases from [redacted] to [redacted] per QALY with inotuzumab compared to standard of care. The corresponding ICERs are [redacted] with [redacted] per inpatient administration of inotuzumab and [redacted] with [redacted] per inpatient administration if the utility five years post HSCT is increased to 0.88.

[redacted]

	Utility 0.88 for (a)	**Utility 0.76 for (a)**
New basecase: Committee's preferences for (a-e) with UK KOL real-world data used to inform inpatient stays ([redacted])	[redacted]	[redacted]
Scenarios		

➢ *ERG Scenario 1:* New base case, but using [redacted]	[redacted]	[redacted]
➢ *ERG Scenario 2:* New base case, but using [redacted] and 16.8 bed days for standard of care (Dombret et al)	[redacted]	[redacted]
➢ *ERG Scenario 3:* New base case, but using [redacted] and 26 bed days for standard of care (Boluda et al)	[redacted]	[redacted]

3.2 Additional scenarios not requested by the Committee

The company additional scenario 1 replaces the mean number of inpatient days with the median. Using the median in place of the mean is mathematically incorrect and underestimates administration costs.

The company additional scenario 2 removes the cost for veno-occlusive disease (VOD) from the cost-effectiveness analysis. The company response notes that the real world evidence on number of bed days for inotuzumab may be inflated by patients who experience the adverse event of VOD during their admission, and which would induce double counting in the cost-effectiveness analysis. NICE confirmed with the clinical experts that none of the 17 patients that received inotuzumab experienced VOD, and so there is no potential for double counting of bed days. Hence there is no justification for removing VOD costs from the cost-effectiveness analysis.

The company additional scenarios 3 and 4 alter the number of cycles of intouzumab that are costed in the cost-effectiveness analysis. This is out of line with the Committee's stated preferences in ACD2. The Committee has previously discussed the problems that arise in altering the number of cycles received as this reduces the cost of inotuzumab while breaking the link with the data from which the efficacy are generated. The efficacy data in the cost-effectiveness analysis are taken from INO-VATE 1022, which provided inotuzumab in line with the final marketing authorisation, and in which patients received on average [redacted] cycles of intozumab, with a maximum of six cycles. In the INO-VATE 1022 trial [redacted] of patients recieved more than three cycles, including [redacted] of those

that proceeded to HSCT. Introducing a treatment cap, by assuming a maximum of three cycles or by utilising the smaller number of cycles observed in the real world data from the clinical experts, reduces the cost of inotuzumab but leaves the efficacy unadjusted. It cannot be assumed that the same efficacy would have been observed with a smaller amount of cycles. The company argue that [redacted], but this does not provide any indication of how the estimate of efficacy would be affected by a treatment cap as it adjusts only one arm of the randomised trial. Patients who received more than three cycles of inotuzumab do not represent a random sample of those treated. For example, if sicker patients were more likely to receive a larger number of cycles, removing them from the inotuzumab arm but leaving their counterparts in the standard of care arm would overestimate efficacy of inotuzumab.

4 Technical appendix

The Committee previously discussed ICERs generated by the company model 'ID893 inotuzumab ACD comments Pfizer Revised model v0.1 040717 SY [ACIC]' at the second appraisal committee meeting. By continuing to use this model we can ensure that the calculations are in link with those on which the Committee based their earlier recommendations and track back to earlier scenarios.

To generate the ICER of [redacted] that corresponds to the Committee's from ACD2, the base case assumptions listed in column E on the 'Dashboard' sheet should be applied, with the exception of:

- cell D133, which should be altered to 'Scenario applied'
- cell D146, which should be altered to 'ERG administration costs'
- cell D154, which should be altered to 'No'

From this, the Committee's preferred assumptions listed in ACD3 can be reached by altering the following cells across three sheets:

1. Sheet 'Dashboard'

The utilities after HSCT from Kurosawa should be selected in cell D71

The updated PAS for inotuzumab can be entered in cell D113.

The assumed PAS for blinatumomab can be entered in cell D119.

The cost of subsequent therapies can be based on list price by selecting 'No scenario analysis' in the drop down menu in cell D133

2. Sheet 'Costs'

The generic cost for imatinib (£99.99) should be entered into cell E89

3. Sheet 'Resource use'

The number of bed days per inpatient admission while receiving inotuzumab can be entered in cell E25

The number of bed days per inpatient admission while receiving standard of care must be entered in three cells (E36, AND E44, AND E52).