

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

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

8th March 2018

Dear Dr. Sutcliffe,

This document provides responses to points raised and requests for clarification in the emails from NICE to Pfizer dated 9th February and 28th February 2018. The following was requested from Pfizer:

1. More detail behind Pfizer's interpretation of the committee preferred assumptions, and how this translates into the analyses, including the individual changes to the model assumptions and an updated model that allows implementation of the changes individually.
2. A list of all new Pfizer assumptions which are not in line with the committee-preferred assumptions in the FAD (and a detailed explanation of rationale for including them), including:
 - (a) how the clinical effectiveness adjustment to the 3 cycles scenario was performed (e.g. were all patients with 3 + cycles removed from the model or the Gompertz OS curve parameters?)
 - (b) a detailed explanation and justification of how the long term survival was estimated
3. Confirmation as to whether or not there is a change to the PAS discount.

This document justifies why Pfizer believe the committee's final ICER from the FAD is better approximated at [REDACTED] per QALY, and not [REDACTED] per QALY, as the former ICER closer reflects the evidence presented to the committee on administration-related inpatient stay. The document then presents further detail on adjustments to the ICER in relation to the upheld appeal points on how many cycles of inotuzumab ozogamicin ("inotuzumab") would be used in practice before stopped, and assumptions around survival and quality of life post-cure point after successful hematopoietic stem cell transplant (HSCT).

In addition, on the 8th March 2018, Pfizer have requested to the Department of Health for the PAS for inotuzumab to be increased, from [REDACTED]. Pfizer have included revised estimates of the ICERs with this new PAS.

Pfizer believe that the ICER, based on our interpretation of the committee's ICER from the FAD, when treatment is stopped at 3 cycles and post-cure point assumptions are aligned with those previously approved by NICE, is £33,649 per QALY including the new PAS (or £38,030 per QALY if applied to NICE's approximation of the committee's ICER from the FAD). This demonstrates that inotuzumab is a highly cost-effective therapy for this rare patient population under a willingness to pay threshold of £50,000 per QALY.

Yours sincerely,

[REDACTED]

[REDACTED]

1. The committee's preferred ICER from the FAD and detail behind Pfizer's interpretation.

In the email sent from NICE to Pfizer dated 28th February 2018, it was stated that the committee based its FAD decision on the preferred base-case of █████ per QALY minus adjustments to number of inpatient days to administer inotuzumab, and the cost included in the model for subsequent therapies. The committee's final preference for these two assumptions was:

- *Subsequent therapy costs*: "The committee agreed with the ERG that the cost of subsequent therapy based on the safety population could be included, but it is not appropriate to use the list prices for the calculation of the cost." (FAD, section 3.21)
- *Administration related inpatient stay*: "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 care, but that the ratio is likely to be larger than the ratio used in the company's analysis (1/14)." (FAD, section 3.22)

In order to adjust the █████ per QALY ICER for these two preferences to thus calculate the committee's specific final ICER, NICE, in the 28th February email, stated the midpoint should be used between Pfizer's estimates in its ACD response with respect to these two assumptions and the ICER of █████ per QALY. NICE concluded from this that the committee's preferred ICER from the FAD, with the committee's preferences for subsequent therapies and administration-related inpatients stay, was thus approximately █████ per QALY $(\frac{1}{2} \times \text{Pfi} + \frac{1}{2} \times \text{NICE})^a$. In order for the model to generate this ICER of █████ however, the following needs to be assumed:

- Inpatient administration related costs:
 - 11.3 days for inotuzumab and 14 days for FLAG chemotherapy are the estimates which produce the approximate midpoint between the ICER of █████ per QALY and the adjustment Pfizer proposed in the response to ACD (█████ per QALY)
- Subsequent therapies:
 - Blinatumomab is the only therapy included in the model in the list of subsequent therapies for which the list price had been used when there was in fact an active PAS. A █████ PAS must be applied to blinatumomab is the estimate which produces the approximate midpoint between the ICER of █████ per QALY and the adjustment Pfizer proposed in the response to ACD (█████ per QALY).^b

The committee's preference was that the number of days of inpatient stay to administer inotuzumab was greater than 1, but less than chemotherapy's (<14). The committee saw written statements from clinical experts in the response to the ACD that suggested there may actually be 0 days of inpatient stay specifically related to administration, including:

"Patients can receive the agent as out patients if they have no other reason for inpatient hospitalisation"

"It can be given in an outpatient setting and most patients do not require hospital admission."

(Clinical expert comments submitted during the consultation on the ACD, 04 July 2017)

Given this, Pfizer believe the committee's preference for number of inpatient day stays would likely fall at the lower end of the stated range (1-14), however NICE's approximation of the committee's ICER requires an assumption of 11.3 days for administration-related inpatient stay. Pfizer propose an estimate that better reflects the committee's preferences and the clinical expert advice: 3 days of administration-related inpatient stay for inotuzumab. This estimate of 3 days, conservative when considering expert comments, allows for some inpatient stay to administer inotuzumab in each cycle of treatment.

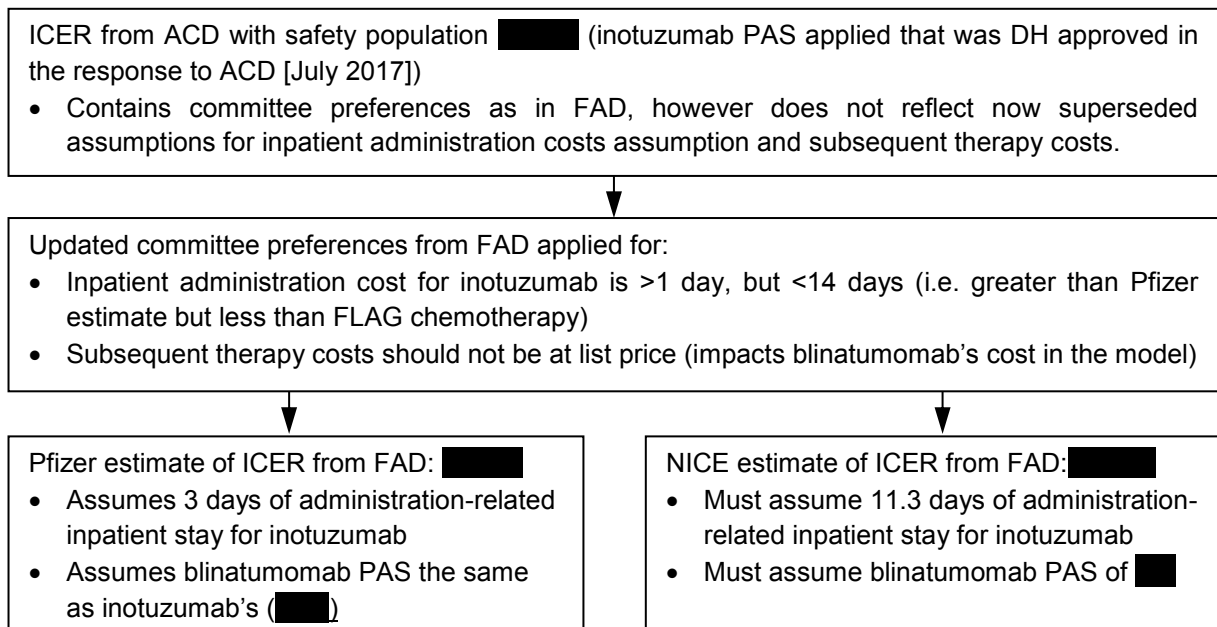
^a Pfizer calculate NICE's equation to produce an ICER of █████, not the █████ estimated in NICE's email. This difference is very small however, so Pfizer have conducted calculations based on NICE's █████.

^b Generic imatinib costs are not included in these ICER estimates

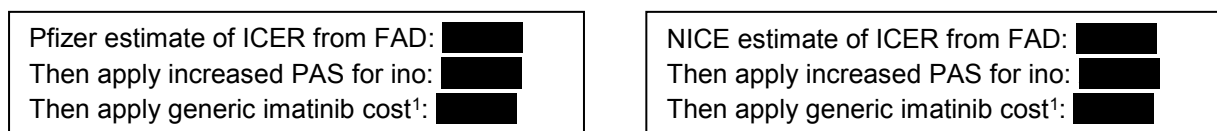
With respect to the inclusion of subsequent therapy costs in the model, the committee preferred list prices not to be used where applicable. In the list of subsequent therapies, there are two which offer a PAS: blinatumomab and inotuzumab (inotuzumab is a subsequent therapy in the chemotherapy arm). The PAS for inotuzumab was already included, meaning blinatumomab the only therapy which had failed to have been costed with its PAS. Pfizer do not know the PAS for blinatumomab. In order to not include the list price so to align with the committee's preferences however, for simplicity, Pfizer have assumed the PAS for blinatumomab is the same as that for inotuzumab.

Pfizer's believe the ICER that best reflects the committee's preferences is one that includes 3 days of administration-related inpatient stay for inotuzumab, plus a PAS for blinatumomab the same as inotuzumab's (previously [REDACTED]). Pfizer disagrees with NICE's approximation of the committee's preferred ICER that uses arbitrary midpoints, as this assumes 11.3 days of administration inpatient stay and a [REDACTED] PAS for blinatumomab. However, for transparency, both approaches are presented in Figure 1.

Figure 1. Pfizer's and NICE's estimate of committee's ICER from FAD (with the [REDACTED] PAS)



In this response, NICE have asked for the generic cost for imatinib to now be included in the model. Also, Pfizer have increased the PAS from [REDACTED] With these, the estimates of ICERs from the FAD now become:



Imatinib was previously costed £973.32 per 100mg 60 tabs, but generic is now £99.99¹

2. Pfizer assumptions that differ from the committee-preferred assumptions in the FAD

(a) how the clinical effectiveness adjustment to the 3 cycles scenario was performed

The Appeal Panel have agreed that it is appropriate that this appraisal for inotuzumab should consider treatment modelled in line with expected practice, i.e. stopped at a maximum of 3 cycles. Previously, in the company's original submission and the response to ACD, a scenario which capped treatment costs at a maximum of 3 cycles was presented to reflect the expected use in practice.

In Pfizer's response dated 2nd February 2018, two scenarios were modelled based on the inclusion of a stopping rule of a maximum 3 cycles of inotuzumab treatment. In the first scenario, efficacy from the trial (in which up to 6 cycles were permitted) is not adjusted. CR/CRi is a typical pre-requisite for HSCT and as all CR/CRi in the trial was achieved within the first 3 cycles, it is plausible to assume the same HSCT rate from the trial would still be observed when treatment is stopped at 3 cycles. In the second scenario, a more conservative approach is modelled which assumes that all patients who had received greater than 3 cycles of inotuzumab in the trial and received a subsequent HSCT (■ of the ■ HSCT patients in the inotuzumab arm) would instead never have reached HSCT under a 3 cycle treatment stopping rule. To model this scenario, the proportion of patients that reach the model's post-HSCT state in the inotuzumab arm is reduced, decreasing inotuzumab's average OS in the model and increasing the ICER (Table 1).

Table 1. Adjustment to transplant rate in the inotuzumab arm in the model

	Original model	New scenario
No CR/CRi	■	■
CR/CRi & no HSCT	■	■
HSCT	■	■

The Gompertz survival curve that is used to estimate OS in the *post-HSCT* state in the model, in the inotuzumab arm, is based on the survival data from all ■ patients from the trial who received inotuzumab and reached a subsequent HSCT; this included the ■ patients who received more than 3 cycles of inotuzumab prior to their HSCT. The new scenario impacts the proportion of patients reaching the *post-HSCT* state, but does not remove these ■ patients' data from the survival distributions that inform the *post-HSCT* state. Including these ■ patients' survival in the distributions to which the *post-HSCT* Gompertz distribution is fitted is not expected to bias inotuzumab. Survival post-HSCT is driven by the success of HSCT and, as previously discussed by the committee, the potential for prior induction treatment to influence post-HSCT outcomes as a result of the level of residual disease (the rate of MRD-negativity). In the inotuzumab arm, 99% of MRD-negativity was achieved within the first 3 cycles of treatment; hence, removing the post-HSCT survival data of the ■ patients that treated beyond 3 cycles will not impact the rate of MRD-negativity, and so should not impact survival post-HSCT.

(b) a detailed explanation and justification of how the long term survival was estimated

The appeal decision document recommended the committee to consider and explain the differences in assumptions post-cure point in this appraisal compared to previously published guidance on blinatumomab.⁵ As set out in Pfizer's response dated 2nd February 2018, there are no differences expected in the patient experience into the longer term (beyond the cure-point) driven by the induction therapy received several years before, pre-HSCT.

Long term survival

In Pfizer's response to NICE dated 2nd February 2018, ICERs were presented for an "additive" approach, which was accepted by NICE in the appraisal of blinatumomab (TA450). This approach was described in Pfizer's response to the ACD:

"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." (*Company response to ACD, 04 July 2017*)

In the appraisal for blinatumomab (TA450, company submission, section 5.3.2.2²), because the long term Gompertz distributions asymptotically approach zero, it was assumed that the hazard rates for OS (i.e. the gradient in the Gompertz) reflected disease-specific mortality. This hazard rate was then "added" to the general population survival distributions to create distributions for long term survival that were lower than the general population's. Likewise, in the inotuzumab model, the distribution used in the post-HSCT state to determine long term survival is the Gompertz, and it also asymptotically approaches zero. This "additive" approach in the appraisal for blinatumomab was validated by comparing with matched patients from *Study 20120310*, which was a retrospective pooled analysis of historical data available from 1990 to 2013 for 1139 adult patients with R/R Ph- B-cell ALL. Although the outcomes from this study are redacted and not available to Pfizer, they have previously been used to validate this "additive" approach and this validation was submitted to NICE, and accepted, in TA450.

Pfizer agree that it is plausible to use an elevated risk of mortality beyond the cure point, but as there are no expected differences in the patient experience related to induction treatment the previously accepted "additive" approach should be used. However, for transparency and comparison, ICERs are presented in this document that include the estimates the committee previously had presented to them. These other estimates previously considered were:

- 4x elevated mortality risk above general population post-cure point (ERG report)
- 2.5x elevated mortality risk above general population post-cure (company response to ACD) – midway between that accepted for blinatumomab TA450 and the current committee preference

The additive approach was validated in TA450 using *Study 20120310*, a study which can be considered a more up-to-date and relevant source of evidence than the Martin (2010)³ study (upon which the committee's preferences are currently based). Issues with using Martin include that the cohort dates back to patients transplanted around 50 years ago, the cohort is a mix of autologous and allogeneic transplant (not reflecting current practice), and the cohort included >10 different malignancies of which ALL patients were only 16%. Using the 4x mortality rate from Martin (the committee's current preference) is further conservative when considering that the model estimates 70% of patients are still alive at 20 years, from those alive at 5 years post-HSCT, whereas Martin estimate the survival rate in patients without recurred disease at 5 years to be 80.4%. Using the 2.5x mortality rate in the model produces an 80% survival rate alive at 20 years, from those alive at 5 years post-HSCT, better aligning with Martin's 20 year rates.

Utility

In Pfizer's response to NICE dated 2nd February 2018, ICERs were presented where the same post-cure point utility accepted in the appraisal of blinatumomab was applied (TA450).² The assumption applied is that all patients, regardless of disease status or prior induction therapy, return to the utility of the general population if they are alive past the cure-point. ICERs including the post-cure utility from TA450 are presented, along with estimates previously considered by the committee, for transparency:

- Accepted in TA450: Apply general population utility for all patients post cure-point
- 0.74/0.76 utility for patients disease-free, but 0.3 for progressed disease post cure-point
- General population utility for disease-free, but 0.3 for progressed disease post cure-point – midway between that accepted for blinatumomab TA450 and the current committee preference

Summary

The step-by-step ICER changes are presented below in Table 2 using Pfizer's estimate of the committee's preferred ICER from the FAD, and in Table 3 using NICE's estimate of the committee's preferred ICER from the FAD. As noted in the FAD, the probabilistic ICERs are expected to be approximately £2,000 per QALY higher than the deterministic presented below.

Table 2. Step-by-step ICER change using Pfizer's estimate of the committee's ICER from FAD

Pfizer's estimate of ICER from FAD (■■■ PAS): ■■■			
Increased PAS applied of ■■■ (March 2017) and updated cost of imatinib: ■■■			
Treatment stopped at 3 cycles			
No efficacy adjustment: £54,730		Efficacy adjusted and reduced (new data): £56,728	
<ul style="list-style-type: none"> • 4x increased risk of mortality • Utility does not return to normal for disease-free patients 		<ul style="list-style-type: none"> • 4x increased risk of mortality • Utility does not return to normal for disease-free patients 	
Utility and OS accepted in blinatumomab appraisal TA450: £33,649	Middle ground utility and OS, between TA450 and ID893 FAD: £46,150	Utility and OS accepted in blinatumomab appraisal TA450: £35,472	Middle ground utility and OS, between TA450 and ID893 FAD: £47,421
<ul style="list-style-type: none"> • Additive approach to increased risk of mortality • Normal utility for all patients past cure point 	<ul style="list-style-type: none"> • 2.5x increased risk of mortality • Normal utility <i>only</i> for disease free patients 	<ul style="list-style-type: none"> • Additive approach to increased risk of mortality • Normal utility for all patients past cure point 	<ul style="list-style-type: none"> • 2.5x increased risk of mortality • Normal utility <i>only</i> for disease free patients

Table 3. Step-by-step ICER change using NICE's estimate of the committee's ICER from FAD

NICE's estimate of ICER from FAD (■■■ PAS): ■■■			
Increased PAS applied of ■■■ (March 2017) and updated cost of imatinib: ■■■			
Treatment stopped at 3 cycles			
No efficacy adjustment: £61,835		Efficacy adjusted and reduced (new data): £64,457	
<ul style="list-style-type: none"> • 4x increased risk of mortality • Utility does not return to normal for disease-free patients 		<ul style="list-style-type: none"> • 4x increased risk of mortality • Utility does not return to normal for disease-free patients 	
Utility and OS accepted in blinatumomab appraisal TA450: £38,030	Middle ground utility and OS, between TA450 and ID893 FAD: £52,148	Utility and OS accepted in blinatumomab appraisal TA450: £39,273	Middle ground utility and OS, between TA450 and ID893 FAD: £54,320
<ul style="list-style-type: none"> • Additive approach to increased risk of mortality • Normal utility for all patients past cure point 	<ul style="list-style-type: none"> • 2.5x increased risk of mortality • Normal utility <i>only</i> for disease free patients 	<ul style="list-style-type: none"> • Additive approach to increased risk of mortality • Normal utility for all patients past cure point 	<ul style="list-style-type: none"> • 2.5x increased risk of mortality • Normal utility <i>only</i> for disease free patients

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

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Date completed 19/04/2018

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 26th March 2018. The company post-appeal response consisted of an 8 page document and an updated model. The company post-appeal response seeks to emulate the Committee most plausible ICER by making the Committee's suggested adjustments to the preferred ICER from the FAD. The company also propose alternative set of adjustments that produce a lower ICER. The response provides new information on the number of patients in the INO-VATE 1022 trial who received more than three cycles of inotuzumab before proceeding to HSCT and an updated PAS. Finally, the company post-appeal response includes a new alternative modelling approach for mortality and a new proposed efficacy adjustment in a scenario where treatment is restricted to a maximum of three cycles of inotuzumab.

This report consists of:

1. A commentary on the company post-appeal response
2. Verification of the numbers provided in the company response

2 ERG commentary on the post appeal response

2.1 The Committee's preferred ICER

The final appraisal determination was that inotuzumab was not recommended within its marketing authorisation. An appeal was lodged on the grounds that NICE had failed to act fairly (Ground 1a) and that the recommendation was unreasonable in the light of the evidence submitted to NICE (Ground 2).

Section 3.23 of the FAD describes the Committee's most plausible ICER for decision making. The Committee's most plausible ICER was composed of the Committee's preferred assumptions (Section 3.16 of the FAD) with further amendments to the cost of subsequent therapies and the number of inpatient days required for administration of inotuzumab. The Committee also recalled that the company had presented ICERs based on a deterministic analysis instead of the preferred probabilistic analysis, which they anticipated to increase the ICER by £2,000.

The recommendation was based on an ICER that cannot be identified precisely. Using the Committee's preferred assumptions and the original PAS consisting of a [REDACTED], the ICER for inotuzumab compared to standard of care was [REDACTED]. The Committee previously saw the ICER with the cost of subsequent therapies included based on list price, [REDACTED], however they believed this to be underestimated noting that a confidential PAS is in place for blinatumomab and that generic imatinib is available. The Committee's preferred assumptions included the ERG's application of NHS reference costs for administration of inotuzumab or standard of care, which implies a weighted

average of 9.47 days stay. In response to the ACD the company presented a revised base case with one day stay assumed for only the first inpatient administration in the first cycle for inotuzumab and zero inpatient admissions thereafter, and with 14 days stay for standard of care (■■■■). The Committee indicated that this ICER was underestimated and that the number of inpatient days for patients admitted while receiving inotuzumab could be higher than one, but fewer than that required for administration of standard of care (FAD Section 3.22).

As a starting point for the post appeal considerations the company were provided with an approximate midpoint ICER of ■■■■ estimated by NICE based on the following calculation ■■■■. This midpoint ICER of ■■■■ was intended to reflect alterations to the cost of subsequent therapies and alterations to the number of inpatient days for patients who received inotuzumab on an inpatient basis.

While the ICER that informed the recommendation cannot be identified, it is possible to estimate the impact of altering the assumed PAS for blinatumomab and the number of inpatient days. From including the cost of subsequent therapies at list price, the adjustment to generic price of imatinib (£99.99) instead of the price for the brand name drug Gleevec (£973.73) increases the ICER from ■■■■ by ■■■■ to ■■■■. The extent of the PAS for blinatumomab is confidential but for every 10% increase in the assumed PAS for blinatumomab, the ICER increases from ■■■■ by ■■■■.

There is no evidence concerning the length of stay for those patients in INO-VATE 1022 who received inotuzumab as an inpatient. In the absence of any evidence the ERG used NHS Reference cost information.

" The company base case calculates the cost per inpatient day of administration based on the NHS Reference cost for an elective inpatient "Acute Lymphoblastic Leukaemia with CC score 0-1", which is associated with a cost of £3,651 for an average length of stay of 4.91 days. The ERG notes that there are costs available for higher complication and comorbidity scores: "Acute Lymphoblastic Leukaemia with CC score 2-4" costing £5,060 for an average length of stay 7.26 and "Acute Lymphoblastic Leukaemia with CC score 5+" costing £12,685 for an average length of stay 19.02.(27) By taking a weighted average across all CC score categories, the ERG calculated a weighted average administration cost of £6,543 and a weighted average length of stay of 9.5 days, giving a cost per bed day of £691. In the ERGs preferred base case the length of stay is kept consistent with the source of the cost per bed day by basing both on the NHS reference cost data."

(ERG report p117-118)

The ERG considered it appropriate to apply inpatient costs to all cycles of inotuzumab that were administered on an inpatient basis in INO-VATE 1022. Starting from the NHS reference cost

weighted average length of stay of 9.47 days, every one day reduction in the length of stay for administration of inotuzumab reduces the ICER from [REDACTED].

2.2 The appeal points

The appeal points upheld in light of the Committee's decision to not recommend inotuzumab were:

Ground 1a.3 Pfizer: The committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for post-HSCT period and submitted in response to the consultation.

Ground 2.1 Leukaemia CARE and joint appellant: An incorrect assumption on the number of cycles of inotuzumab ozogamicin.

Ground 2.1 Pfizer: The appraisal committee's reasons for disregarding key assumptions used for the purposes of the NICE blinatumomab appraisal did not explain the choices made in relation to inotuzumab.

2.2.1 Ground 1a.3 Pfizer

"The committee has provided no explanation for its decision to reject the utilities proposed in the revised Pfizer base case for post-HSCT period and submitted in response to the consultation."

The post appeal response contains no new evidence relating to the utilities in the post-HSCT period. The Committee have previously seen and discussed the use of the general population utilities versus the use of utilities from a published study by Kurosawa et al for patients after HSCT, and noted in the FAD Section 3.20 that the utilities from Kurosawa are preferred. A brief history of the evidence already seen and discussed is provided.

Original submission

The company original submission included a systematic review of health related quality of life values. The studies picked up in the review included the blinatumomab submission to the Scottish Medicines Consortium (SMC). In their base case the company presented utilities for the post-HSCT health state taken from a study comparing allogeneic haematopoietic cell transplant (allo-HCT) versus chemotherapy in acute myeloid leukaemia (company submission Section 5.4.5, page 213). In a scenario analysis the company applied the same utilities as had been used in the economic analysis accompanying the blinatumomab submission to the SMC (company submission Section 5.8.3, page 253), which correspond to general population utilities after the cure point. The ERG commended the company for their systematic literature review and preferred the company base case in which utility

values were based on a published study. The ERG did not believe that the use of these utilities was conservative:

"....existing epidemiological data indicates that surviving HSCT patients continue to experience higher mortality and morbidity for a sustained period, relative to the general population."

(ERG report Section 5.2.7, page 95)

Response to ACD

In response to the ACD the company noted that, during the course of the appraisal, final guidance had been issued for blinatumomab which was recommended by NICE. The company submitted a revised base case and an amended model that applied normal population utilities for disease free patients post HSCT (company response to ACD, Table 7, page 9). The ERG did not find any reason to accept this revision and preferred to retain utility values from a relevant published study.

Post appeal response

In the post appeal response the company again present two sets of results, one with the post-HSCT utilities based on Kurosawa, and one in which the utility post-HSCT is assumed to return to normal population values for disease free patients.

2.2.2 Ground 2.1 Leukaemia CARE and joint appellant

"An incorrect assumption on the number of cycles of inotuzumab ozogamicin."

The ERG note that throughout the appraisal for inotuzumab the Committee were aware that the number of cycles of inotuzumab was informed by the INO-VATE 1022 trial on which the company submission was based. A brief history of the evidence already seen and comment on the post appeal response is provided.

Original submission

In the company original base case the number of cycles of inotuzumab was kept consistent with the INO-VATE 1022 trial from which the efficacy was taken. The company noted that the administration of inotuzumab in INO-VATE 1022 was in line with the expected license (company submission Section 4.3, page 71). The company noted that as patients recruited to INO-VATE 1022 were required to be fit for intensive therapy and able to progress to HSCT it was considered that the population of the trial was consistent with what would be expected in a UK patient population (company submission Section 4.5.2, page 87). The INO-VATE 1022 trial was deemed by the clinical

adviser to the ERG (ERG report page 42) and the NICE Committee (FAD Section 3.3) to be broadly applicable to patients seen in NHS practice.

In the INO-VATE 1022 trial protocol, the draft marketing authorisation and the final marketing authorisation, patients can receive **up to** 6 cycles of inotuzumab. The draft marketing authorisation and recommended dosing that was applied in INO-VATE 1022 is as follows:

"For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle can be given if patients have not achieved CR/CRi and minimal residual disease (MRD) negativity after two cycles. Approximately 5-6 weeks is recommended between the last dose and proceeding to HSCT. For patients not proceeding to HSCT, additional cycles of treatment, up to a maximum of 6 cycles, may be administered. Patients who do not achieve CR/CRi within three cycles should discontinue treatment."

The median number of cycles received in INO-VATE 1022 was 3.0, and the mean duration of treatment corresponded to █████ cycles (company submission Section 5.5.2.3, page 230). The cost applied in the company base case model corresponded to the actual number of cycles received by patients in INO-VATE 1022 (company submission Table 63 page 227). The information provided about the proportion of patients by actual number of cycles delivered is repeated here in Table 1, which indicates that █████ of patients received four or more cycles and █████ received six cycles. A scenario analysis was presented in which the cost of inotuzumab was capped at a maximum of three cycles. The ERG report considered that the company base case was appropriate as it was consistent with the draft marketing authorisation and ensured consistency with the source of the efficacy data (ERG report Section 5.2.3 page 68).

Table 1. Number of patients by cycle of inotuzumab administered in INO-VATE 1022.

█████		█████	

Response to ACD

In response to the ACD the company again presented the scenario analysis in which treatment costs for inotuzumab were capped at a maximum of three cycles. The ERG again concluded that it was inappropriate to make costing assumptions that were inconsistent with the efficacy data used in the model (Section 2.6 ERG response to ACD comments page 10).

Post-appeal response

The post appeal response contains new information that [REDACTED] of the 77 patients who proceeded to HSCT in the inotuzumab arm of INOVATE-1022 received more than three cycles of inotuzumab. The ERG is of the opinion that this supports the view that it cannot be assumed that the same efficacy results would have been observed had treatment been capped at three cycles.

The company post appeal response includes a proposed 'efficacy adjustment' to accompany scenarios in which treatment costs are capped at a maximum of three cycles of inotuzumab. The ERG note that any attempt to adjust efficacy based on the amount of treatment patients were observed to receive is fundamentally flawed and breaks randomisation. As such, the ERG believe this analysis is unhelpful and should be disregarded.

The ERG note that the company proposed to make adjustments for only [REDACTED] of the [REDACTED] patients who received more than six cycles of inotuzumab. The analysis presented does not match the company's description that those [REDACTED] patients would never have reached HSCT. The presented 'efficacy adjustment' deletes the [REDACTED] patients from the inotuzumab arm for the purposes of calculating the proportion of patients entering the model in each health state, and fails to reassign them to an alternative outcome such as 'CR/CRi & no HSCT'. Furthermore, as these [REDACTED] patients are not a random selection from the inotuzumab arm of the trial, deleting them from the inotuzumab arm means that any comparison against the proportion of patients entering each health state under standard of care is biased. In addition to introducing bias through breaking randomisation, the company retain the [REDACTED] patients in the survival analysis which forms the basis of extrapolation in the 'HSCT & post HSCT' subgroup of the model. As this extrapolation informs the magnitude of the treatment effect of inotuzumab, which results in a higher proportion of patients reaching HSCT compared to standard of care, this is inappropriate.

2.2.3 Ground 2.1 Pfizer

"The appraisal committee's reasons for disregarding key assumptions used for the purposes of the NICE blinatumomab appraisal did not explain the choices made in relation to inotuzumab."

The post appeal response contains no new evidence that would inform the modelling assumptions. The ERG previously noted in response to the ACD comments that the company comparison to the blinatumomab appraisal is unhelpful as the focus on only two assumptions, namely mortality and utility values after the 'cure point', fails to acknowledge all the reasons why the appraisals differ. The issue of utility values has been addressed under appeal point 1a.3 in Section 2.2.1.

The ERG note that both appraisals make consistent assumptions that mortality is increased after the cure point. The ERG note that the company approach to modelling inotuzumab differs fundamentally from that used for modelling blinatumomab and it is this that prevents mortality after the cure point being estimated using the same method applied in the blinatumomab appraisal.

A brief history of the evidence already seen and commentary on the post appeal response is provided.

Original submission

The company original base case assumed that the mortality risk after the cure point was equivalent to that of the general population. The ERG noted that this assumption did not appear to be supported by the available evidence. The ERG base case included increased mortality after the cure point by using the lowest estimate for the increased relative risk identified in a review of the literature.

"The ERG notes that several clinical studies have more formally assessed the long term survival after allogeneic HSCT which appear to have consistently reported lower long-term survival compared to the general population.

....

In their response, the company highlighted that the studies cited by the ERG were conducted on historical patient cohorts and hence were likely to overestimate the mortality rates in current clinical practice. "

(ERG report page 90-91)

" The ERG considers that there remains significant uncertainty surrounding the longer-term survival of post HSCT patients. For example, the study by Martin et al (2011) concluded that while "mortality rates improve dramatically during the first 5 years after HCT" they "remain four to nine-fold higher than the general population for at least 25 years thereafter". The ERG acknowledges that many of the studies are derived from historic cohorts and hence may over-estimate mortality compared to current practice. However, significant concerns persist regarding the late effects of HSCT and have led to recent initiatives to improve longer term outcomes."

(ERG report page 91-92)

" The extent of the elevated risk is uncertain, but several studies have compared the long-term survival of hematopoietic stem cell transplantation against the general population and against cancer survivors who did not receive HSCT. These studies differ in the sample size, duration of follow up, and the inclusion criteria regarding survival post HSCT. Wingard et

al. included patients that received HSCT between 1980-2003 and has one of the largest cohorts, with a median follow-up of 9 years; they calculate that the relative risk of mortality for ALL 2-year survivors of HSCT remains greater than 10 for up to 15 years post-transplant. The study by Martin et al. included patients that received HSCT between 1970-2002 and has longer follow-up (median 13.1 years); it reports that in 5-year survivors of HSCT mortality remains four to nine-fold higher than the general population for up to 25 years post-transplant. The more recent study by Chow et al. included patients that received HSCT between 1992-2009 and reports increased morbidity and mortality for HSCT survivors both compared to the general population and compared to non-HSCT cancer survivors.

The ERG preferred base case is to use a fourfold higher mortality rate, in line with the lower bound of the range estimated in Martin et al. (2010). The use of the lower bound is conservative, but could mitigate concerns about the historic nature of the cohort required for this type of long-term outcome analysis."

(ERG report page 116)

Response to ACD

In response to the ACD the company presented a revised base case in which mortality risk was elevated after the cure point, but proposed that the elevated mortality risk be reduced from 4 to 2.5 times the general population mortality. The ERG noted that the calculations used to determine the figure of 2.5 lacked a coherent logic and were mathematically incorrect. Furthermore, that the company had in fact implemented differential increased mortality risk according to MRD negativity which introduced an additional treatment effect not seen in the original company submission nor supported by the evidence. The company revised base case in actuality applied an increased mortality risk of 2.5 times general population mortality after the cure point for patients who received standard of care and 1.9 times general population mortality after the cure point for patients who received inotuzumab.

Post appeal response

In the post appeal response the company propose an analysis that they claim matches the "additive approach" used in the blinatumomab appraisal. The company also present again an analysis using an increased mortality risk of 2.5 times the general population mortality after the cure point.

The ERG considers that the "additive approach" used in the blinatumomab submission cannot be replicated in the model structure used in the inotuzumab submission. In the blinatumomab appraisal

survival was extrapolated by fitting parametric curves to each arm of a randomised trial. In the blinatumomab appraisal these survival models were fit to describe mortality in the trial population from a starting point of initiating treatment and with no explicit modelling of response or HSCT. In the inotuzumab appraisal the randomised trial population was first split into three sub populations, including a post randomisation ‘HSCT & post HSCT’ subset which formed the primary basis for extrapolation. The survival model in the 'HSCT & post HSCT' group was fit to describe mortality in the post HSCT period, and hence describes survival after a curative secondary intervention, omits the period from commencement of treatment with inotuzumab, omits patients who failed to reach HSCT.

The company could potentially match the assumptions used in the blinatumomab appraisal by fitting parametric curves to each arm of INO-VATE 1022 trial in its entirety, but such an analysis has never been presented. It is not possible to equate any interpretation of the survival analysis fit to the randomised trial data from TOWER in the appraisal of blinatumomab with the survival analysis fit to a post randomisation post HSCT subset of the INO-VATE 1022 trial. The ERG does not consider the new analyses about the increased risk of mortality after the cure point presented in the post-appeal response to be scientifically sound.

3 ERG estimate of ICERs relating to post appeal submission

The ERG has concerns about the validity of the company’s post appeal economic model. Applying only the changes reported in the post-appeal response document produced different results depending on whether the post ACD or post appeal company model is run. The discrepancy is in part due to additional undocumented changes in the post appeal model that alter the amount of outpatient visits required for administration of inotuzumab and the proportion of inpatient stays to which a cost is applied. The ERG advocates that caution ought to be taken when interpreting the company’s post appeal estimated ICERs.

The ERG has replicated the relevant company analyses using the post ACD model in order to maintain consistency with the numbers the Committee saw in the original submission and in the response to ACD. Table 2 reports the individual impact of the four scenarios that may inform the Committee’s most plausible ICER, and an additional scenario with treatment capped at a maximum of three cycles.

Table 1: Scenario analyses from the unadjusted preferred ACD base case

	Inotuzumab PAS [REDACTED]		Inotuzumab PAS [REDACTED]	
	ICER	Change from unadjusted ICER	ICER	Change from unadjusted ICER
Unadjusted committee preferred assumptions from the FAD	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
1. Including cost of subsequent therapies based on safety population	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
2. Including cost of subsequent therapies assuming a [REDACTED] PAS for blinatumomab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
3. Imatinib costed at its generic price (£99.99)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
4. Inotuzumab and SoC administration-related inpatient visits set to 3 days and 14 days stay respectively	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
5. Maximum number of treatment cycles for inotuzumab set to 3 (no adjustment to efficacy)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Combination without maximum number of treatment cycles cap (1 + 2 + 3 + 4)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Combination with maximum number of treatment cycles cap (1 + 2 + 3 + 4 + 5)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The ERG has also estimated the impact of changes to the price of imatinib and to the maximum number of treatment cycles from a starting point of the approximate midpoint ICER of █████ estimated by NICE. This midpoint ICER is intended to already reflect adjustments to the price of blinatumomab and the length of inpatient stay for administration of inotuzumab.

Table 3 shows the result of the analysis using the post ACD model. The company suggest that this midpoint can be reached from the unadjusted ICER of █████ by setting the blinatumomab PAS to █████ and the length of stay for any inpatient admission during administration of inotuzumab to 11.3 days (with 14 days stay for stadard of care inpatient admissions). However, in the post ACD model these settings produce an ICER of █████. In the post ACD model the midpoint ICER can be reached by various combinations of assumed blinatumomab PAS and adjustment to the length of stay for inpatient admissions during administration of inotuzumab. For example, █████ blinatumomab PAS combined with 3.87 days, or █████ blinatumomab PAS combined with 4.84 days, or █████ blinatumomab PAS combined with 5.81 days.

Table 2: Scenario analyses from the NICE adjusted ACD base case

	Inotuzumab PAS █████		Inotuzumab PAS █████	
	ICER	Change from adjusted ICER	ICER	Change from adjusted ICER
Approximate midpoint ICER	█████	█████	█████	█████
1. Imatinib costed at its generic price (£99.99)	█████	█████	█████	█████
2. Maximum number of treatment cycles for inotuzumab set to 3 (no adjustment to efficacy)	█████	█████	█████	█████
Scenario combination (1 + 2)	█████	█████	█████	█████

