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

3rd Appraisal Committee meeting (post-appeal)

Committee C

ERG: Centre for Reviews and Dissemination and Centre for Health Economics, University of York

NICE technical team: Victoria Kelly and Sally Doss

26th April 2018

Public observer slides – contains no ACIC

Background

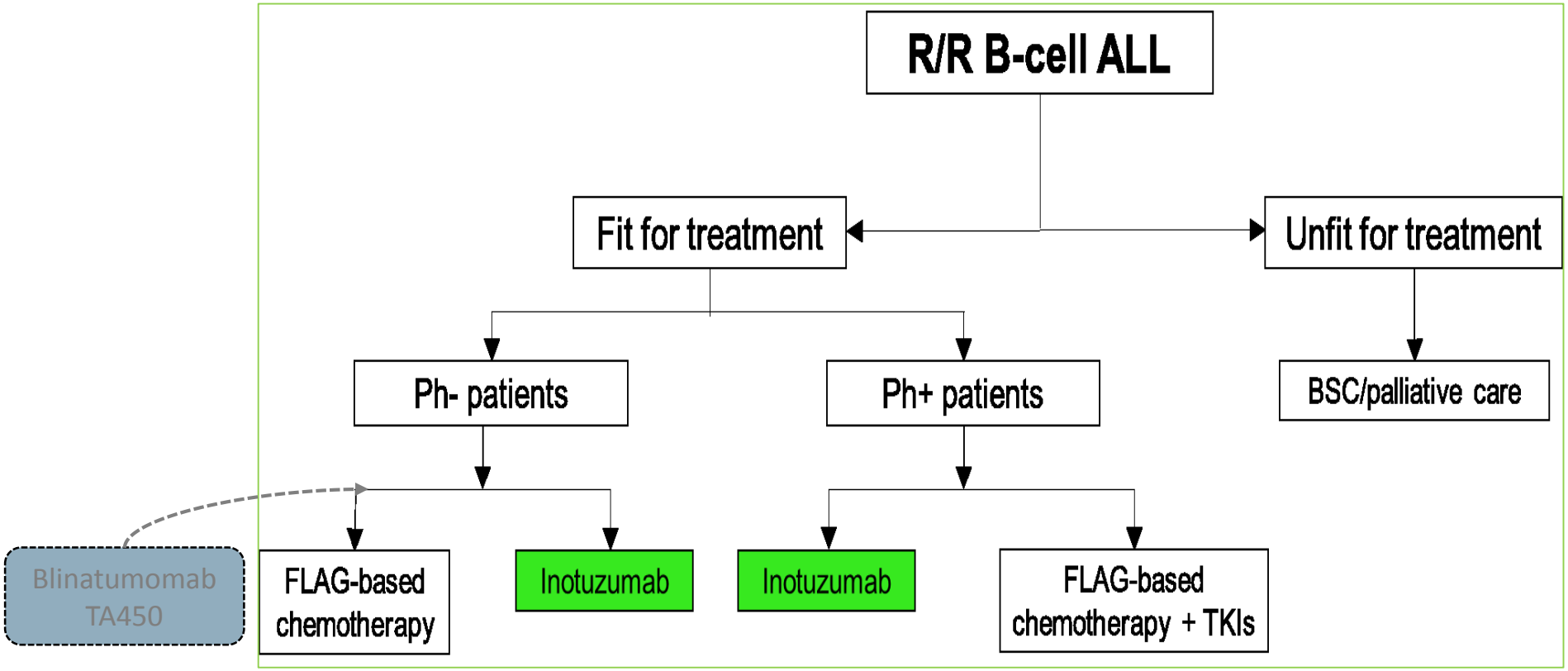
Appraisal Timeline

- 1st appraisal committee meeting: 16th May 2017
  - negative preliminary recommendation
- 2nd appraisal committee meeting: 12th July 2017
  - negative recommendation
- Appeal panel meeting: 3rd November 2017
  - upheld 3 appeal points
- 3rd appraisal committee meeting: today

Inotuzumab ozogamicin, Pfizer

Marketing authorisation (30 June 2017)	Monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia chromosome positive (Ph+) relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor.
Administration & dose	Intravenous infusion at a starting dose of 1.8 mg/m^2 per cycle (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15). Cycle 1 lasts for 21 days, and each subsequent cycle lasts for 28 days. Once a patient is in complete remission, or complete remission with incomplete haematological recovery, the dose on day 1 of each cycle is reduced to 0.5 mg/m^2 for the duration of treatment.
Mechanism of action	Inotuzumab ozogamicin is an antibody-drug conjugate of a monoclonal antibody.
Cost	Solution for infusion: £8,048 per 1-mg vial, confidential patient access scheme approved (simple discount) Over the course of treatment, it is estimated that an average of [redacted] vials will be administered: [redacted]

Company: proposed placement of inotuzumab



Key: ALL, acute lymphoblastic leukaemia; BSC, best supportive care; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; Ph-, Philadelphia chromosome negative; Ph+ Philadelphia chromosome positive; R/R, relapsed or refractory; TKIs, tyrosine kinase inhibitors.

Committee’s preferred assumptions in FAD

Issue	Committee's conclusion
Clinical effectiveness	Does not increase OS but increases rate of HSCT (based on INO-VATE 1022 [n=326] open-label, phase III, RCT) (FAD 3.4)
Utilities	INO-VATE 1022 pooled values and adjusted for age: 3–5 years post HSCT utilities = 0.74; post 5 years = 0.76; 0.3 for progressed disease. (FAD 3.10 & 3.16)
“Cure-point”	4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond (FAD 3.9 & 3.16)
Cost of subsequent therapies	Can be based on safety population, but the use of list prices is not appropriate. The cost is between the ERG’s estimate and the company's estimate (FAD 3.21).
Inpatient days	The value is between the ERG’s estimate of 9.5 & 9.5 and the company's estimate of 1 & 14 days (FAD 3.22).
Most plausible ICER	> £50,000 per QALY gained (FAD 3.23)
EOL	Meets both criteria for end-of-life (FAD 3.24)

FAD appeal panel decisions

Summary of upheld FAD appeal panel points and actions for committee (1)

Ground 1: **In making the assessment that preceded the recommendation, NICE has a) Failed to act fairly:**

- Appeal 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 appraisal committee must now take all reasonable steps to explain clearly its decision to reject utilities proposed by Pfizer in response to the ACD*

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE:

- Appeal ground 2.1 (Pfizer): The appraisal committee's reasons for disregarding key assumptions used for the purposes of the NICE blinotumumab appraisal did not explain the choices made in relation to inotuzumab

    - *The appraisal committee must now take all reasonable steps to consider and explain the differences in assumptions post cure point made in this appraisal explicitly compared to previously published guidance on blinatumomab*

Summary of upheld FAD appeal panel points and actions for committee (2)

- Appeal ground 2.1 (Leukaemia CARE and joint appellants - Royal College of Pathologists, Royal College of Physicians and the Association of Cancer Physicians): An incorrect assumption on the number of cycles of inotuzumab ozogamicin.
  - *The appraisal committee must now take all reasonable steps to reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional third, if needed, and a costing model based on appropriate stopping rules may be considered*

- **All other appeal points were dismissed**

From paragraphs 94-96 of appeal decision

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. Paras 47-49 of the appeal decision conclusions include:

- The appeal panel feels that that it is not incumbent on any NICE technology appraisal committee to accept or use the assumptions of another technology appraisal committee and indeed the committees have the freedom (and the duty) to individually come to independent conclusions. However, in the rare instance where the patient population to which the technology is applied exactly the same (not just similar), and where the treatment under consideration has no direct impact on the assumptions used, then it is incumbent on the later appraisal committee to explicitly clarify why they have chosen assumptions different from assumptions used (and accepted) for the same population by a previous committee. This is particularly the case where the treatment under consideration has no direct impact on the assumptions used.
- This appeal ground 1a.3 was also heard with 2.2 (Pfizer): ***The Committee has seemingly misunderstood the utilities submitted by Pfizer in response to consultation on the ACD***. The appeal panel was satisfied that the appraisal committee had clearly understood the utilities submitted by Pfizer in relation to the consultation on ACD'...the appeal panel therefore dismissed appeal point 2.2. However the appraisal committee will now have to consider which utility values to use and give a reason for that choice, and the panel can express no view as to the rationality of that future decision.

Committee consideration of post-HSCT utility values in the FAD

- Company originally submitted post-HSCT utilities from Kurosawa et al. (2016):
  - 0.74 (3–5 years post-HSCT) and
  - 0.76 (5 years post-HSCT)
- In response to the ACD company preferred to use utility of the general population (0.88). It cited the blinatumomab appraisal were the NICE committee accepted that patients who pass the cure point post-HSCT can expect a return to the utility of the normal population
- ERG, in its response to the company's ACD comments, could not find any reference to committee discussion of this issue in the FAD for blinatumomab.
- Committee preferred assumption (from section 3.20 of FAD): ".. *The ERG noted that the utility values used in the company's original base case post-cure (0.74 and 0.76) were based on a relevant published study (Kurosawa et al. 2016) and are preferable to the new assumption, which is not supported by evidence… The committee concluded ……. utilities from Kurosawa et al. 2016 for disease-free patients are its preferred assumptions"*

Post-HSCT utility values: ERG comments

ERG report and report addendum in response to ACD comments:

- ERG consider the use of utility values based on a published study: Kurosawa et al. (2016), more appropriate and do not consider the values to be 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)

Ground 2.1, Pfizer

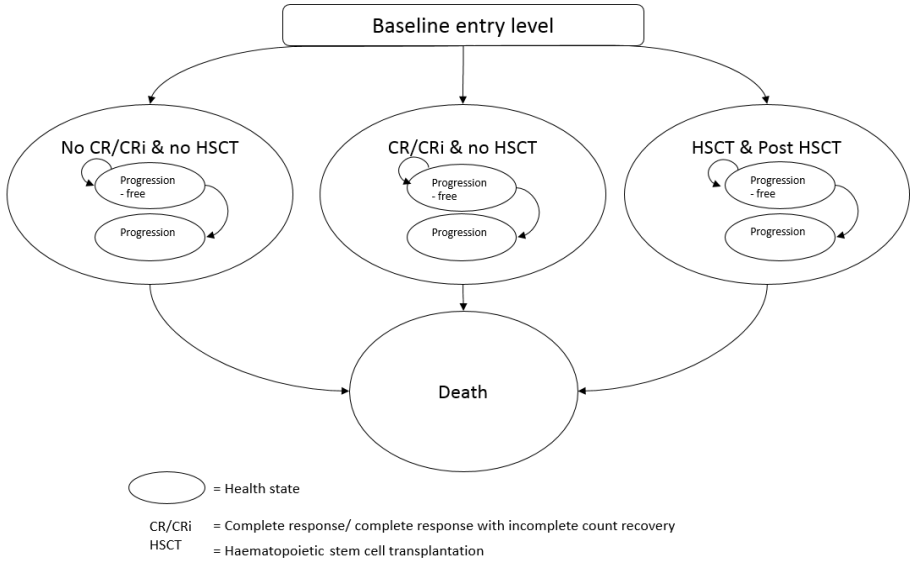
- **The appraisal committee's reasons for disregarding key assumptions used for the purposes of the NICE blinatumomab appraisal do not explain the choices that were made in relation to inotuzumab:**
  - The panel was clear that there is a good explanation of differences up to the "cure" point but it was unclear why there were different assumptions after the "cure" point. The panel felt that it was important for the appraisal committee to have considered and explained the differences in assumptions post "cure" point explicitly. The panel cannot say that such an explanation does not exist nor that it would necessarily be unreasonable when given its conclusion is simply that this aspect of the appraisal is presently unsupported by relevant reasons and so is unreasonable.
  - The appeal panel felt that scenario post the point of cure needs to be clarified, the assumptions discussed and a case made clearly for the assumption chosen (similar or different as may the case be from other appraisals).
  - *The appraisal committee must now take all reasonable steps to consider and explain the differences in assumptions post cure point made in this appraisal explicitly compared to previously published guidance on blinatumomab*

Overview of blinatumomab and inotuzumab appraisals

	Inotuzumab ID893	Blinatumomab TA450
EMA license	29th June 2017 (under additional monitoring) • orphan designation	23rd November 2015 (under additional monitoring) • orphan designation • conditional approval
Marketing authorisation	R/R B-Cell ALL	R/R B-Cell ALL Philadelphia-chromosome-negative only
Appraisal committee meeting (ACM) 1	16th May 2017 • ACD: no	9th March 2017 • FAD: yes
FAD meeting	12th July 2017 (not recommended)	Recommended; guidance published 28th June 2017
Clinical effectiveness	No difference in OS, but increases HSCT rate (see slide 6)	Increased OS vs SOC (HR 0.71; 95% CI 0.55 to 0.93)*
Most plausible ICER	>£50,000 per QALY gained	£49,190 per QALY gained
EOL met?	Yes, both criteria	Yes, both criteria

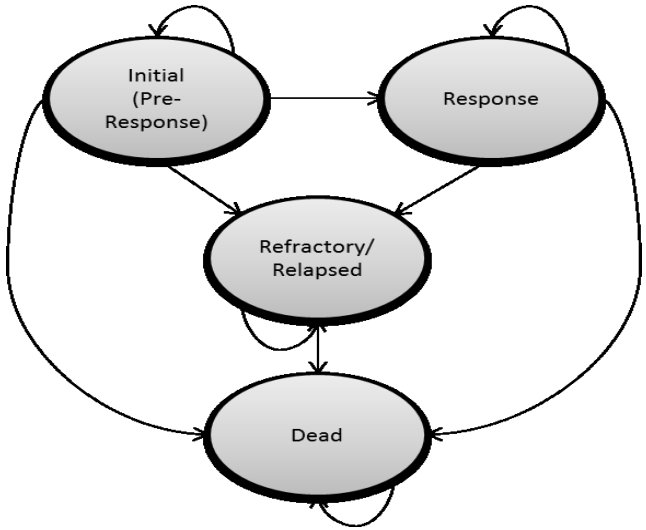
***From TA450: The committee concluded that blinatumomab is clinically effective in improving overall survival compared with standard care in the short term, but there is uncertainty about the long-term overall survival benefit**

Overview of blinatumomab and inotuzumab company models



Inotuzumab model:

- Three partitioned survival models with 8 health states
- Each model: sub states for progression free and progressed disease
- PFS and OS modelled using covariates (safety population)



Blinatumomab model:

- partitioned survival model which captures the difference in area between OS and EFS survival curves
- patients enter in “initial” state and remain for 12 weeks (unless they die).
- After 12 weeks either the “refractory/relapsed” state or “response” state

Committee consideration of cure points and long term survival in the FAD (1)

- **Cure points**:
  - Blinatumomab (from TA guidance 450) “The committee concluded that the company's assumption of patients being cured at 48 months (4-years) was potentially a conservative estimate.”
  - Inotuzumab (from FAD section 3.9) “It agreed that the company’s time point of 3 years is plausible for decision-making but that other time points may be also suitable”.
- **Survival post-cure**:
  - Blinatumomab (from company submission and ERG report – not included in the FAD). Mortality after 4 years is equal to the sum of parametric distributions fit to trial data and UK general population mortality rates
  - Inotuzumab (from FAD section 3.20) “The committee agreed with the ERG and recalled that assuming a 4-fold increase in mortality for patients from 3 years after HSCT is at the lower end of the range in Martin et al. 2010”

Committee consideration of cure points and long term survival in the FAD (2)

Committee preferred (from FAD sections 3.9 and 3.20)	Company's preferred assumption (post appeal)
Mortality risk is: • 4x elevated mortality risk above general population post-cure *(from Martin et al. 2010. which estimates mortality risk from a cohort in the United States who underwent transplants between 1980 and 2002)*	Mortality risk is: • "additive approach" which is post-cure point assumptions are aligned with those previously approved by NICE (ie. Assumes general population mortality)

- Company's justification for its assumptions:
  - 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).
  - Issues with using Martin et al 2010 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%.

Committee consideration of cure points and long term survival in the FAD: ERG comments

From ERG response post appeal pages 10-11

- ERG notes that the company comparison to the blinatumomab appraisal is unhelpful as the focus on assumptions after the 'cure point', fails to acknowledge all the reasons why the appraisals differ:
  - In the blinatumomab appraisal survival was extrapolated by fitting parametric curves to each arm of a randomised trial
  - 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
- ERG consider it is possible for the company to match the assumptions used in the blinatumomab appraisal by fitting parametric curves to each arm of INOVATE-1022 trial, but this has not been presented
- Not possible to equate any interpretation of 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 INOVATE-1022 trial.

Ground 2.1, Leukaemia CARE and joint appellant*

An incorrect assumption on the number of cycles of inotuzumab ozogamicin:

- …..Not all of the committee's reasons for not having considered this group of patients at length "added up". The fact that the use case was raised late in the day was unfortunate, but the significance of the scenario was such that if more time was needed to consider it then that time should be found. The suggestion that it was difficult to identify transplant eligible patients in advance was difficult to sustain in the light of Professor Marks' comments (and indeed this caused the appeal panel some concern under appeal ground 1a.2 above, although it was content that the correct approach was to deal with this defect under rationality rather than unfairness). The panel could see no reason why appropriate and simple to implement stopping rules could not be devised. The panel was not in a position to say whether the concern that the trial data did not support use as a bridge to transplant only was reasonable, because the committee's stated reasons on the point were so telegraphic.
- The appeal panel felt it was not reasonable to fail to consider properly and rigorously a model of treatment which is the norm in UK practice. Whether following such consideration it will be possible to make a recommendation for use will be a matter for the appraisal committee. (para 89 and 91 of appeal decision)
- *The appraisal committee must now take all reasonable steps to reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional third, if needed, and a costing model based on appropriate stopping rules may be considered*

**Royal College of Pathologists, Royal College of Physicians and the Association of Cancer Physicians*

Inotuzumab: Summary of product characteristics

- For patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients who do not achieve a complete remission (CR) or complete remission with incomplete haematological recovery (CRi) and minimal residual disease (MRD) negativity after 2 cycles.

- 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 a CR/CRi within 3 cycles should discontinue treatment.

Committee consideration of inotuzumab treatment cycles in the FAD

- Most plausible ICER included up to 6 cycles of treatment with inotuzumab in line with the trial data submitted by the company
- Company did present a 3-cycle treatment scenario in its original submission

	INO-VATE-1022	MAX 3 cycles scenario
MEAN	[redacted]	[redacted]
MEDIAN	[redacted]	[redacted]
IQR	[redacted]	[redacted]
Range	[redacted]	[redacted]
Average number of vials	[redacted]	[redacted]

Calculations based on table 63 of company submission

Committee consideration of inotuzumab treatment cycles in the FAD (2)

- Following the appeal the company have submitted the following scenarios:

1. Unadjusted scenario (Company preferred: costs capped after 3-cycles no adjustment to trial data):
   - CR/CRi is a pre-requisite for HSCT and all CR/CRi was achieved within 3 cycles: it is plausible to assume that same HSCT rate would be observed when treatment is stopped at 3 cycles.
2. Adjusted scenario:
   - assumes that patients with >3 cycles of inotuzumab and subsequent HSCT ([redacted] of the [redacted] HSCT patients) would not reach HSCT.
   - the [redacted] patients are removed from calculating proportion of patients reaching the noCR/CRi, CR/CRi and post-HSCT states, but included when estimating survival distributions in the post-HSCT state.

Committee consideration of inotuzumab treatment cycles in the FAD: ERG comments

- In response to the ACD, the ERG noted that that it was inappropriate to make costing assumptions that were inconsistent with the efficacy data used in the model.
- Any attempt to adjust efficacy based on the amount of treatment patients were observed to receive is fundamentally flawed and breaks randomisation:
  - The ‘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 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.

Company's post appeal new evidence and updated model assumptions

Company's post appeal new evidence (1)

- Most plausible ICER considered by the committee was [redacted] per QALY but this did not include adjustments to:
  - **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 is too low, and that it is likely that there is a difference in the number of inpatient days for inotuzumab 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)*
- To account for these 2 assumptions the midpoint should be used between Pfizer's estimates in its ACD response and [redacted] per QALY.
- This equates to a midpoint ICER of approximately [redacted] per QALY gained.

Company's post appeal new evidence(2)

- Company noted that in order to generate the ICER of [redacted] the following assumptions are implied:
  - Inpatient administration related costs are:
    - 11.3 days for inotuzumab and
    - 14 days for FLAG chemotherapy
  - Subsequent therapies:
    - Assumes a blinatumomab PAS discount
- Company in its post appeal submission want the committee to consider:
  - Post cure point mortality (additive approach) and utility values in line with blinatumomab
  - 3 cycles of treatment (unadjusted trial data)
  - 3 inpatient stays for inotuzumab and 14 for FLAG
  - Inclusion of subsequent treatment costs
  - An increased PAS discount

Company's post appeal new evidence: ERG comments

- 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 markedly different results depending on which 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.
- Therefore the ERG advocates that extreme caution ought to be taken when interpreting the company's post appeal estimates of cost-effectiveness.
- The ERG's scenario analyses use the company's post ACD model.

Company's preferred assumptions post appeal

<table>
<tr><td colspan="4">Company's new ICER with increased PAS = [redacted] This includes:
• Committee's preferred mortality & utilities assumptions
• 3 INO & 14 FLAG inpatients days
• cost of generic imatinib & assuming a PAS for blinatumomab</td></tr>
<tr><td colspan="4">Treatment stopped at 3 cycles</td></tr>
<tr><td colspan="2">No efficacy adjustment:
£54,730</td><td colspan="2">Efficacy adjustment:
£56,728</td></tr>
<tr><td colspan="4">Company scenario analyses based on the appeal points</td></tr>
<tr><td>Company preferred ICER: utility and mortality as in TA450 (blinatumomab):
£33,649

• Additive approach to increased risk of mortality
• Normal utility for all patients past cure point</td><td>Middle ground between TA450 and inotuzumab FAD:
£46,150

• 2.5x increased risk of mortality
• Normal utility only for disease free patients</td><td>Utility and mortality as in TA450 (blinatumomab):
£35,472

• Additive approach to increased risk of mortality
• Normal utility for all patients past cure point</td><td>Middle ground between TA450 and inotuzumab FAD:
£47,421

• 2.5x increased risk of mortality
• Normal utility only for disease free patients</td></tr>
</table>

Company's post appeal scenario analyses – using midpoint ICER assumptions for inpatient days

<table>
<tr><td colspan="4">NICE's estimate of ICER from FAD (old PAS): [redacted] This assumes:
• Committee's preferred mortality & utilities assumptions from the FAD
• 11.3 INO & 14 FLAG inpatients days
• Cost of branded imatinib & assuming a PAS for blinatumomab</td></tr>
<tr><td colspan="4">Increased inotuzumab PAS and generic cost of imatinib: [redacted]</td></tr>
<tr><td colspan="4">Treatment stopped at 3 cycles</td></tr>
<tr><td colspan="2">No efficacy adjustment:
£61,835</td><td colspan="2">Efficacy adjusted and reduced:
£64,457</td></tr>
<tr><td colspan="4">Company scenario analyses based on the appeal points</td></tr>
<tr><td>Utility and mortality as in TA450 (blinatumomab):

£38,030

• Additive approach to increased risk of mortality
• Normal utility for all patients past cure point</td><td>Middle ground between TA450 and inotuzumab FAD:
£52,148

• 2.5x increased risk of mortality
• Normal utility only for disease free patients</td><td>Utility and mortality as in TA450 (blinatumomab):

£39,273

• Additive approach to increased risk of mortality
• Normal utility for all patients past cure point</td><td>Middle ground between TA450 and inotuzumab FAD:
£54,320

• 2.5x increased risk of mortality
• Normal utility only for disease free patients</td></tr>
</table>

ERG scenario analyses using company's post ACD model

	Inotuzumab old PAS		Inotuzumab new PAS	
	ICER	Change	ICER	Change
Committee preferred assumptions from the FAD	[redacted]	[redacted]	[redacted]	[redacted]
1. Cost of subsequent therapies based on safety population	[redacted]	[redacted]	[redacted]	[redacted]
2. Cost of subsequent therapies assuming a PAS for blinatumomab*	[redacted]	[redacted]	[redacted]	[redacted]
3. Generic imatinib (£99.99)	[redacted]	[redacted]	[redacted]	[redacted]
4. Inotuzumab and SoC inpatient visits set to 3 days and 14 days	[redacted]	[redacted]	[redacted]	[redacted]
5. Max treatment cycles for INO set to 3 (no adjustment to efficacy)	[redacted]	[redacted]	[redacted]	[redacted]
No max treatment cycles cap and (1 + 2 + 3 + 4)*	[redacted]	[redacted]	[redacted]	[redacted]
With 3 max treatment cycles and (1 + 2 + 3 + 4 + 5)*	[redacted]	[redacted]	[redacted]	[redacted]

*results using actual Blinatumomab PAS presented in Part 2

ERG scenario analyses from the NICE adjusted ACD base case

- ERG has also estimated the impact of changes to the price of imatinib and to the maximum number of treatment cycles using the midpoint ICER of [redacted].
- ERG note that 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.

	Inotuzumab old PAS		Inotuzumab new PAS	
	ICER	Change	ICER	Change
Approximate midpoint ICER	[redacted]		[redacted]	
1. Generic imatinib (£99.99)	[redacted]	[redacted]	[redacted]	[redacted]
2. 3 Max cycles for INO (no adjustment to efficacy)	[redacted]	[redacted]	[redacted]	[redacted]
Scenario combination (1 + 2)	[redacted]	[redacted]	[redacted]	[redacted]

Key issues for discussion

- Appeal point 1a.3 Pfizer
  - Committee must now take all reasonable steps to clearly explain its decision to reject utilities proposed by Pfizer in response to the ACD
- Appeal point 2.1 Pfizer
  - Committee must now take all reasonable steps to consider and explain the differences in assumptions post cure point made in this appraisal explicitly compared to previously published guidance on blinatumomab
- Appeal point 2.1 Leukaemia CARE and joint appellant
  - Committee must now take all reasonable steps to reconsider inotuzumab in the context of the UK practice of 2 cycles plus an additional third, if needed, and a costing model based on appropriate stopping rules may be considered
- Company's post appeal new evidence and updated model assumptions:
  - What is the committee view of the company's approach to the cost of subsequent therapy?
  - Inpatient days: what is the committee view of the company's new 3 INO/14 FLAG ratio?
- What is the most plausible ICER?