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

4th Appraisal Committee meeting (post ACD2 consultation)

Committee C

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

NICE technical team: Victoria Kelly and Sally Doss

27th June 2018

Slides for public

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 – 3 upheld appeal points:
  - 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
  - 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
  - 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.
- 3rd appraisal committee meeting: 26th April 2017
  - Minded no; committee requested new analyses from company

Inotuzumab ozogamicin, Pfizer

Marketing authorisation received on 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 (TKI).
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. When inotuzumab ozogamicin binds to a CD22 antigen on a B-cell, it is absorbed into a malignant cell and leads to cell death.
Cost	Solution for infusion: £8,048 per 1-mg vial (there is a confidential PAS) Over the course of treatment, it is estimated that an average of [redacted] vials will be administered.

ACD 2: minded no recommendation

- Unable to make recommendations on inotuzumab ozogamicin as an option for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults.
- Further analyses requested from the company, which should include a revised cost-effectiveness analysis comparing inotuzumab ozogamicin with standard care, including the committee's preferred assumptions in the company's model:
  a) utility values for all patients 5 years post-haematopoietic stem cell transplant (HSCT) between 0.76 and 0.88
  b) A 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond
  c) the same number of treatment cycles for inotuzumab ozogamicin as given in INNO-VATE 1022 (up to 6 cycles)
  d) the cost of subsequent therapy from the safety population using the generic price for imatinib and the list price for blinatumomab
  e) using robust clinical data to inform the number of inpatient days for inotuzumab and standard chemotherapy (usually FLAG).

ACD 2 consultation

- Consultee comments from:
  - Company
  - National Cancer Research Institute – Association of Cancer Physicians – Royal College of Physicians (NCRI-ACP-RCP; joint response)
  - Adele Fielding – Clinical Expert, nominated by Royal College of Pathologists
  - David Marks – Clinical Expert, nominated by Royal College of Pathologists
  - Leukaemia care

ACD 2 consultation comments (I)

Adele Fielding (Clinical expert):

- Length of hospital stay: 9.5 days for both treatments is not reflective of clinical practice – *This was first raised before the appeal and again at ACM3 - clinical experts submitted unpublished data for this meeting to support increasing the average inpatient stay in the model for SOC*
- Number of treatment cycles for inotuzumab should be capped at 3:
  - 6 cycles would never be used in clinical practice
  - SPC recommends no more than 3 cycles for HSCT
  - Majority of patients in INO-VATE 1022 received no more than 3 cycles

David Marks (Clinical expert):

- 5-year post HSCT utility: “the fairest number to adopt is a midway point of 0.82”
- Mortality post cure using data from Martin et al (4-fold increase) is inappropriate. The data is out of date and not reflective of current transplant practice such as less chronic GVHD and better prevention of infection. At the previous committee I suggested a 3-fold increase was more appropriate.
- Disagrees with not capping the number of treatment cycles for inotuzumab as it is not reflective of clinical practice

ACD 2 consultation comments (II)

NCRI-ACP-RCP:

- The clinical community would support the use of inotuzumab only as a bridge to transplant and only to a maximum of 3 cycles.
- 9.5 inpatient days for both inotuzumab and standard of care is incorrect and not reflective of clinical practice

Leukaemia care:

- Cap inotuzumab treatment costs at 3 cycles to reflect clinical practice
- ACD does not clearly address the rationale for differences between this appraisal and TA450 blinatumomab:
  - 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).

Company's response to consultation

- Updated a systematic literature review (SLR) to identify additional evidence on inpatient days in UK clinical practice
- Amended the adverse event costs in the model
- Provided Kaplan-Meier data to compare OS from the IO arm of INO-VATE 1022 between patients who had 3 cycles vs 4+ cycles.
- Company updated model to include committee preferred assumptions using clinical expert unpublished data to inform the number of inpatient days
- Company also included 4 scenario analyses:
  - Using median inpatient days for inotuzumab from clinical expert data
  - Removing double counting of adverse events
  - Capping treatment costs at 3 cycles
  - Using clinical expert data to inform treatment cost (average [redacted] cycles for IO)

How the company model calculates administration costs

% of patients who received inotuzumab per cycle from INNO-VATE 1022	
Cycle 1	[redacted]
Cycle 2	[redacted]
Cycle 3	[redacted]
Cycle 4	[redacted]
Cycle 5	[redacted]
Cycle 6	[redacted]
Average administrations required	[redacted]

- The model calculates an administration cost based on the number of cycles delivered as an inpatient or outpatient.
- All SoC is delivered as an inpatient

Breakdown of patient treatment setting per cycle from INNO-VATE 1022

	Inpatient %	Outpatient %
Cycle 1	[redacted]	[redacted]
Cycle 2	[redacted]	[redacted]
Cycle 3	[redacted]	[redacted]
Cycle 4	[redacted]	[redacted]
Cycle 5	[redacted]	[redacted]
Cycle 6	[redacted]	[redacted]
Total	[redacted]	[redacted]

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

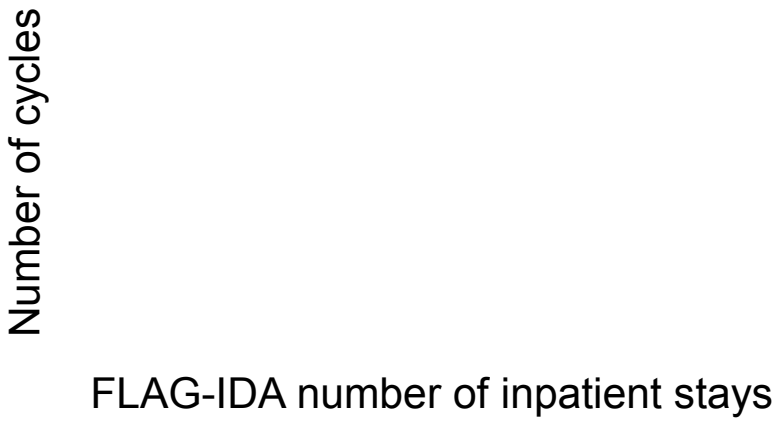
New evidence: Clinical expert data (1)

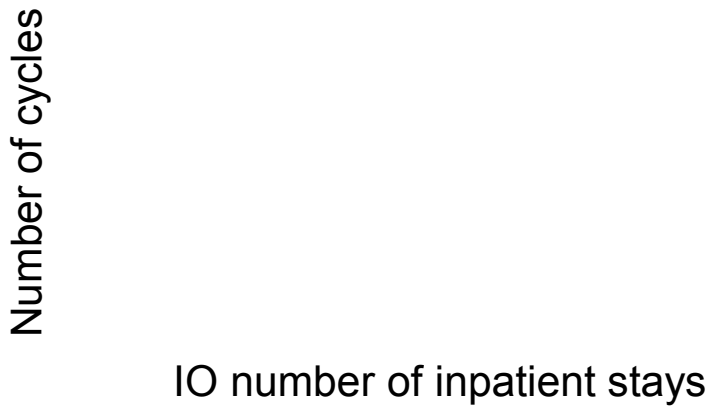
- Unpublished data taken from IO compassionate use program used at UCLH and Bristol Jul 2016-2017 (IO treated patients approximately [redacted]

Patient characteristics		[redacted]	[redacted]
Gender	Male	[redacted]	[redacted]
	Female	[redacted]	[redacted]
Age	Median	[redacted]	[redacted]
	Average	[redacted]	[redacted]
Disease status	Primary refractory	[redacted]	[redacted]
	Relapse	[redacted]	[redacted]
	Unknown	[redacted]	[redacted]
Number of previous lines of treatment	Zero	[redacted]	[redacted]
	One	[redacted]	[redacted]
	Two	[redacted]	[redacted]
	Three	[redacted]	[redacted]
	Four	[redacted]	[redacted]
Previous allograft	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]

New evidence: Clinical expert data (2)

	[redacted]	[redacted]
Mean days admitted:	[redacted]	[redacted]
Median days admitted:	[redacted]	[redacted]
Range:	[redacted]	[redacted]
Mode:	[redacted]	[redacted]
Total inpatient days:	[redacted]	[redacted]
Number of cycles:	[redacted]	[redacted]





ERG comments: Inpatient days

- Inotuzumab is less expensive in terms of inpatient admissions compared with standard of care as a proportion of cycles can be delivered on an outpatient basis
- The question of whether there are further cost savings from a reduction in the length of stay among patients who are admitted with inotuzumab compared with SOC has remained uncertain - *the cost-effectiveness results are very sensitive to the assumed difference in length of stay per hospitalisation*.
- The real world evidence from the compassionate use programme, submitted by the clinical experts, has a small sample size and data are observational and unadjusted
- Patients are younger than the average patient treated in INO-VATE 1022 (mean of [redacted] years for inotuzumab and [redacted] years for FLAG-IDA vs [redacted] years in INO-VATE 1022).
- [redacted] in the inotuzumab group should be excluded (as they were never admitted) from the calculation therefore average number of inpatient days for inotuzumab is [redacted] Right skewed data is typical of resource use data. The mean is the most appropriate measure as it captures all the administration costs

Company's new evidence: SLR for inpatient days

- Company updated a SLR to establish if there is any new published UK data to inform the number of inpatient days with either inotuzumab or standard of care - **No new UK based evidence found.**
- 1 x Spanish and 1 x French study were previously excluded by company as not UK based
- ERG noted results of these studies in their original report but did not include results in their preferred analyses

Reference	Population	Average length of hospital stay
Boluda 2016	Spanish, n=32,Ph- B-cell ALL, R/R FLAG-Ida	42 inpatient stays in 31 patients. Inpatient stays per patient = 1.4 Average length of hospitalisation = 26 days
Dombret 2016	French, n=32, Ph- B-cell ALL, R/R Chemotherapy	71 inpatient stays in 32 patients. Inpatient stays per patient = 2.2 Average length of hospitalisation = 16.8 days

Company's new evidence: adjustment to AE costs in model

- Model was originally set up costing inpatient days associated with AEs separately from those related to administration
- The new data is for all-cause hospitalisation resulting in double counting of AE hospitalisations which biases against inotuzumab
- AE costs are driven by the cost of treating veno-occlusive disease (VOD) with defibrotide
- The company's model estimated approximately £54,710 in costs per patient related specifically to hospitalisation for VOD
- If these VOD hospitalisation costs are now removed, the ICER reduces

ERG:

- *NICE confirmed with the clinical experts that none of the* [redacted] *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.*

Company's new evidence: treatment cycles

- [redacted]

- Company suggests this analysis shows that a [redacted]
- When cost is capped at 3 cycles, the efficacy associated with inotuzumab need not be adjusted in order to interpret the ICER appropriately.

ERG comments: treatment cycles

- From ACD2 *"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. 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"*
- 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 inotuzumab, with a maximum of 6 cycles
- In the INO-VATE 1022 trial [redacted] of patients received more than three cycles, including [redacted] of those that proceeded to HSCT
- The company argue that [redacted] but patients who received more than 3 cycles of inotuzumab do not represent a random sample of those treated so does not provide any indication of how the estimate of efficacy would be affected by a treatment cap

Company's updated model results

	5-year post HSCT utility 0.88	5-year post HSCT utility 0.76
New basecase: IO and SoC inpatient days set to [redacted] for IO and [redacted] for FLAG *(means)**	£33,749	£37,497
Scenario1*: New basecase, but IO inpatient days set to [redacted] *(median)	[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 using mean treatment duration from clinical expert data for IO ([redacted])**	[redacted]	[redacted]

includes 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond. Up to 6 cycles of IO as given in INNO-VATE 1022 and cost of subsequent therapy from the safety population using the generic price for imatinib and the list price for blinatumomab (results with blinatumomab PAS in part 2).

ERG's updated scenario analyses

- *Results generated using the company's post ACD1 model (ERG noted additional undocumented changes to the company's post ACD2 model which they could not verify)*

	5-year post HSCT utility 0.88	5-year post HSCT utility 0.76
Company's new basecase: IO and SoC inpatient days set to [redacted] for IO and [redacted] for SoC*	[redacted]	[redacted]
ERG Scenario 1: **New base case, but using [redacted] bed days for IO and [redacted] days for SoC**	[redacted]	[redacted]
ERG Scenario 2: **New base case, but using [redacted] bed days for IO and 16.8 bed days for SoC (Dombret et al)**	[redacted]	[redacted]
ERG Scenario 3: **New base case, but using [redacted] bed days per for IO and 26 bed days for SoC (Boluda et al)**	[redacted]	[redacted]

includes 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond. Up to 6 cycles of IO as given in INNO-VATE 1022 and cost of subsequent therapy from the safety population using the generic price for imatinib and the list price for blinatumomab (results with blinatumomab PAS in part 2).

Key issues for discussion

1. Average length of hospitalisation
   - What is the most appropriate average length of hospitalisation to use in the economic model for inpatient treatment with IO and SOC?
2. Number of treatment cycles
   - What is the appropriate number of treatment cycles to use in the economic model
3. AE Costs
   - Is it appropriate to remove VOD hospitalisation costs from the model if using clinical expert data?
4. What is the most plausible ICER?