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

2nd Appraisal Committee meeting

Committee C

Lead team: Mike Chambers, John Hampson and David Chandler

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

NICE technical team: Marcela Haasova and Sally Doss

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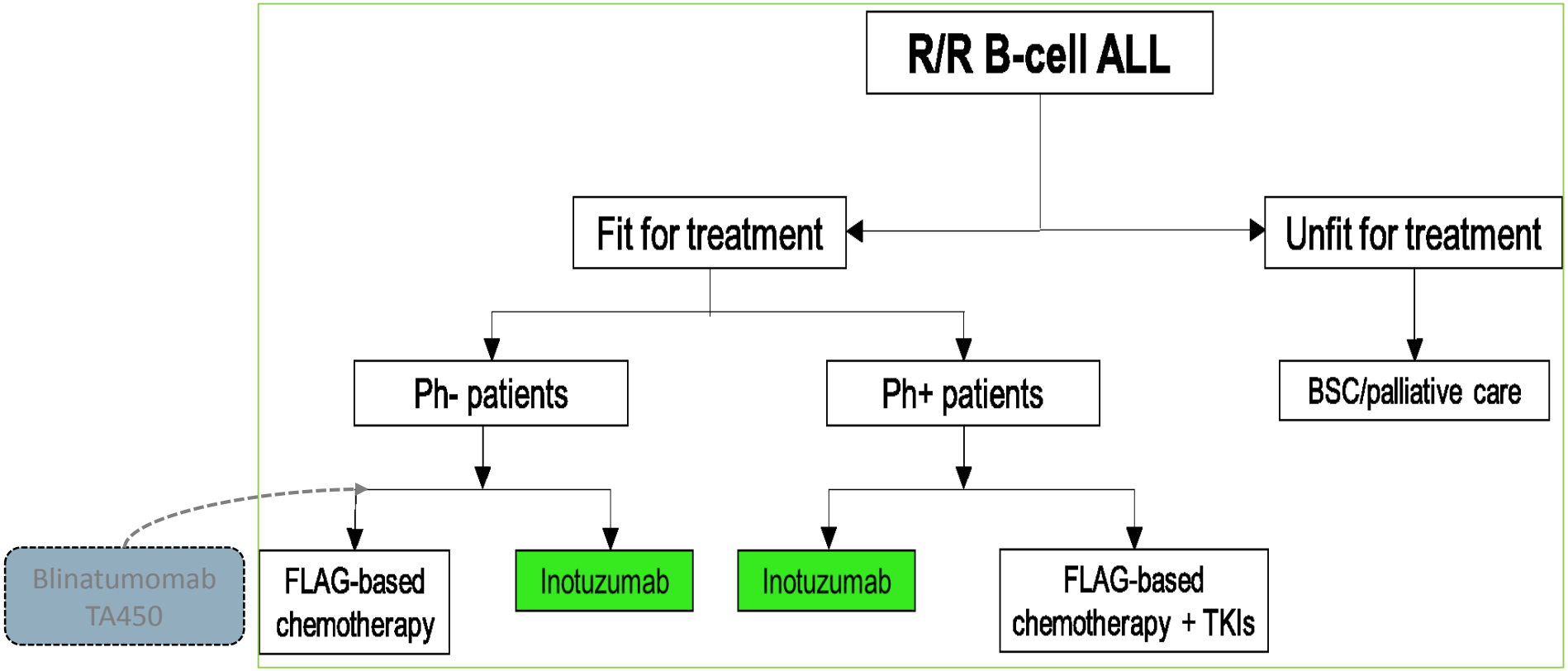
Slides for Public–AiC & CiC redacted

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 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.

ACD: preliminary recommendation

- Inotuzumab ozogamicin is not recommended for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults.
- The evidence on whether inotuzumab ozogamicin increases the overall length of time people live was uncertain. But increasing the number of people who can have a stem cell transplant may increase survival.
- The incremental cost effectiveness ratio (ICER) of inotuzumab ozogamicin compared with current treatment is more than £100,000 per quality-adjusted life year (QALY) gained; higher than acceptable for end-of-life treatments and therefore it was not recommended for routine use in the NHS.

Trial evidence: INO-VATE1022

Design	• Open-label, multicentre phase 3 open-label RCT
Location (sites)	193 sites in 25 countries 8 sites in the UK = 5.2% of enrolled patients; 4 in inotuzumab ozogamicin (inotuzumab) and 5 in standard of care (SoC)
Population	• Adults (18yrs +) with R/R CD22-positive ALL (ECOG 0-2) due to receive either Salvage 1 or Salvage 2 therapy • Patients with Ph+ ALL failed treatment with at least 1 second- or third-generation TKI.
Intervention and comparator	ITT=326: Inotuzumab (n=164) and SoC (n=162) • FLAG based regimen: (63%; 102/162) • Cytarabine plus mitoxantrone: (23%; 38/162) • HIDAC based regimen: (14%; 22/162)
Primary outcome	CR (including CRi) and OS: last follow-up at March 2016 (data cut-off of 37.7 months).
Secondary outcomes	PFS, minimum residual disease (MRD), duration of remission (CR and CRi), rate of subsequent HSCT, EORTC QLQ-C30, EQ-5D, safety

Key: CR, complete remission; CRi, CR with incomplete haematologic recovery; EQ-5D, EuroQoL 5 Dimension questionnaire, FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; HIDAC, high dose cytarabine; HSCT, haematopoietic stem cell transplant; Ph+ Philadelphia chromosome positive; TKI, tyrosine kinase inhibitor.

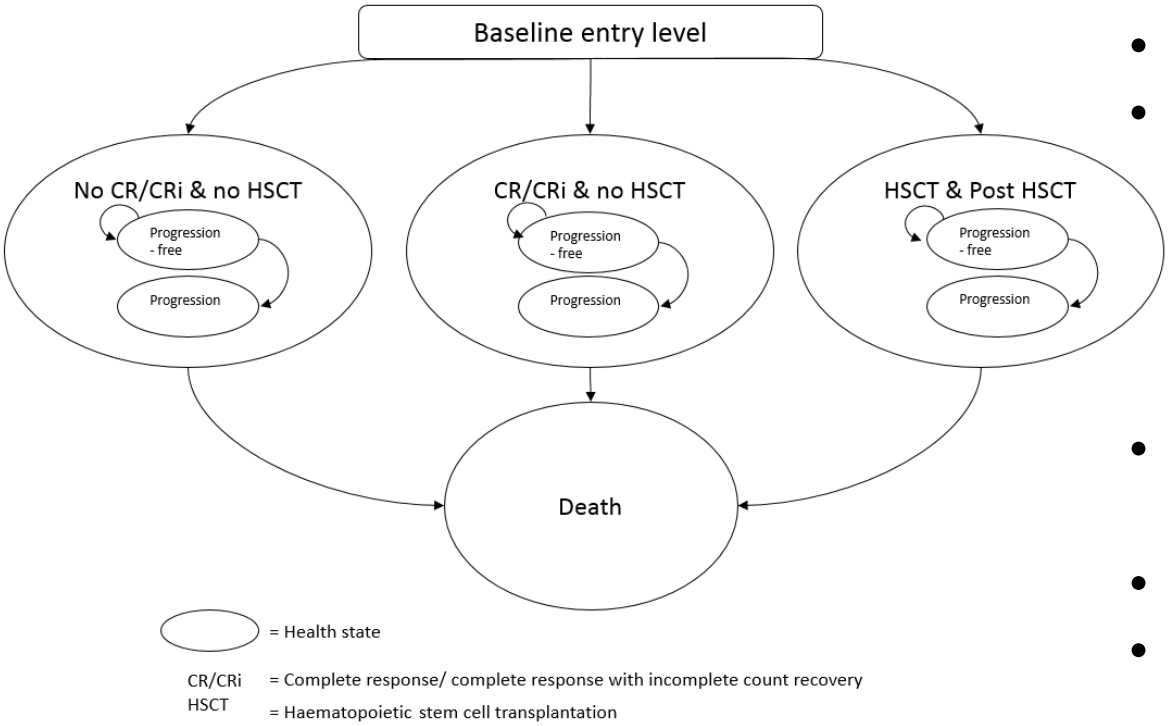
INO-VATE1022: results

ITT population	Inotuzumab N=164	SoC N=162	Rate difference	P-value
CR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
CR/CRi, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Had HSCT, n (%)	[redacted]	[redacted]	-	-
OS: RMST truncation time (months) (95 % CI)				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	7.7 (6.0, 9.2)	6.7 (4.9, 8.3)	-	-
Deaths, n (%)	122 (74.4)	130 (80.2)	-	-
Median PFS, months (95% CI)	5.0 (3.7, 5.6)	1.8 (1.5, 2.2)	-	-

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematologic recovery; RMST, restricted mean survival time; SoC, standard of care.

Company's model

- Three partitioned survival models with 8 health states
- Tunnel states within HSCT & post HSCT represent the wait for HSCT
- Each model: sub states for progression free and progressed disease
- PFS and OS modelled using covariates (safety population)



- UK NHS perspective
- Costs and QALYs discounted at an annual rate of 1.5% (base case) and 3.5% (scenario analyses)
- Cycle = 28 days + half cycle correction
- Lifetime horizon = 60ys
- Starting age = 46 (ITT)

Key: CR, complete response; CRi, complete response with incomplete count recovery; HSCT, haematopoietic stem cell transplant. **Note**: Patients receiving HSCT (after entry to the model) enter the 'HSCT and Post HSCT' partitioned survival sub-model, whether or not they achieve CR or CRi.

ACD: company's base case

Deterministic results

	Costs	QALYs	LYs	Incremental Costs	Incremental QALYs	Incremental LYs	ICER
Costs and benefits discounted at 1.5%							
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£40,013
SoC	[redacted]	[redacted]	1.49				
Costs and benefits discounted at 3.5%							
Inotuzumab	[redacted]	[redacted]	6.66	[redacted]	[redacted]	5.18	£55,869
SoC	[redacted]	[redacted]	1.49				

Probabilistic results

	Incremental Costs	Incremental QALYs	Incremental LYs	ICER
Costs and benefits discounted at 1.5%				
Inotuzumab vs SoC	[redacted]	[redacted]	4.69	£48,459
Costs and benefits discounted at 3.5%				
Inotuzumab vs SoC	[redacted]	[redacted]	4.70	£67,575

Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SoC, standard of care.
Note: results do not include fix provided by company during clarification process.

ACD: ERG analyses (3.5% discount)

Scenario (ERG analysis)	Inc. cost	Inc. QALY	ICER	Change
Company base case (3.5% discount)	[redacted]	[redacted]	£55,869	-
Company corrected base case (1)	[redacted]	[redacted]	**£55,779**	-£90
CS scenario pooled OS with MRD (2)	[redacted]	[redacted]	£77,783	+£21,914
KM OS & pooled post-HST (7a)	[redacted]	[redacted]	£83,060	+£27,191
KM OS & separate post-HST (7b)	[redacted]	[redacted]	*£56,483*	*+£614*
HSCT pts: 4x population mortality (8)	[redacted]	[redacted]	£68,381	+£12,512
Age-adjusted utilities (3)	[redacted]	[redacted]	£60,260	+£4,391
Pooled on-treatment utilities (5)	[redacted]	[redacted]	£55,992	+£123
Chemo as subsequent therapy (6)	[redacted]	[redacted]	£61,594	+£5,725
Imatinib & IDA cost removed (4)	[redacted]	[redacted]	£57,287	+£1,418
Inotuzumab administration cost (9)	[redacted]	[redacted]	£57,804	+£3,165
ERG non-parametric preferred analysis *(1+3+4+5+6+7a+8+9)*	[redacted]	[redacted]	**£122,174**	+£66,305
ERG parametric preferred analysis *(1+2+3+4+5+6+8+9)*	[redacted]	[redacted]	**£114,078**	+£58,299

Key: IDA, idarubicin.

ACD: End of life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Life expectancy for R/R B-cell ALL adult patients is around 3-6 months • Median OS in INO-VATE 1022 for SoC is 6.7 months using the primary OS analysis and 9.9 months for the RMST analysis.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• RMST analysis: inotuzumab significantly extends OS to 13.9 vs. 9.9 months with chemotherapy (37.7 months truncation time); gain of 4-months • Economic model: 1.49 mean life years for SoC and 6.66 for inotuzumab; gain > 3-months • Although the survival benefits of inotuzumab are subject to high uncertainty, it is likely that by increasing the rate of HSCT, inotuzumab will increase the mean survival for patients with R/R B cell ALL by more than 3 months. The committee concluded that both the life expectancy and life extension criteria were met.

Key: OS, overall survival; RMST, Restricted mean survival time ; SoC, standard of care.

ACD: committee's preferred assumptions

Issue	Committee's conclusion
Discount rate	3.5% cost and QALYs discount rate
OS data	ERG's pooled OS and minimal residual disease status as a covariate fitted to *HSCT & Post-HSCT* is preferred
"cure point"	Assumption of the "cure point" at 3 years not appropriate: mortality improves after HSCT, but remains 4-9 times higher compared with general population
Utilities	• INO-VATE 1022: pooled values more appropriate • *HSCT & Post-HSCT*: should be adjusted for age
Costs	• Inotuzumab administration based on INOV-ATE 1022 • 9.5 inpatient days • Chemotherapy as subsequent therapies • Including idarubicin and imatinib costs not appropriate
ICER	>£100,000 per QALY gained

ACD consultation responses

- Consultee comments from:
  - Company
  - Leukaemia CARE
  - 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

- No comments
  - Department of Health

ACD consultation comments (I)

- Clinical expert

Disappointed with this decision on behalf of patients as this agent has merit for the therapy and that has been adequately demonstrated

Concerns regarding fairness: why inotuzumab was not recommended when blinatumomab was.

Concerns regarding modelling: consultees noted differences in modelling assumptions between blinatumomab and inotuzumab ozogamicin.

- Leukaemia CARE

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

ACD consultation comments (II)

- *NCRI-ACP-RCP*

'Our experts highlight the need for novel therapies in TYA ALL patients who relapse. …The overall survival in patients who relapse on treatment is only 7% at 5 years, even though many of these patients received FLAG-Ida and an allogeneic haemopoietic stem cell transplant. This highlights the urgent need for agents such as Inotuzumab for these patients, with which patients are likely to achieve a deeper remission (ie MRD negative remission) prior to curative consolidation with an allograft or to allow entry into CAR T cell trials. Whilst the TYA group are no more important than older patients, should they achieve cure they will be expected to have a longer, healthy life subsequently. Our experts question whether this was taken into account in the cost effectiveness analysis.'

Key: TYA, teenage and young adult.

	Blinatumomab Amgen (TA450)	Inotuzumab ozogamicin Pfizer
MA	Adults with Philadelphia-chromosome-negative relapsed or refractory B-precursor ALL	Adults with R/R CD22-positive B-cell precursor ALL; adult patients with Ph+ R/R B-cell precursor ALL should have failed treatment with at least 1 TKI.
Mechanism of action	A T-cell engager antibody targeting CD19 and the CD3/T-cell receptor. When blinatumomab binds to both the cancer cell and T-cell, the T-cell is recruited and activated to destroy the cancer cell	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.
OS	OS in TOWER: • Blinatunomab: **7.7m** (95% CI 5.6-9.6) and SoC: **4.0m** (95% CI 2.9-5.3)	OS in INO-VATE1022: • Inotuzumab 7.7m (95% CI 6.0-9.2) and SoC: 6.7m (95% CI 4.9-8.3) • RMST analysis: **13.9m** inotuzumab and **9.9m** SoC($p<0.05$)

Key: ALL, acute lymphoblastic leukaemia; Ph+ Philadelphia chromosome positive; R/R, relapsed or refractory; TKIs, tyrosine kinase inhibitors RMST, restricted mean survival time; SoC, standard of care.
Note: Statistical significant difference highlighted in bold.

Company's ACD response and new evidence

Issue	Committee's conclusion
Discount rate	3.5% cost and QALY's discount rate ✓
OS data	**Original analysis used: Separate parametric curves fitted to KM data post-HSCT**
"cure point"	**A new increased mortality risk added and general population utilities used post "cure" as in TA450**
Utilities	• INO-VATE 1022: pooled values more appropriate ✓ • *HSCT & Post-HSCT*: should be adjusted for age ✓
Costs	**New assumptions for calculation of inpatient days for inotuzumab and FLAG, and cost of subsequent therapies based on safety population (not ITT)** • Including IDA and imatinib costs not appropriate ✓
ICERs	with proposed PAS of [redacted] (PAS submitted to DH)

Note: ✓ denotes where the company have new evidence including committee-preferred assumptions; text in bold (and no ✓) denotes where the company have presented a difference from committee-preferred assumptions.

Company's new evidence revised base-case

- Company have submitted a proposed confidential discount PAS to the DH
- Includes some changes preferred by committee:
  - 3.5% discount rate for costs and QALYs
  - Age-adjusted utilities
  - Pooled on-treatment utilities
  - Imatinib & idarubicin cost removed
- Changes not accepted:
  - Modelling OS post-HST: reverted to original base-case
  - Long term survival: mortality risk is 2.5x general population for the standard of care, and 1.9x for inotuzumab (equates to mortality risk 3.0x general population for MRD+ and 1.6x for MRD- patients)
  - Cost of subsequent therapy: based on safety population
  - Inpatient days: 1 & 14 days for inotuzumab & FLAG respectively
- Additional changes to model:
  - Use of general population utilities post "cure" for people without progressed disease.

Company: modelling OS post-HST

Company's original base-case	Committee preferred base-case	Company's revised base- case and scenario
Separate parametric curves fit to KM data for survival post-HSCT	Pooled OS data post-HSCT, but allow covariate MRD to drive differences in curves via covariate analysis with other covariates kept in	Parametric curves fitted to KM data for survival post-HSCT + Scenario: Assume same survival post-HSCT but allow only a covariate for MRD-negativity

- The committee's preferred base-case inconsistent with TA450.
- Company's revised base-case: the original base-case modelling is used
- Scenario analysis: MRD-negativity is the only driver of differences in survival and modelled data fit the observed KM better.

ERG critique

- No new information presented and the original analysis was rejected at ACM1. Post-HSCT data are based on a small, post-randomisation sub-population and methods attributing all survival gains to treatment received are inappropriate.
- Scenario analysis: any analysis based on this sub-population is highly uncertain, but one that adjusts for a greater number of observed confounders is preferable to one that adjusts only for rates of MRD negativity.

Company: cure point and long term survival

Company's original base-case	Committee preferred base-case	Company's revised base-case and scenario
Mortality risk equal to the general population	Mortality risk is 4x the general population for all patients (Martin et al. 2011)	Mortality risk is 2.5x general population for SOC & 1.9x for INO (equates to 3.0x general population for MRD+ & 1.6x for MRD-)

- Martin et al. 2011: estimates mortality risk from a cohort in the United States who underwent transplants between 1980 and 2002, however survival probability from 1987-2002 to 2003-2006 had almost doubled
- Company's revised base-case: 2.5-fold risk of mortality above the general population as more relevant than the historic 4-fold risk (noting this is still not reflective of 2017) and is considered to be a conservative approach

ERG critique

- The choice of new references and the new analyses are flawed.
- Addition of a new treatment effect on survival by differentiating the risk of mortality post "cure" according to MRD negativity is not supported by evidence.

Company: cost of subsequent therapy

Company's original base case	Committee preferred base-case	Company's revised base case
Include both cost and efficacy of subsequent therapies using ITT population	Replace cost of innovative therapies with cost of chemotherapy due to unknown use of innovative therapies in safety population	Include both cost and efficacy of subsequent therapies as applicable to safety population

- Company's revised base-case: includes the cost of subsequent therapy from the safety population.
  - including or excluding the additional [redacted] patients in the model has minimal impact on the ICER in the revised base case.

ERG critique

- It is appropriate to include the costs of subsequent therapy in the safety population as observed in the trial, but
  - if inotuzumab used it is changing the appraisal to sequencing decision
- However, the use of list prices will substantially overestimate the costs of these subsequent therapies to the NHS and underestimate the resulting ICER.

Company: administration cost

Company's original base case	Committee preferred base-case	Company's revised base case and scenario
• Inotuzumab: 0 inpatient days • FLAG: 6.2 days inpatient stay	• Inotuzumab and FLAG: 9.5 inpatients stay	• Inotuzumab: 1 inpatient day • FLAG:14 days inpatient stay + Scenario: 3 cycles of inotuzumab

- Company's revised base-case: guidance from company's clinical experts informed the revised base-case (considered to be a conservative estimate)
  - "Several weeks" of inpatient stay common for some patients on FLAG
  - INO-VATE administration cost is inaccurate: e.g. including hospitalisation due to underlying disease, comorbid conditions and AEs
- Scenario: all patients with CR/CRi & MRD negativity achieved it in first 3 cycles

ERG critique

- No new information has been presented. No explanation or justification for the differential length of stay was provided.
- Scenario: did all patients with CR/CRi and/or HSCT have no more than 3 cycles? [redacted]. The scenario is not consistent with the efficacy data.

Company: post ”cure” utilities

Company’s original base-case	Committee preferred base-case	Company’s revised base-case
Post HSCT: • 3–5 years’ post=0.74 • >5 years post=0.76		General population=0.88

- Company's revised base-case: general population utilities used as they were accepted in TA450

ERG critique

- The original utility values based on a relevant published study are preferable to this new assumption which lacks supporting evidence.

Company: new evidence and analyses

Revised Pfizer base case assumption with PAS		ICER	ERG check*
Committee preferred base-case with PAS (ERG analysis)		[redacted]	[redacted]
(1) OS post-HST	(i) original company base: KM OS post-HST		
	(ii) New assumption: same OS post-HST but only MRD-negativity is covariate	[redacted]	[redacted]
(2) post-cure point survival	New assumption: Mortality risk 3.0x general population for MRD+ and 1.6x for MRD-	[redacted]	[redacted]
(3) Cost of subsequent therapy	New assumption: Include both cost and efficacy from safety population	[redacted]	[redacted]
(4) Administration costs	New assumption: INO 1st administration in 1st cycle & FLAG 14 days inpatient stay	[redacted]	[redacted]
(5) post-cure utilities	New assumption: normal population utilities for disease-free	[redacted]	[redacted]
Revised base-case	**1(i) + 2 + 3 + 4 + 5**	[redacted]	[redacted]
Revised base-case	**Probabilistic ICER**		-
	Scenario analyses		
Base-case and 1(ii)	1(ii) + 2 + 3 + 4 + 5	[redacted]	[redacted]
Base-case & 3 cycles	1(i) + 2 + 3 + 4 + 5 & max 3 cycles of INO		
ERG & 2 + 3 + 4 + 5	2 + 3 + 4 + 5		
	ERG scenarios		
ERG & FLAG 26 days	26 & 9.5 inpatient days for FLAG & INO		-

Key: * company results using the rate of subsequent therapies from the safety population, for completeness the values were updated based on ITT as was the original base-case.

Key issues for discussion

1. OS data modelling in *HSCT & Post-HSCT*
   - Is the new company's scenario analysis more plausible than committee preferred OS modelling in *HSCT & Post-HSCT* OS?
2. Long-term mortality and utilities
   - What is the mortality risk post-HSCT?
   - What is the committee view of the use of normal population utilities for disease-free patients post "cure point"?
3. Costs
   - What is the number of inpatient days for inotuzumab and FLAG?
   - Is the use of safety population to model subsequent therapies appropriate?
4. End of life criteria, innovation and equality issues.
5. What is the most plausible ICER?