For public – CiC and AiC information redacted

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

1st Appraisal Committee meeting

Cost effectiveness

Committee C

Lead team: Mike Chambers

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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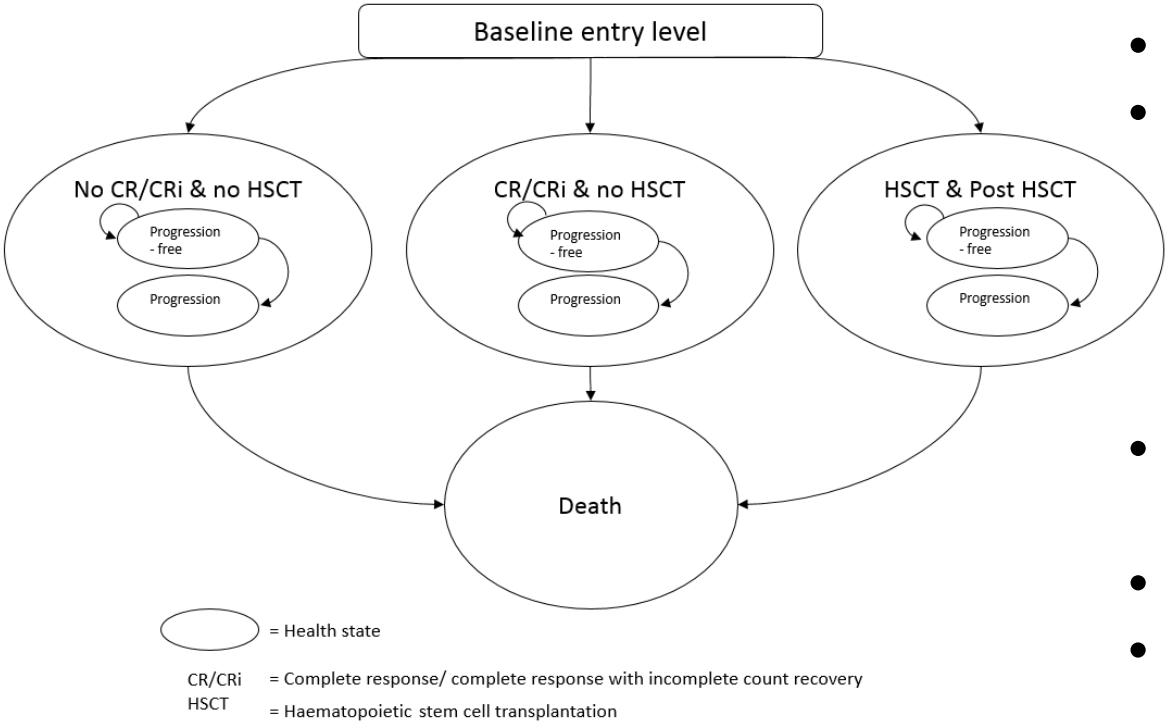
Key Cost effectiveness discussion points

1. Is 1.5% cost and QALY's discount rate appropriate for decision making?
2. OS data
   - Is the OS modelling in *HSCT & Post-HSCT* appropriate?
   - Is the assumption of the "cure point" at 3 years appropriate?
   - What is the mortality rate after HSCT?
3. Cost
   - How should the administration cost of inotuzumab be modelled?
   - Is it appropriate to add the cost of idarubicin and imatinib to the cost of SoC?
   - Should the cost of subsequent therapies be included in the model?
4. Which utility values should be used in the model?
5. Are the end-of-life criteria met?
6. What is the most plausible ICER?

Company's model

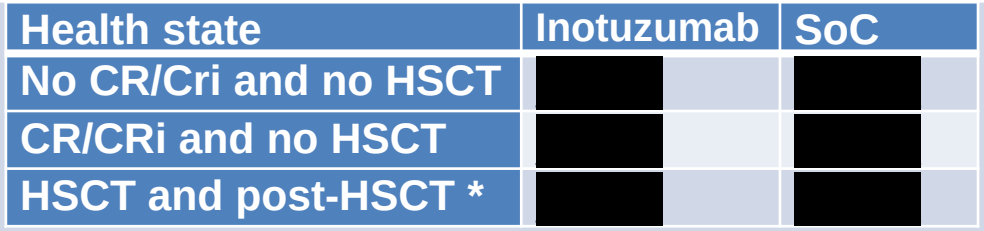
- Three partitioned survival models with 8 health states
- Tunnel states within HSCT & post HSCT represent the wait for HSCT
- Each model: sub states for progression free and progressed disease
- PFS and OS modelled using covariates (safety population)



- 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.

Company's model - summary

Clinical data	INO-VATE 1022 (safety population)
Treatment response	Assumption: patients' response to treatment is determined within 1 cycle: all enter in Cycle 0 = baseline entry level (first cycle) and transition during Cycle 0…
Health states	 * [redacted] inotuzumab & [redacted] SoC pts received HSCT prior to any post induction therapy
Comparators	SoC = FLAG-IDA and FLAG + imatinib for Ph+ patients (based on INO-VATE 1022 SoC of FLAG, CM and HIDAC) Efficacy assumption: FLAG = FLAG-IDA = FLAG + imatinib; only cost added
Utilities	Progression free: • No CR/CRi and no HSCT and CR/CRi and no HSCT: INO-VATE 1022 • HSCT & post HSCT: treatment independent, based on time post HSCT: Kurosawa et al. 2016 Progressed patients: Aristides et al. 2015
AE	AE accounted for in the on-treatment utility disutility for veno-occlusive disease (VOD; 0.208) GvHD captured in post-HSCT utilities from Kurosawa et al. 2016
Cure point	Patients alive after 3 years cured - life expectancy = normal population

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; HSCT, haematopoietic stem cell transplant; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor therapy; FLAG-IDA, FLAG and idarubicin; GvHD, graft versus host disease; CM, Cytarabine plus mitoxantrone; HIDAC, high dose cytarabine; SoC, standard of care.

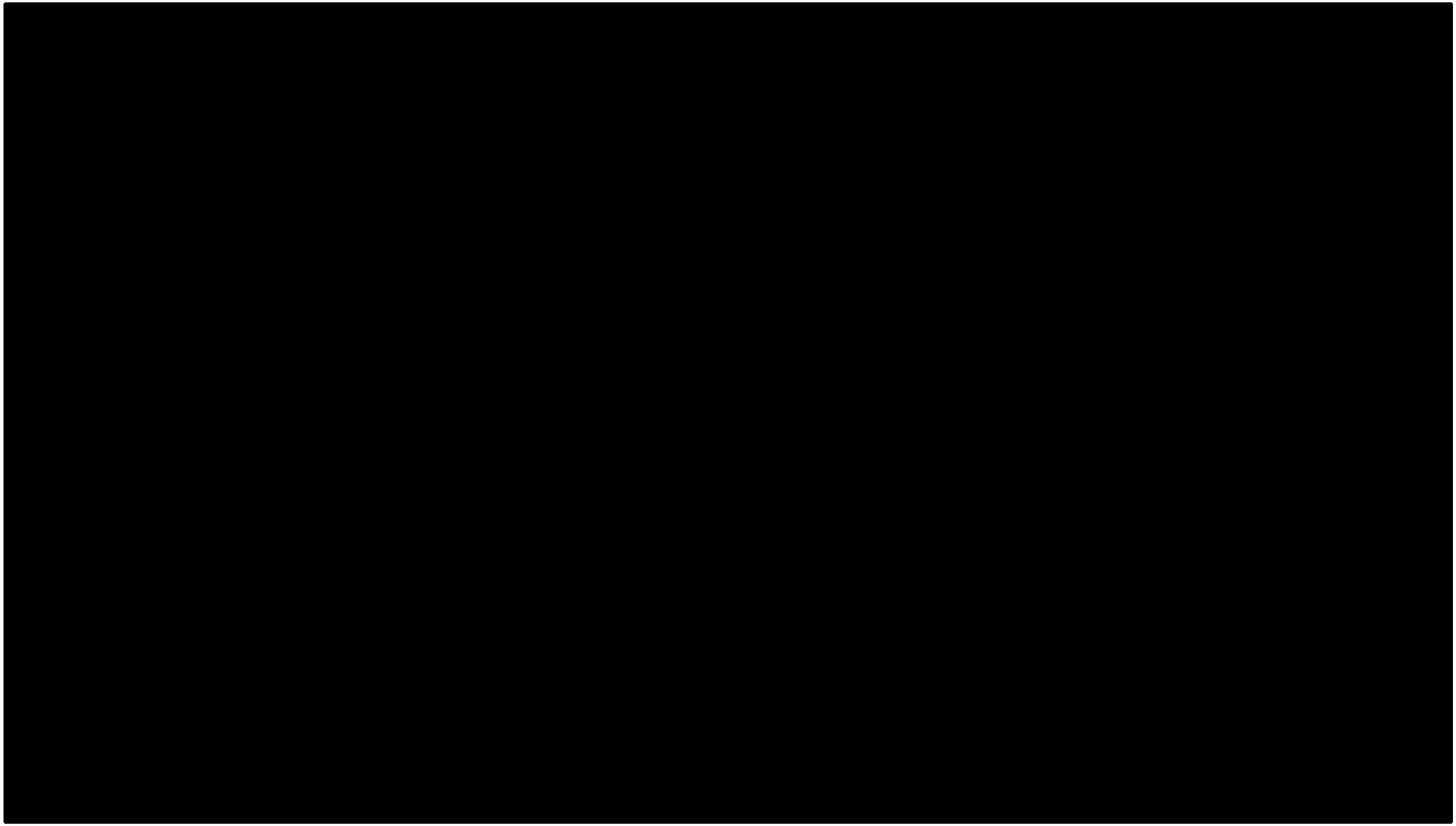
Company's model - PFS and OS

Health state		Parametric curve	Goodness of visual fit	Best statistical fit	Clinically plausible
No CR/CRi & no HSCT	OS	Log-logistic	Yes	No	Yes
	PFS	Log-logistic	Yes	Yes	Yes
CR/CRi & no HSCT	OS	Log-logistic	Yes	Yes	Yes
	PFS	Log-normal	Yes	Yes	Yes
HSCT & Post-HSCT	OS	Gompertz	Yes	Yes	Yes
	PFS	Gompertz	Yes	No	Yes

- Same parametric curves applied to both arms
- Covariates: treatment, age, duration of first remission, salvage status, Ph-status, prior HSCT, region
- Available OS KM data:
  - *No CR/CRi & no HSCT*: [redacted]* & [redacted]* years for inotuzumab & SoC (OS complete); *CR/CRi & no HSCT*: [redacted] & [redacted] years for inotuzumab & SoC ([redacted]& [redacted] survival probability for inotuzumab & SoC respectively); *HSCT & post HSCT*: [redacted] & [redacted] years for inotuzumab & SoC ([redacted]& [redacted] survival probability for inotuzumab & SoC respectively)

Key: *, estimated from Figure 30 and 31 CS page 177 and 178 CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care.

Company’s model OS in No CR/CRi & no HSCT and CR/CRi & no HSCT



- log-logistic curves (mustard) were selected

Key: OS, overall survival; SoC, standard of care arm.

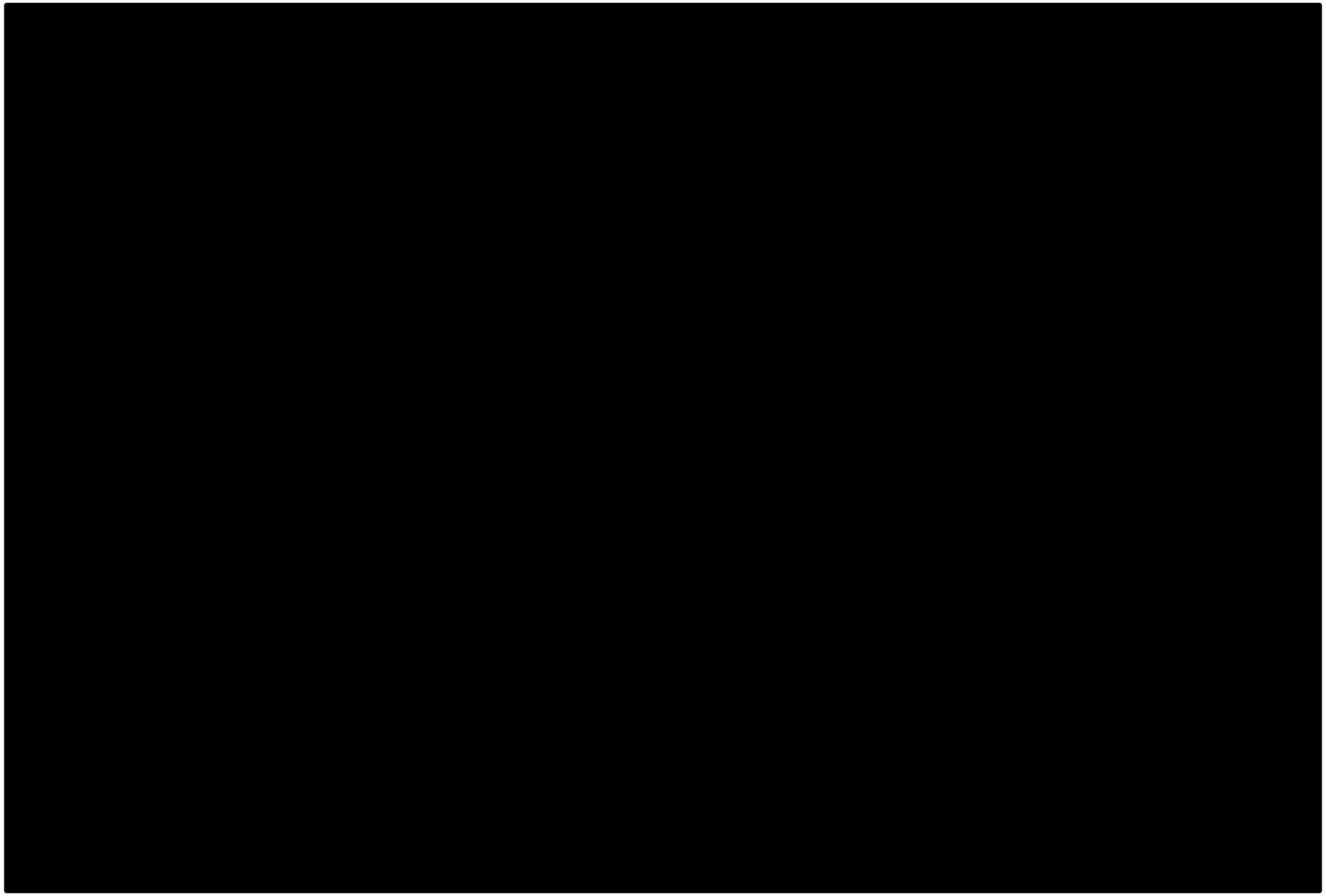
Company's model – HSCT and post HSCT parametric OS curves

- Gompertz curves (light blue; top for inotuzumab and bottom for SoC) selected to represent OS in HSCT & Post HSCT state up to cure point (3 years)

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; SoC, standard of care.

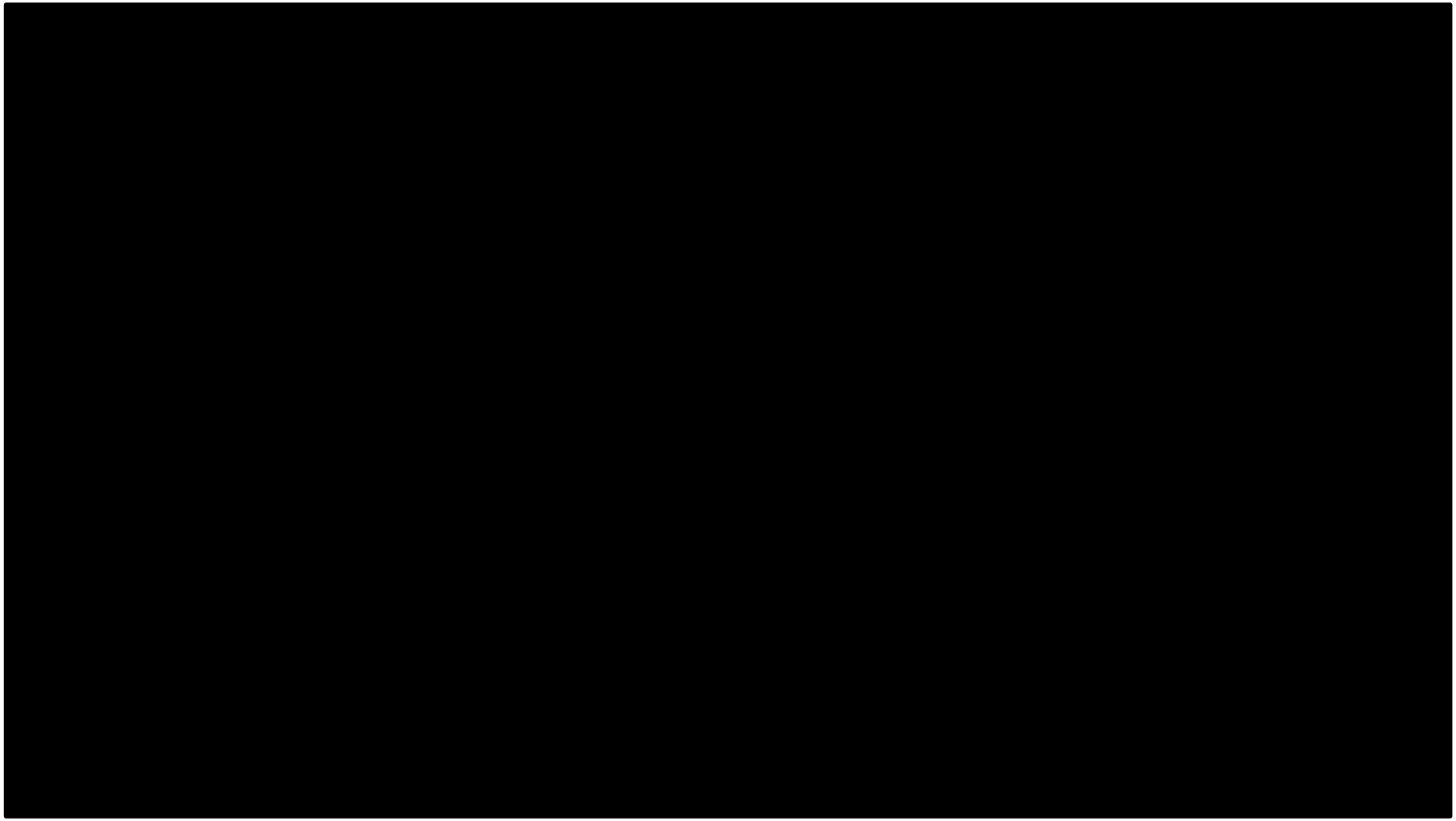
Company's model: OS in HSCT & post HSCT

General population age-specific mortality rates used after cure point (3 years)



Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; PFS, progression-free survival; RMST, restricted mean survival time; SoC, standard of care.

Company’s model: Post-HSCT OS: pooled KM data split by MRD status



Key: MRD, Minimal residual disease; OS, overall survival.

ERG review: *HSCT & post HSCT* state

- Approximately 95% of QALY gain conferred in *HSCT & Post HSCT*
  - The majority of the differences in PFS, OS and hence QALYs are derived after the follow-up period of the trial
- [redacted]
- Small number of patients in *HSCT & Post HSCT* beyond 2 years and this subgroup is not randomised
- Uncertainty around the company "cure point" of 3 years post HSCT
  - survival gains estimated at 3 years are extrapolated over a lifetime.
- Mortality rate after HSCT is greater than general population
  - mortality improves in 5 years after HSCT, but remains 4-9 times higher for at least 25 years thereafter (Martin et al. 2011)
- ERG suggests pooling OS for *HSCT & Post-HSCT* → as in CS Appendix 7 scenario analysis with MRD status covariate adjustment **SoC**

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; KM, Kaplan–Meier; MRD, Minimal residual disease; PFS, progression-free survival; RMST, restricted mean survival time; SoC, standard of care.

Company's model – treatment costs

Drug acquisition cost		Cost	% Patients	Total cost
SOC	FLAG-IDA	[redacted]	[redacted]	[redacted]
	CM	[redacted]	[redacted]	
	HIDAC	[redacted]	[redacted]	
	TKI (Imatinib) Ph+ ALL	[redacted]	[redacted]	
Inotuzumab				[redacted]

Administration cost

- SOC: total cost per patient for average course of treatment = **£4,632.81**
- Inotuzumab: total cost per patient for average course of treatment = **£2,582.80**

Cost of subsequent induction therapies

- Salvage therapies based on INO-VATE 1022 ITT (not all therapies included: CAR-T cell therapy, growth factors, [redacted])
- Inotuzumab: **£7,625** and SOC: **£19,199** (average costs per cohort member)

Cost of HSCT per cycle (only for those patients receiving HSCT): **£60,891.72**

- Post-HSCT in first 6 months = **£4,891.42**
- Post-HSCT from 6–12 months = **£3,360.07**
- Post-HSCT from 12–24 months = **£1,212.35**

Key: CM, cytarabine plus mitoxantrone; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor and idarubicin; HIDAC, high dose cytarabine; SoC, standard of care; TKI, tyrosine kinase inhibitor

ERG review: treatments and salvage therapy

- Company added cost of idarubicin and imatinib, but same efficacy assumed (FLAG = FLAG-IDA = FLAG & imatinib)
  - ERG excluded these costs to ensure consistency between the efficacy outcomes and cost assumptions for comparators
- Company's cost of subsequent therapies
  - Cost derived from the ITT, not safety population
  - More patients in SoC had subsequent induction
  - ERG: this creates positive bias towards inotuzumab
  - ERG: inclusion of these costs potentially inappropriate
- Company's administration cost for inotuzumab
  - Modelled in outpatient setting
  - [redacted] inotuzumab patients were hospitalised during Cycle 1
  - ERG: this does not reflect UK clinical practice
  - ERG: Should be based on INO-VATE 1022

Key: FLAG, Fludarabine, cytarabine and granulocyte-colony stimulating factor (GCSF) based combination chemotherapy; CM, cytarabine plus mitoxantrone; HIDAC, high dose cytarabine.

Company's model - utilities

State		Utility value: mean (SE)	95% CI	Source
Baseline		InO: 0.69 (0.02) SoC: 0.67 (0.03) *Pooled: 0.69 (0.02)**	0.65–0.74 0.62–0.73 -	INO-VATE 1022
No CR/CRi & no HSCT		[redacted]	[redacted] -	
CR/CRi & no HSCT		[redacted]	[redacted] -	
Post-HSCT	**<1 year post**	0.59 (0.10)	0.40–0.78	AML utilities from Kurosawa 2016 (include GvHD disutility)
	1–2 years' post	0.75 (0.03)	0.69–0.82	
	3–5 years' post	0.74 (0.02)	0.70–0.78	
	>5 years post	0.76 (0.03)	0.71–0.81	
Progression		0.30 (0.04)	0.22–0.38	Aristides 2015
VOD after HSCT applied for 1 cycle		0.208	-	Acute liver failure pretransplant (SMC)

Key: *, used in sensitivity analyses; SoC, standard of care; InO, inotuzumab; HSCT, haematopoietic stem cell transplant; VOD, veno-occlusive disease.

ERG review: utilities

- Company use of INO-VATE 1022 data
  - ERG: open-label design introduces potential bias for subjective outcomes (HRQoL)
  - ERG: pooled utility values may be more appropriate

- Company: *HSCT & Post-HSCT*
  - utilities derived using Japanese value set
  - ERG: over the 60-year lifetime horizon values exceed general population estimates declining with age
  - ERG: utilities should be further adjusted for age

- Company: disease progression
  - 0.3 applied to progression in all 3 model states
  - progression is assumed to influence HRQL but does not impact OS (cure point = general population mortality)

ERG: large impact on the estimated QALY gains as the model predicts progression in [redacted] and [redacted] of patients with HSCT following SoC and inotuzumab respectively

Key: HRQL, Health-related quality of life; HSCT, haematopoietic stem cell transplant; OS, overall survival; QALY, quality adjusted life years.

Company's base case

Deterministic results

	Costs	QALYs	LYs	Incremental			ICER
				Costs	QALYs	LYs	
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			ICER
	Costs	QALYs	LYs	
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.

Company's probabilistic sensitivity analysis (discount rate of 1.5%)

- At a £50,000 WTP threshold, the probability that inotuzumab is a cost-effective treatment option versus SoC is 45% for a discount rate of 1.5%

Key: ICER, incremental cost-effectiveness ratio; PSA, patient access scheme; QALY, quality-adjusted life year.
Note: results do not include fix provided by company during clarification process

Company's base case: QALY by health state

Summary of discounted QALY gain by health state (1.5% discount)

Health state	QALY inotuzumab	QALY SoC	Increment
No CR/CRi	[redacted]	[redacted]	[redacted]
CR/CRi & no HSCT	[redacted]	[redacted]	[redacted]
HSCT & Post HSCT	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

- the majority of the QALY gain is conferred within the *HSCT & Post HSCT* state

Key: CR, complete remission; CRi, complete remission with incomplete haematologic recovery; QALY, quality-adjusted life year; HSCT, hematopoietic stem cell transplant; SoC, standard of care.

Company's univariate sensitivity analysis (1.5% discount rate) – 10 most influential parameters

- The ICER was most sensitive to the cost of HSCT, choice/cost of subsequent induction treatments and the utility of progressive disease.

Key: ICER, incremental cost-effectiveness ratio; PSA, patient access scheme; QALY, quality-adjusted life year
Note: results do not include fix provided by company during clarification process

Company's deterministic sensitivity analysis (discounted at 1.5%)

Inputs varied	Scenario	ICER
Base case		**£40,013**
Reflective of UK clinical practice	Max 3 cycles, as per SPC	£34,311
	No prior HSCT	£37,382
Comparator	All FLAG-IDA in SoC	£39,027
	All CM in SOC	£41,714
	All HIDAC in SOC	£42,101
Utilities from UK HTA in ALL	utility from the blinatumomab SMC	£35,660
Post HSCT cure point (base case 3 years)	2 years	£44,464
	5 years	£39,301
Cost of HSCT	No costs of HSCT applied	£30,576
Time to HSCT (tunnel states)	Up to 3 cycles	£40,084
	Average time to HST	£37,515
Age adjusted utilities	Age adjusted utilities	£43,909
Discount rate	QALYs 1.5%, Costs 3.5%	£39,473
	QALYs 3.5%, Costs 3.5%	£55,869
Time horizon	5 years	£253,651
	10 years	£130,513
	20 years	£70,333
	30 years	£51,174

Comparison of OS in INO-VATE 1022, CS submission and ERG analysis

OS at 3 years: Company base case: [redacted] for inotuzumab and [redacted] SoC
ERG non-parametric: [redacted] for inotuzumab and [redacted] SoC
ERG parametric: [redacted] for inotuzumab and [redacted] SoC

[redacted]

Key: OS, Overall survival; K-M; Kaplan-Meier; SoC, standard of care.

Exploratory 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 patients: 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

Company: End of life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Adults with R/R ALL experience reported median OS as low as 3 months with current therapies. • Median OS in INO-VATE 1022 for SoC (representative of UK clinical practice) 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	• Using the RMST analysis, inotuzumab significantly extends OS to 13.9 months vs 9.9 months with chemotherapy (p=0.0023), for a gain in OS of 4-months with a limited 37.7 months of follow-up. • The economic model presents mean life years for SoC as 1.49 and 6.66 for inotuzumab, showing an increase greater than the 3 months.

ERG:

- Life expectancy for R/R B-cell ALL adult patients is around 3-6 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.

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

Innovation and Equality issues

Company:

Inotuzumab represents a step-change in disease management in a population for whom there is a poor prognosis, significant unmet need and limited treatment options with:

- Improved efficacy
- Novel mode of action and improved safety profile
- Improved administration

Equality issues:

No equality or equity issues were identified by the company or the ERG

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