For public (redacted)

Blinatumomab for previously treated B-precursor acute lymphoblastic leukaemia [ID804]

1st Appraisal Committee meeting
Cost effectiveness
Committee A

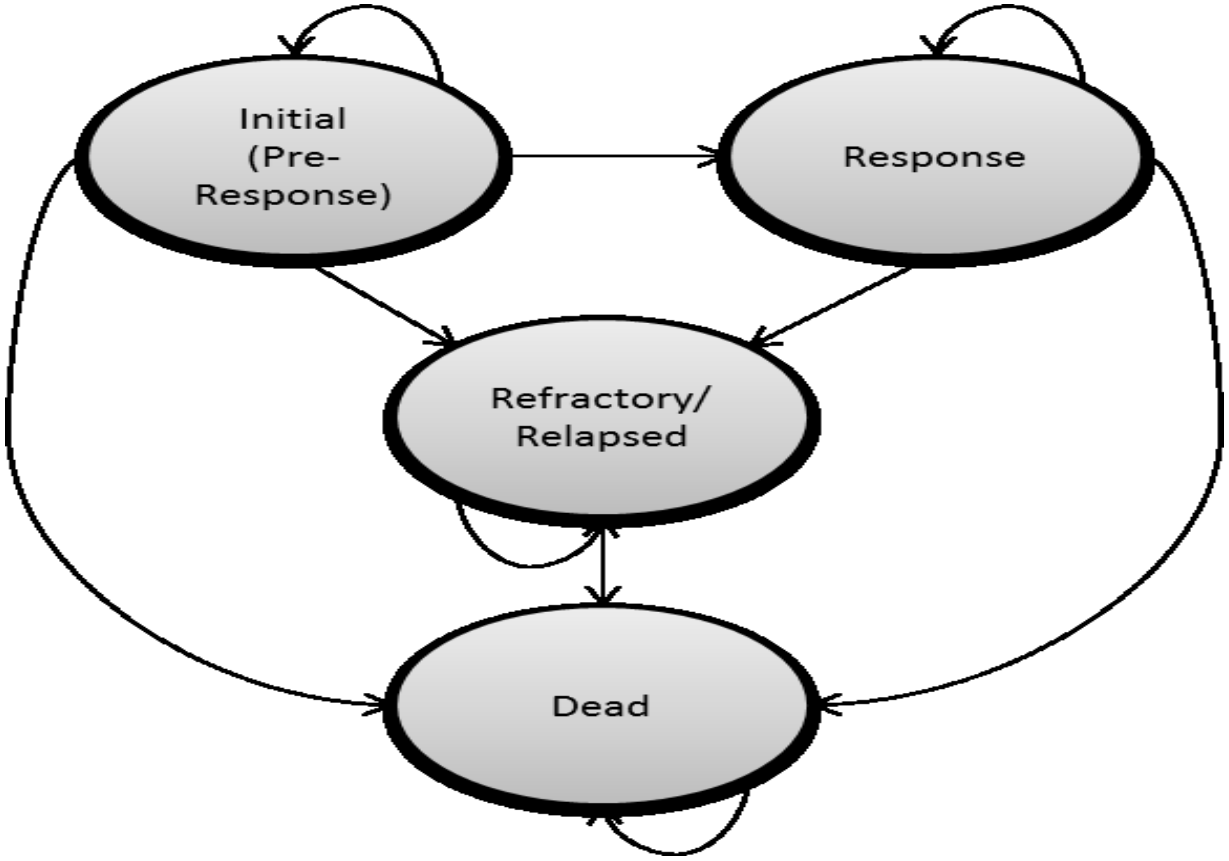
Lead team: John Watkins, Nerys Woolacott, Pam Rees
ERG: Warwick Evidence
NICE technical team: Thomas Palmer, Eleanor Donegan, Janet Robertson

9 March 2017

Key decision points

- Does the committee consider the extrapolation of OS and EFS in the company model to be appropriate?
- Is the treatment effectiveness of SOC from TOWER generalisable to FLAG-IDA?
- Are all of the benefits of blinatumomab included in the QALY calculation?
- To what extent will blinatumomab be administered in an outpatient setting?
- Does the committee consider the company or the ERG model to represent the most plausible ICER?
- Does the committee consider end-of-life criteria to be met?
- The company has requested that because this condition is so rare the committee use the same criteria as for HST topics – what is the committee's view?

Model structure



- Partitioned survival model
- Patients enter model in “initial” state and remain in this state for 12 weeks (unless they die)
- After 12 weeks either enter the “refractory/relapsed” state or “response” state
- Weekly model cycle
- 50-year time horizon
- Baseline characteristics from TOWER

Model details

- Model uses a partitioned survival model approach – which captures the difference in area between OS and EFS survival curves
- Patients receive either blinatumomab or FLAG-IDA
- Effectiveness of the whole SOC chemotherapy arm of TOWER used as a proxy for the effectiveness of FLAG-IDA
  - Costs based on FLAG-IDA
- All clinical parameters in base case derived from TOWER RCT (ITT population)
- OS and EFS among responders extrapolated by company with parametric survival curves fitted to the Kaplan Meier plots
- Patients with relapse after greater than 12 months in remission were not represented in the model as they were not included in TOWER
- Patients alive after 4 years cured - same HR for OS for with blinatumomab and SOC
- Costs considered in the model included drug acquisition and administration costs for blinatumomab and FLAG-IDA, cost of allo-SCT, the costs of subsequent salvage therapy, and terminal care costs
- These costs were calculated independently of the model states

Overall survival in submitted clinical evidence (AIC)

Company overall survival extrapolation (AIC)

Restricted Gompertz

Extrapolation of outcomes – ERG critique

- OFS and EFS have been estimated based on fitting parametric curves to Kaplan-Meier plots of observed blinatumomab data and assuming proportional hazards to determine the treatment effect
- ERG consider that the proportional hazard assumptions not met, given that the Kaplan-Meier plots appear to cross from month 15 through the remainder of the trial time horizon
  - Company reject this argument, saying that very few patients at risk at time point after curves overlap
- Company assume that patients alive at 4 years are cured - hazard rates for OS are the same for blinatumomab and SOC chemotherapy after 4 years
  - The ERG clinical advisor suggests people who survive 5 years or more are likely to be cured which is consistent with the Scottish Medicines Consortium submission/ model for blinatumomab
- Parametric fit was chosen by a combination of visual inspection of goodness-of-fit, long-term plausibility informed by historical data and expert opinion, and using the Bayesian Information Criterion (BIC)
- Gompertz model was used in OS base case analysis- this is the 8th best fitting model (BIC)
- ERG explored alternative survival curves in the model but were limited by data availability and were unable to find a more clinically plausible OS curve

Other clinical parameters

Parameter	Blinatumomab	FLAG-IDA	Source
Response rate (%)	43.9	24.6	TOWER
Duration of benefit (months)	48	-	Company assumption
Parameters used in calculating costs only			
Patients receiving allo-SCT (%)	24.4	23.9	TOWER
Patients receiving subsequent innovative therapies (%)	[redacted]	[redacted]	TOWER
Patients receiving other subsequent therapies (%)	[redacted]	[redacted]	TOWER

Health-related quality of life – Utility values

Health states	Blinatumomab (N=271) Mean (SE)	SOC Chemotherapy (N=134) Mean (SE)
Initial (Pre-response)	[redacted]	[redacted]
Response	[redacted]	[redacted]
Relapsed/refractory	[redacted]	[redacted]
Terminal decrement		[redacted]

- TOWER collected information on HRQoL (EORTC QLQ-C30) which was mapped to EQ-5D by the company
- All observed adverse events were assumed to occur while people are on treatment and receiving inpatient/outpatient care, and would have been captured by the EORTC QLQ-C30.
- Utility values from the general population were used for people surviving more than four years - unclear if any uncertainty around these estimates was used to inform the probabilistic sensitivity analyses
- Utility values not a key driver of cost-effectiveness

EQ-5D, EuroQol five dimensions; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30; FAS, full analysis set; SD, standard deviation; SOC, standard of care.

Costs

	Costs (£)	Sources
Blinatumomab cost per patient (using list prices)	[redacted]	NHS Reference Costs, 14/15 Dosing regimens from TOWER
FLAG-IDA cost per patient	14,240	BNF (2016); NHS Generic Pharmaceuticals eMit (2015)
Total allo-SCT costs	104,000	UK Stem Cell Strategy Oversight Committee 2014
Subsequent innovative salvage therapy	[redacted]	Assumed same as Blinatumomab
Subsequent systemic salvage therapy	14,240	Assumed same as FLAG-IDA
Terminal care	8,602	Kings Fund 2008 Marie Curie 2012

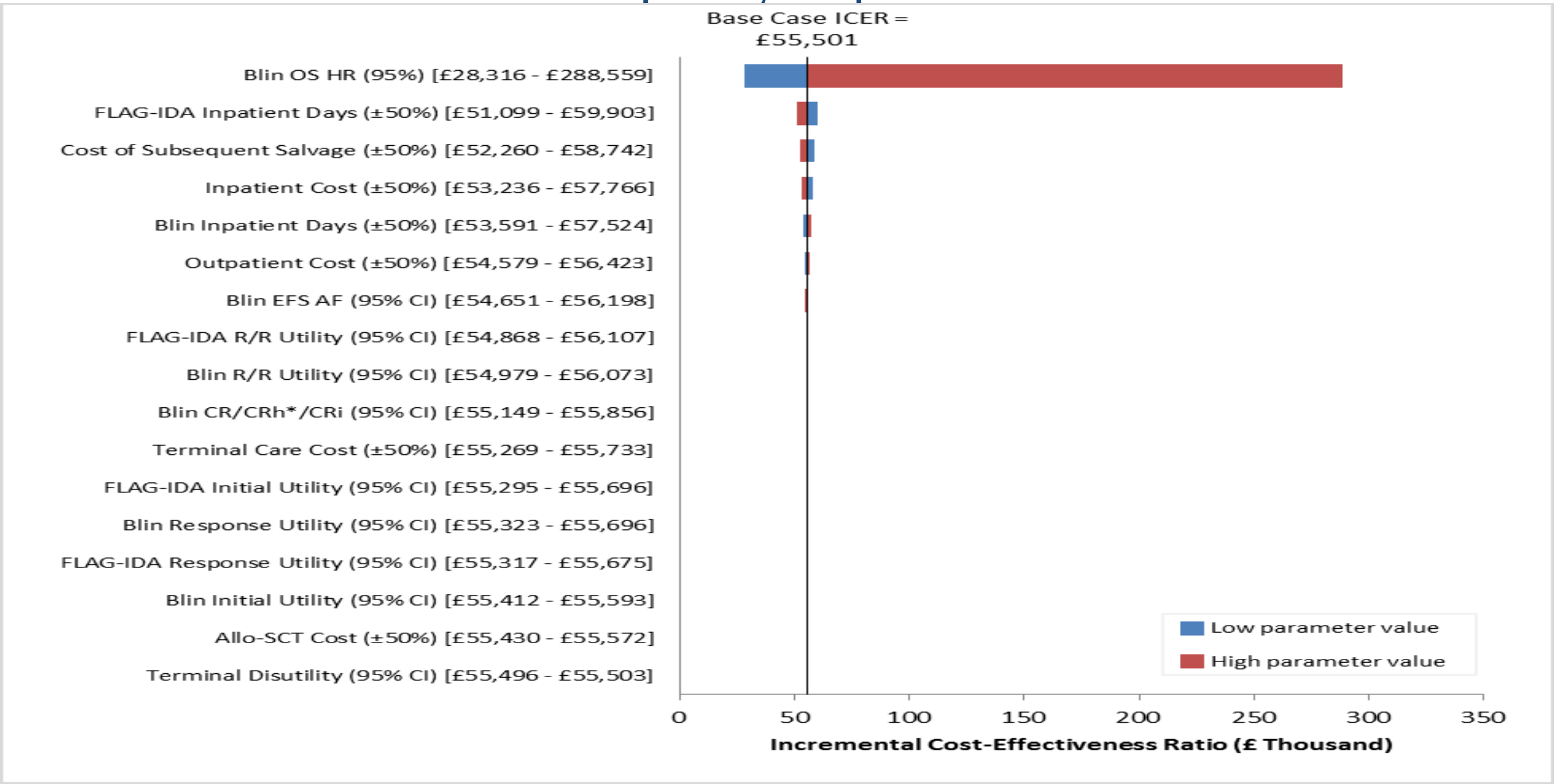
- Blinatumomab costs based on drug acquisition costs, outpatient infusion centre visits, home infusion pump costs and inpatient costs as per the minimum required hospitalisation stated in the SmPC
- ERG advisor suggests that patients frequently hospitalised for the entirety of the treatment cycle
- ERG has undertaken scenario analyses whereby people received all treatment in inpatient care
- Note that company assume no drug wastage

Company base-case results for all patients – blinatumomab PAS price

Treatment	Deterministic			Probabilistic		
	Cost (£)	QALYs	ICER (£/QALY)	Cost (£)	QALYs	ICER (£/QALY)
Blinatumomab	144,611	3.35	55,501	144,692	3.30	57,602
FLAG-IDA	64,165	1.90		64,327	1.91	

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

Tornado diagram (blinatumomab vs FLAG-IDA, all patients) – PAS price, all parameters



Company subgroup analysis- patients with no prior salvage therapy, blinatuomomab PAS price

Treatment	Deterministic			Probabilistic		
	Cost (£)	QALYs	ICER (£/QALY)	Cost (£)	QALYs	ICER (£/QALY)
Blinatumomab	171,879	3.91	49,190	172,220	3.59	58,884
FLAG-IDA	74,703	1.94		75,125	1.94	

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

ERG: "…there is still considerable uncertainty in terms of the treatment efficacy, as the TOWER trial was not powered to detect these differences, and clinical results for the difference between subgroups did not reach statistical significance"

Scenario analysis results- all patients, PAS price

Scenario number	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	Base Case (No Prior Salvage)	80,446	1.45	55,501
1	Safety analysis set (No Prior Salvage)	74,256	1.34	55,314
2	Subgroup of patients that were intended to receive a FLAG-IDA SOC therapy regimen at randomization	78,459	2.42	32,371
3	OS Based on RCS Log-Logistic	80,824	0.47	171,487
4	Survivors Cured - 36 Months	78,866	1.81	43,527
5	Survivors Cured - 48 Months	79,280	1.60	49,485
6	Survivors Cured - 60 Months	79,572	1.45	55,017
7	EFS Based on Lognormal	80,461	1.45	55,659
8	36-Month Duration of Benefit	80,446	1.39	57,754
9	60-Month Duration of Benefit	80,444	1.47	54,696
10	10-Year Model Timeframe	80,466	0.63	126,896
11	20-Year Model Timeframe	80,455	1.02	78,878
12	60-Year Model Timeframe	80,444	1.46	55,135
13	1.5% Discount Rate	80,852	1.97	41,081
14	10 Inpatient Days Blinatumomab All Cycles	88,069	1.45	60,760
15	Zero cost for Blinatumomab Cycle 6+	72,179	1.45	49,798
16	Blinatumomab home IV bag changes for Cycle 3+	79,677	1.45	54,971
17	Clofarabine Included in FLAG-IDA	76,206	1.45	52,576
18	Rate of allo-SCT from MT103-211	87,085	1.45	60,081
19	EORTC-8D Utilities	80,446	1.49	53,910
20	TTO Utilties from Vignette Study	80,446	1.40	57,438

ERG Comments (1)

- A notable number of patients in the blinatumomab arm received more than the five cycles specified in the marketing authorisation [redacted]
- Generalisability of SOC chemotherapy to FLAG-IDA uncertain
- TOWER not powered for subgroup analysis
- Concerns over extrapolation of treatment effectiveness
  - Conservative interpretation of Kaplan-Meier plots is that additional costs and benefits are unlikely to accrue past the trial time horizon, and extrapolation of effectiveness beyond the trial time horizon is thus unnecessary
  - ERG explored a “within-trial” analysis, which assumes no treatment effect beyond the 2-year trial period based on OS curves overlapping at 15 months
  - Caution that this may underestimate costs and benefits, given that some SOC patients received subsequent treatment with blinatumomab or other therapies
  - ERG was limited by data availability and clinical plausibility in exploring the feasibility of alternative survival curves in the economic model

ERG Comments (2)

- Concerns over health care utilisation
  - ERG clinical advisor suggests that the minimum hospitalisation requirements used in model are unrealistic – hospitalisation for entirety of first two treatments likely and that daily bag changing for intravenous chemotherapy more likely
  - NHS England: “not all patients will be inpatients for full 4 weeks…second cycle of therapy is likely to have an increased outpatient component… unlikely that any outpatient treatment will just use 1 day infusion bags”

ERG preferred base case – PAS price

inpatient treatment in cycles one and two, daily bag changes in subsequent cycles

Treatment	Deterministic			Probabilistic		
	Cost (£)	QALYs	ICER (£/QALY)	Cost (£)	QALYs	ICER (£/QALY)
Blinatumomab	167,644	3.35	69,746	167,590	3.22	73,383
FLAG-IDA	66,550	1.90		66,543	1.85	

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

ERG Deterministic scenario analysis – two-year time horizon ("within- trial" analysis), PAS price

Treatment	Total		Incremental		ICER (£)
	Cost (£)	QALYs	Cost (£)	QALYs	
Blinatumomab	144,120	0.57	80,442	0.19	432,478
FLAG-IDA	63,678	0.38			

FLAG-IDA, fludarabine, cytarabine, granulocyte colony stimulating factor, idarubicin; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life-years.

Innovation, equality and end-of-life

Innovation

Company consider blinatumomab to be innovative:

- First-in-class mechanism of action that harnesses the body's own immune system to recognise and eliminate malignant cancer cells
- There are no targeted treatments licensed specifically for this disease
- The company have requested that blinatumomab be evaluated taking into account a wider range of criteria about the benefits and costs, as NICE does for HST appraisals

Equality

No equality issues relating to use of blinatumomab for the treatment of adult R/R Ph- B-precursor ALL were identified at scoping stage or in submissions

End-of-life criteria

Criteria	Normal range	TOWER (months)
Short life expectancy	<24 months	4.0
Extension to life	≥3 months	3.7

Key decision points

- Does the committee consider the extrapolation of OS and EFS in the company model to be appropriate?
- Is the treatment effectiveness of SOC from TOWER generalisable to FLAG-IDA?
- Are all of the benefits of blinatumomab included in the QALY calculation?
- To what extent will blinatumomab be administered in an outpatient setting?
- Does the committee consider the company or the ERG model to represent the most plausible ICER?
- Does the committee consider end-of-life criteria to be met?
- The company has requested that because this condition is so rare the committee use the same criteria as for HST topics – what is the committee's view?