NICE National Institute for Health and Care Excellence

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]

Lead team presentation

1st Appraisal Committee Meeting

Background and clinical effectiveness

Committee C

Lead team: Andrew Renehan, Paul Tappenden, David Chandler

Evidence Review Group: CRD and CHE Technology Assessment Group, University of York

NICE technical team: Alan Lamb, Nicola Hay

Company: Novartis

22nd August 2018

Key issues – clinical effectiveness

- Would the following populations be treated with tisagenlecleucel -T (tis-T):
  - patients with primary refractory ALL,
  - patients with Philadelphia chromosome positive ALL.
  - patients previously treated with anti CD-19 therapies (e.g. blinatumomab)
- Is it appropriate to use clofarabine as a proxy for FLA-IDA salvage chemotherapy?
- Is blinatumomab an appropriate comparator?
- Are the patient populations in the clinical evidence generalisable to NHS clinical practice?
- Which studies are appropriate to use as clinical evidence for the comparators?
- Is there sufficient evidence that tis-T should be considered a curative therapy?
- Should efficacy analysis include the entire ITT population?

Acute lymphoblastic leukaemia (ALL): Disease background

- Acute form of cancer of the white blood cells
- Rare - 0.2% of new cancers in UK
- Predominately disease of childhood but affects adults too
- Symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever & sweating
- 64% of cases of ALL in patients aged 0–24 years
- Precursor B-cell is the most common type of ALL representing 80–85% of cases in children
- Approximately 3% of children with precursor B-cell ALL have acquired chromosomal abnormality known as Philadelphia chromosome positive disease – which is associated with a poorer prognosis and is challenging to treat

Acute lymphoblastic leukaemia (ALL): Disease background

- Currently no NICE clinical guidelines on treatment of ALL
- NICE technology appraisal guidance for ALL includes:
  - TA 408: pegaspargase is recommended for untreated ALL in children, young people and adults
  - TA 450: blinatumomab is recommended for treating Philadelphia-chromosome-negative relapsed or refractory precursor B-cell ALL in adults (funding extended to children by NHS England)
  - TA 451: ponatinib is recommended for treating Philadelphia-chromosome-positive ALL in adults under certain conditions
  - Final appraisal document (FAD) for appeal [ID893]: Inotuzumab ozogamicin is recommended, for treating relapsed or refractory CD22- positive B-cell precursor acute lymphoblastic leukaemia in adults

Tisagenlecleucel (Novartis)

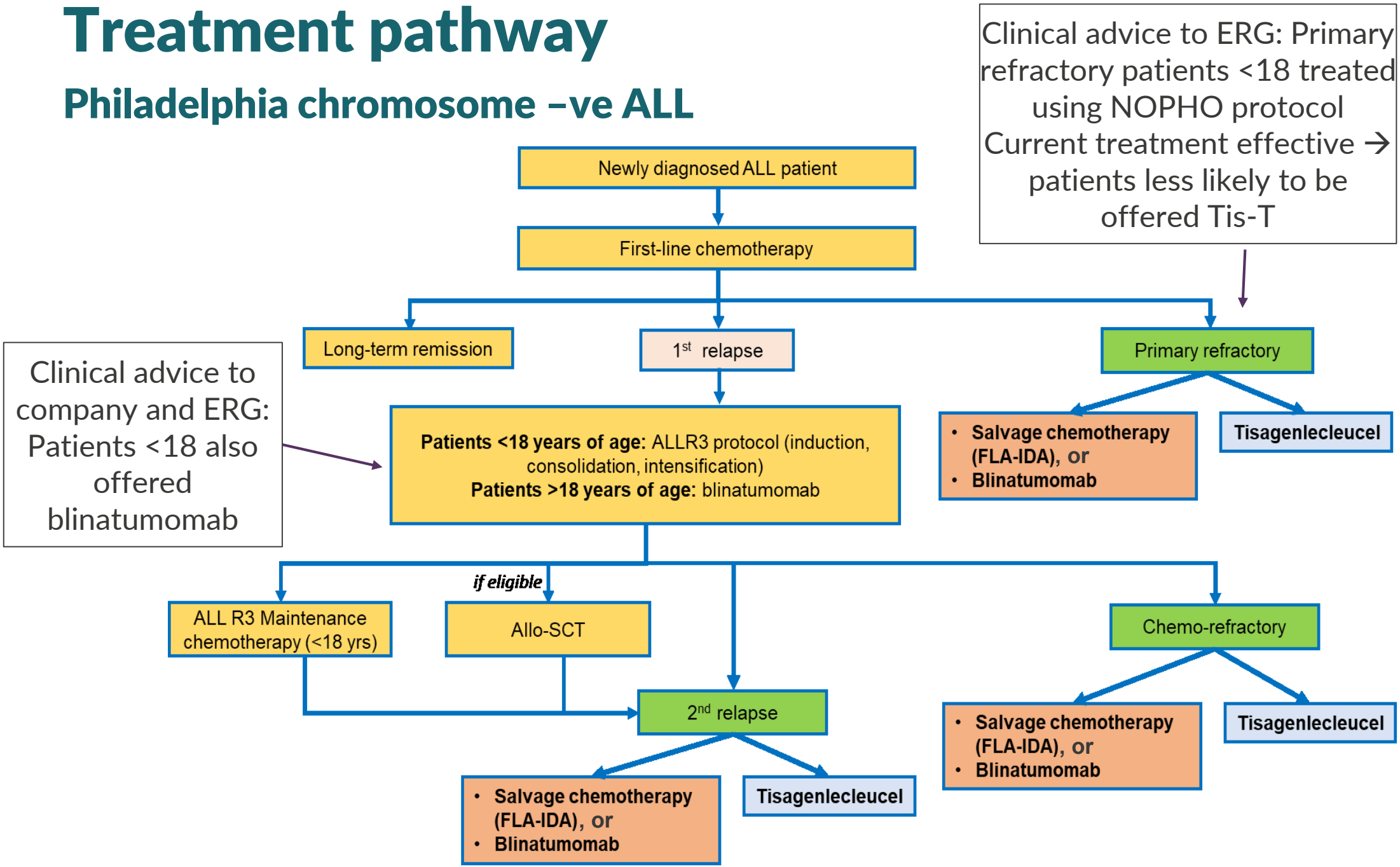
Mechanism of action	A chimeric antigen receptor (CAR) T-cell therapy that uses autologous T cells engineered to express a novel surface receptor directed against the tumour antigen CD19

Administration and dosage	• Patients T cells are extracted via leukapheresis
	• Patients are administered lymphodepleting chemotherapy of cyclophosphamide 500 mg/m^2 IV and fludarabine 30 mg/m^2 IV (cytarabine and etoposide may be used if cyclophosphamide treatment is not suitable)
	• Genetically altered T cells are administered as a single dose intravenous infusion at the following dosage:
	  • For patients ≤50 kg: 0.2 to 5.0×10^6 CAR-positive viable T cells per kg body weight
	  • For patients >50 kg: 0.1 to 2.5×10^8 CAR-positive viable T cells (non-weight based)

Marketing authorisation	Received positive CHMP opinion (June 2018) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse
List price	[redacted]
PAS	Simple discount under discussion with NHS England

Treatment pathway

Philadelphia chromosome –ve ALL



Allo-SCT, allogenic stem cell transplant; NOPHO Nordic Society of Paediatric Haematology and Oncology

Patient and professional group comments – common points

- There is unmet need for new treatments for ALL in the relapsed refractory setting
- CAR T-cell therapy is a novel treatment and has the potential to change the treatment pathway
  - Treatment would be offered with curative intent
- Significant infrastructural changes will be required to deliver CAR T-cell therapy routinely in the NHS
  - Manufacturing, delivery of treatment and management of side effects must be considered

Comments from patient groups

(Bloodwise and Leukaemia CARE)

- Common symptoms of ALL include:
  - Tiredness, bruising, bleeding, infections and weight loss.
- Other symptoms include:
  - Swollen lymph nodes, stomach pain, bone pain and night sweats
- Effective treatment options are limited in the relapsed setting.
- Side effects of chemotherapy include:
  - Fatigue, nausea/sickness, infections, bleeding, organ dysfunction and hair loss
- Treatment with CAR T-cell therapy could offer hope at a time when all other options have failed with fewer side-effects
- Some concerns have been raised about the unknown long-term consequences of genomic editing techniques

Comments from professional groups

Royal College of Pathologists - British Society for Haematology (joint submission)

- Clear unmet need for patients who have unresponsive disease
- Patients who relapse after SCT or are refractory to conventional chemotherapy have an extremely poor prognosis
- CAR T-cell treatment is a game changer in the way leukaemia will be treated in future
- All post allograft relapse would be treated with curative intent
- Implementation needs to planned to manage CAR T-cells and its complications, with investment needed to expand existing infrastructure for collecting, freezing, transporting and receiving these gene modified cells
- Some investment will also be required in creating extra high dependency and intensive care bed capacity

Statement from NHS England (1)

- As an innovation in personalised medicine, this technology has the potential to revolutionise current treatment strategies
- CAR T-cell therapy will require a new service specification
- Severe, life threatening, adverse events are not uncommon and this will have an impact on the pathway, requiring an increase in intensive care support compared to the current pathway.
- Manufacturer to NHS provider contracting, ongoing training, ongoing accreditation, assured access to ITU capacity etc. will be required
- Due to the novelty of the treatment and the logistics involved a phased implementation will be needed if approved.

Statement from NHS England (2)

Rates of stem cell transplant and overall survival for comparators

- Expert opinion to NHS England indicates rate of SCT for blinatumomab is expected to be higher than 24% and thus the long term OS rate is likely to be about 15-18%.
- Expert opinion to NHS England indicates the SCT rate for salvage chemotherapy is likely to be 15-20% and the long term OS rate about 10%.

Cancer Drugs Fund

- Depending on the NICE committee's conclusions as to clinical and cost effectiveness, NHS England regards tis-T as a good candidate for the Cancer Drugs Fund as the EFS and OS results are still not mature and extra follow-up would reduce uncertainty of these results

EFS, event-free survival; OS, overall survival; SCT, stem-cell transplant

Decision problem (1)

	NICE scope	Company
Population	People aged 3 to 25 years with relapsed or refractory B-cell ALL	In line with anticipated marketing authorisation: Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse*
Outcomes	• Overall survival (OS) • Event-free survival (EFS) • Relapse-free survival (RFS) • Response rate (including minimal residual disease [MRD], haematological responses and complete remission [CR]) • Rate of allogenic stem cell transplant (allo-SCT) • Adverse effects of treatment • Health-related quality of life	

*Company noted that due to a lack of data in the Philadelphia chromosome positive population it was not feasible to perform a robust comparison for this subgroup

Decision problem (2)

	NICE scope	Company

Comparators	Established clinical management without tis-T at following lines:
	• Bone marrow relapse
	  • 2nd or later relapse
	  • Relapse within 6 months of allo-SCT
	• Primary refractory disease
	• Philadelphia chromosome +ve ALL
	  • Intolerant/contraindicated to tyrosine kinase inhibitors (TKIs)
	  • Failed 2 TKIs
	  • Ineligible for allo-SCT
		• Salvage chemotherapy (specifically, FLA-IDA [fludarabine, cytarabine and idarubicin])
		• Blinatumomab
		
		The above are stablished clinical practice at following lines:
		• Bone marrow relapse
		  • 2nd or later relapse
		  • Relapse within 6 months of allo-SCT
		• Primary refractory disease

Company rationale for difference from scope	• Ph+ ALL <3% of eligible population → TKIs not relevant comparators • No comparison for Ph+ population presented due to lack of available data for tis-T and relevant comparators	

Sources of clinical effectiveness evidence

Single arm open-label clinical trials of **tis-T**

ELIANA – phase II
International, multicentre
N=97 enrolled, N=79 infused

ENSIGN – phase II
US, multicentre
N=73 enrolled, N=58 infused

B2101J – phase I/IIa
US, single centre
N=66 enrolled, N=56 infused

Pooled analysis
N=193
Used in economic model

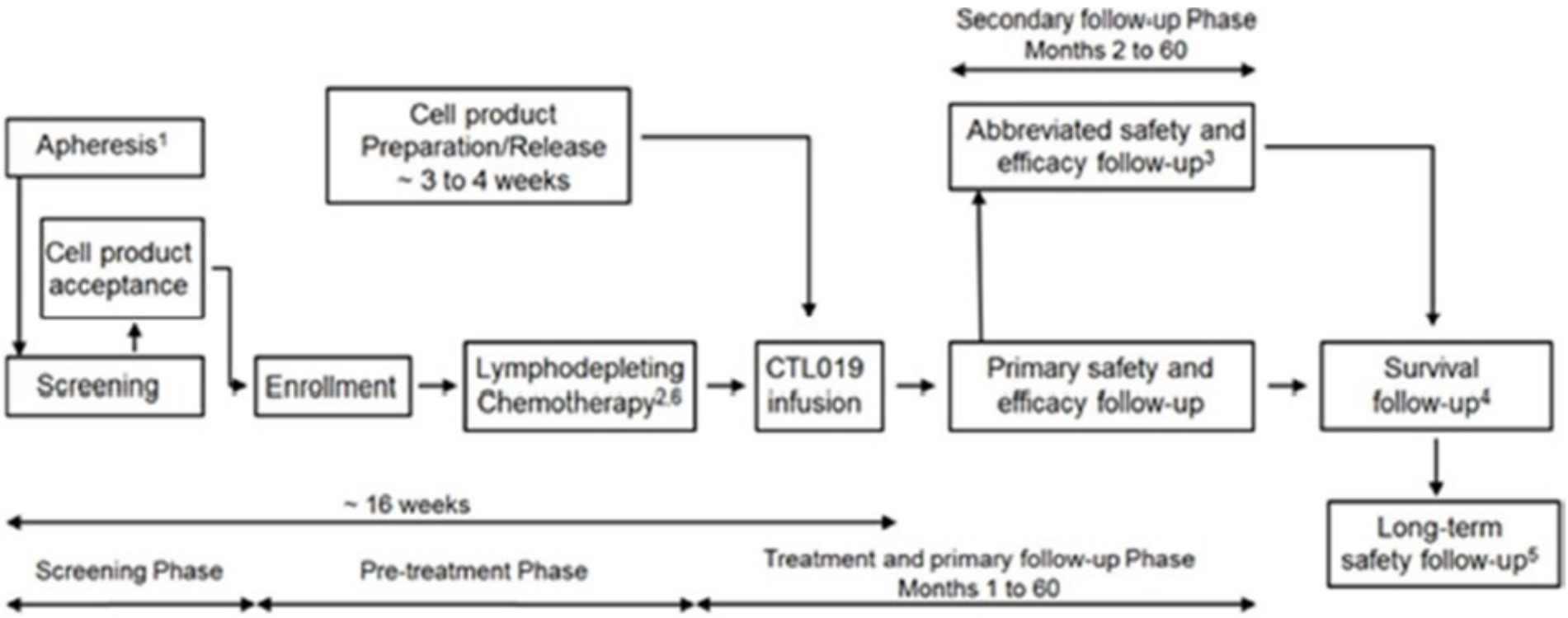
Comparator trials – used in indirect treatment comparisons (naïve and matched)

Blinatumomab – phase II
Von Stackelberg et al (2016)
N=70
Used in economic model

No paediatric trials identified for FLA-IDA → clofarabine used as proxy for salvage chemotherapy

Clofarabine – phase II
Jeha et al (2006)
N=61
Used in economic model

ELIANA – study design



Patients

- Age 3 at screening to 21 at diagnosis
- Relapsed/refractory ALL with
  - 2 or more relapses, or
  - relapse after SCT, or
  - primary/chemo refractory ALL, or
  - Ph+ve ALL if TKI failed/contraindicated
- Kamofsky/Lansky performance status ≥50

Endpoints

1° endpoint

- Overall remission rate (independently-assessed)

2° endpoints used in economic model

- Overall survival
- Event-free survival
- Adverse effects of treatment

ENSIGN and B2101J trials

- Study design similar, key differences between trials include:
  - Leukapheresis could occur prior to or after enrolment in B2101J (patients were enrolled following leukapheresis in ELIANA and ENSIGN)
  - Some patients with lymphoma eligible in ENSIGN and B2101J – no data for patients with lymphoma presented (in line with ELIANA)
  - B2101J was a dose escalation study → patients could receive up to 3 doses of tis-T
  - Median duration of follow up at latest data cuts was;
    - ELIANA: [redacted] for December 2018 data cut presented in company submission (results from a further data cut in April 2018 are consistent with those in the submission)
    - ENSIGN: 19.6 months
    - B2101J: [redacted]

Selected baseline characteristics

Characteristic	ELIANA (full analysis set) (N=79)	ENSIGN (full analysis set) (N=58)	B2101J (full analysis set) (N=56)
Age (years), median (range)	[redacted]	[redacted]	[redacted]
Male, n (%)	[redacted]	[redacted]	[redacted]
Karnofsky/Lansky performance status, n (%)			
100	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]
60, 50 or <50	[redacted]	[redacted]	[redacted]
Prior haematopoietic stem cell transplant (SCT)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
Primary refractory	[redacted]	[redacted]	[redacted]
Philadelphia chromosome +ve	[redacted]	[redacted]	[redacted]

ERG's comments:

- Differences in performance status, number of patients without SCT and proportion with primary refractory disease
- Company presented baseline data for infused patients only rather than full intention-to-treat (ITT) population
    - Fewer patients with performance status 100 in full ITT population

Trial results – summary of individual trials

n (%) Patients receiving infusion only	ELIANA (N=79) (N=77 for ORR)	ENSIGN (N=58) (N=42 for ORR)	B2101J (N=56)
Primary efficacy results			
Overall remission rate (CR+CRi) (95% CI; p value)	[redacted]	29 (69.0) (52.9, 82.4; <0.0001)	[redacted]
Secondary efficacy results			
Event-free survival (used in economic model)			
% event free at 12 months (95% CI)	[redacted]	[redacted]	[redacted]
Median (months) (95% CI)	[redacted]	[redacted]	[redacted]
Overall survival (used in economic model)			
% at 12 months (95% CI)	[redacted]	62.6 (45.8, 75.6)	[redacted]
Median (months) (95% CI)	[redacted]	23.8 (8.8, NE)	[redacted]

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete blood count recovery; NE, not estimable; NR, not recorded.

Pooled trial results – event-free survival

Data cuts: ELIANA, Dec 2017; ENSIGN, Oct 2017; B2101J, Jan 2017
CI, confidence interval; NR, not recorded

Pooled trial results – overall survival

CI, confidence interval; NR, not recorded; OS, overall survival

ERG: Small number of patients at risk after 38 months → interpret median OS with caution

Health-related quality of life

- Patient-reported outcomes collected in ELIANA only
  - Collected for patients ≥8 years old
  - Used PedsQL and EQ-5D questionnaires

Source: Figure 13 of company submission

Adverse events (AEs) – summary

	ELIANA (safety set) (N=79)	ENSIGN (safety set) (N=58)	B2101J (safety set) (N=56)
Median duration of follow up (months)	[redacted]	19.6	[redacted]
Patients with ≥ one AE, n (%)	[redacted]	[redacted]	[redacted]
Suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Death within 30 days post-infusion	[redacted]	[redacted]	[redacted]
Death >30 days post-infusion	[redacted]	17 (29.3)	[redacted]
Patients with serious or other significant events, n (%)			
Serious adverse event (SAE)	[redacted]	[redacted]	[redacted]
SAE suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Grade 3/4 AE	[redacted]	[redacted]	[redacted]
Grade 3/4 AE suspected to be study drug-related	[redacted]	[redacted]	[redacted]
Cytokine release syndrome (CRS), n (%)			
Patients with CRS	[redacted]	47 (81.0)	[redacted]
% of CRS events at grade 3/4	[redacted]	19 (32.7)	[redacted]

ERG's comments – tis-T clinical evidence

- Trials restricted to patients with life expectancy >12 weeks → patients in trial may be healthier/have higher performance status
- Uncertain if tis-T would be offered to patients with primary refractory ALL
- Analyses used in model apply to infused patients only→ excludes non-infused patients who may have poorer prognosis or have benefited from salvage chemo
- Patients previously treated with anti-CD19 therapies excluded from trials → effectiveness after blinatumomab treatment uncertain
- Insufficient follow-up to determine if treatment curative – clinical experts suggest at least 5 years of follow-up required
- [redacted] of patients had SCT after infusion: company stated in response to clarification that some clinicians in clinical trials chose to consolidate response with SCT, whereas SCT would only be an option in the UK for patients who relapse

Technical engagement – treatment pathway

Is treatment with tis-T appropriate for the Philadelphia chromosome positive population?

- **Company and NHSE:** No biologically plausible reason for Ph+ patients not to be treated with tis-T, such patients were included in trials (although patient numbers small)

What is the current treatment pathway for primary refractory patients?

- **NHSE**: Current standard those aged less than 18 years is mainly using the NOPHO protocol with blinatumomab used in young adults → appropriate comparator mainly NOPHO protocol
- **Company**: choice of treatments vary between individual patients and treatment centres → there is not one universally-used protocol

Where is blinatumomab placed in the treatment pathway?

- **NHSE:** Blinatumomab used at both 1st and 2nd relapse for adults and children
  - Tis-T trials excluded patients previously treated with blinatumomab → no evidence of the efficacy of tis-T in patients previously treated with blinatumomab
  - Inotuzumab ozogamicin is likely to rapidly displace much use of blinatumomab and especially so in the relapsed/refractory ALL population
- **Company:** Blinatumomab used at both 1st and 2nd relapse for adults and children
  - Clinical experts stated blinatumomab would typically be given for 1 or 2 cycles at 1st relapse → company states possibility of CD-19 escape is negligible and tis-T can be used subsequently

Comparator clinical evidence – blinatumomab

- Tis-T trials single arm studies so comparator efficacy data drawn from literature
- Company used evidence from von Stackelberg (2016)
  - Study in patients <18 years with relapsing/refractory B-Cell ALL (n=70)
  - Company stated feedback from experts suggested trial population fitter than those in tis-T trials based on proportion of refractory patients and patients with >3 lines of therapy → outcomes with blinatumomab may be poorer in population eligible for tis-T

ERG's critique of blinatumomab evidence

- Clinical expert feedback suggests blinatumomab would most likely be offered after first-relapse → may not be an appropriate comparator for tis-T
- Population considered very high risk based on tumour load, multiple prior relapses and short interval between latest treatment and start of blinatumomab → outcomes could be worse than would be expected for blinatumomab
- Median overall survival of 7.5 months in von Stackelberg lower than the overall survival of 9.9 months reported for the age 18–35 subgroup (n=123) in TOWER study of blinatumomab

Comparator clinical evidence – FLA-IDA

- No clinical trials identified by company's systematic review for FLA-IDA
- Clofarabine monotherapy/combination therapy used as proxy for efficacy of FLA-IDA
  - Studies chosen which aligned with expert feedback that median overall survival with FLA-IDA after 2nd relapse would be around 3 months
  - Studies with combination therapies excluded (scenario analyses based on data from 2 combination studies provided in response to clarification)
  - Jeha (2006) matched criteria and used in York regenerative medicines report, Hettle (2017) → considered most appropriate study by company

ERG's critique of FLA-IDA evidence (1)

- ERG identified 2 further studies providing evidence for efficacy of FLA-IDA
- ERG notes these studies have larger sample size and longer follow up than studies identified by the company → considers these studies more appropriate and reliable
- Kaplan—Meier curves unavailable for Sun → not suitable for use in model
  - Population more aligned with tis-T than Kuhlen, results supportive of Kuhlen

Sun (2017) – retrospective analysis
N=325, study duration 8 years

Patients ≤21 years old with relapsed or refractory B-cell ALL.
Similar baseline characteristics to tis-T studies

Complete remission rates:
51% after 2nd salvage attempt
<40% after 3rd/subsequent attempts

Kuhlen (2017) – retrospective analysis
N=242, median follow up 3.4 years

Paediatric patients with B-Cell ALL in 1st relapse after SCT
Similar baseline characteristics to tis-T studies (key differences on following slide)

Overall survival after 3 years: 20%
Event-free survival after 3 years: 15%

ERG's critique of FLA-IDA evidence (2)

- ERG prefer use of Kuhlen 2017 for FLA-IDA but note several limitations, which tend to favour tis-T:

Limitations of Kuhlen data	Direction of bias
All patients received SCT compared with [redacted] in tis-T trials	Patients who relapse post-SCT have a worse prognosis → underestimates OS
25% of patients in Kuhlen received only palliative care	Patients receiving palliative care less likely to survive long-term→ underestimates OS
Includes patients with T-cell ALL	Patients with T-cell ALL have a worse prognosis → underestimates OS
Includes patients who have relapsed within 6 months of SCT	Patients who relapse soon after SCT have a poorer prognosis → underestimates OS
Includes more patients in first relapse (29% vs [redacted] in B2101J)	Patients in first relapse have a better prognosis → overestimates OS
Includes patients with extramedullary relapse (20%) not included in tis-T trials	Patients with extramedullary relapse have a better prognosis → overestimates OS

Technical engagement – comparator data

Is there any evidence to support the equivalence of FLA-IDA and clofarabine?

Company:

- Clinical expert feedback indicated outcomes from Jeha consistent with practice
- Scenario analyses show results of economic model robust to alternative data sources of clofarabine efficacy → uncertainty in use of Jeha data addressed
- Differences in the Kuhlen study (such as 26% rate of 2nd SCT) do not reflect UK clinical practice → Kuhlen is not a more appropriate source of data than Jehan

NHSE:

- Clofarabine monotherapy data old (last data cut in Jeha in 2004)
- Supportive care improved (access to and speed of access to SCT donors improved
- Outcomes likely to be inferior to more contemporary use of FLA-IDA → use of clofarabine data as proxy for FLA-IDA inappropriate
- Heterogeneity of the data in any indirect comparisons of tis-T with chemotherapy and also with blinatumomab is noteworthy

Summary of key issues – clinical effectiveness

- Are the patient populations in the clinical evidence generalisable to NHS clinical practice?
- Is blinatumomab an appropriate comparator?
- Would the following populations be treated with tis-T:
  - patients with primary refractory ALL,
  - patients with Philadelphia chromosome positive ALL.
  - patients previously treated with anti CD-19 therapies (eg blinatumomab)
- Is it appropriate to use clofarabine as a proxy for FLA-IDA salvage chemotherapy?
- Which studies are appropriate to use as clinical evidence for the comparators?
- Is there sufficient evidence that tis-T should be considered a curative therapy?
- Should efficacy analysis include the entire ITT population?

NICE National Institute for Health and Care Excellence

Tisagenlecleucel-T for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [ID1167]

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Cost effectiveness

Committee C

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Evidence Review Group: CRD and CHE Technology Assessment Group, University of York

NICE technical team: Alan Lamb, Nicola Hay

Company: Novartis

22nd August 2018

Key issues – cost effectiveness

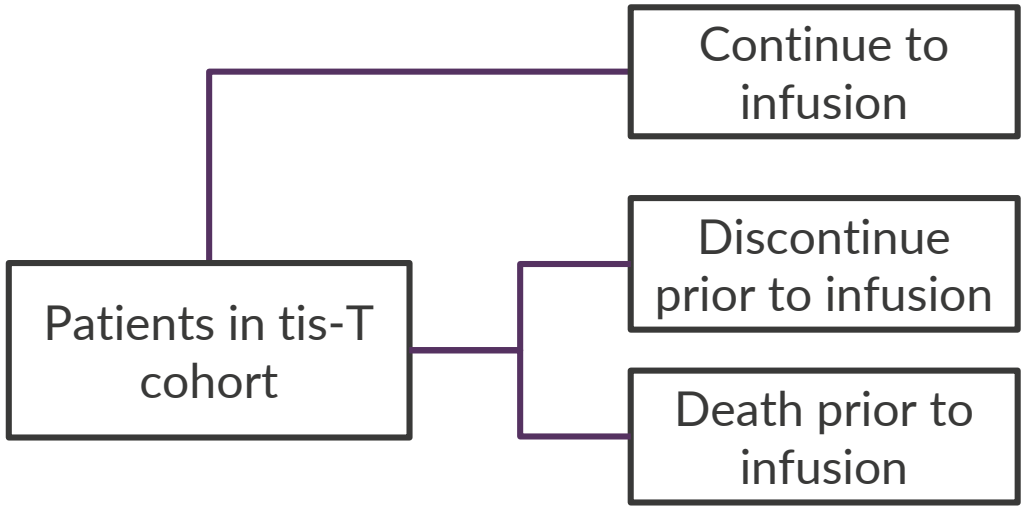
- Is it valid to assume a curative effect for tis-T (and comparators) in the model?
- Is blinatumomab an appropriate comparator?
- What is the most appropriate comparator data source for salvage chemotherapy?
- What is the most appropriate overall survival extrapolation?
- Addressing other uncertainties in the model:
  - Prevalence and duration of B-cell aplasia
  - Prevalence of stem-cell transplants
- Are the end of life criteria met?
- Should the 1.5% discount rate be applied?

Company's model scope

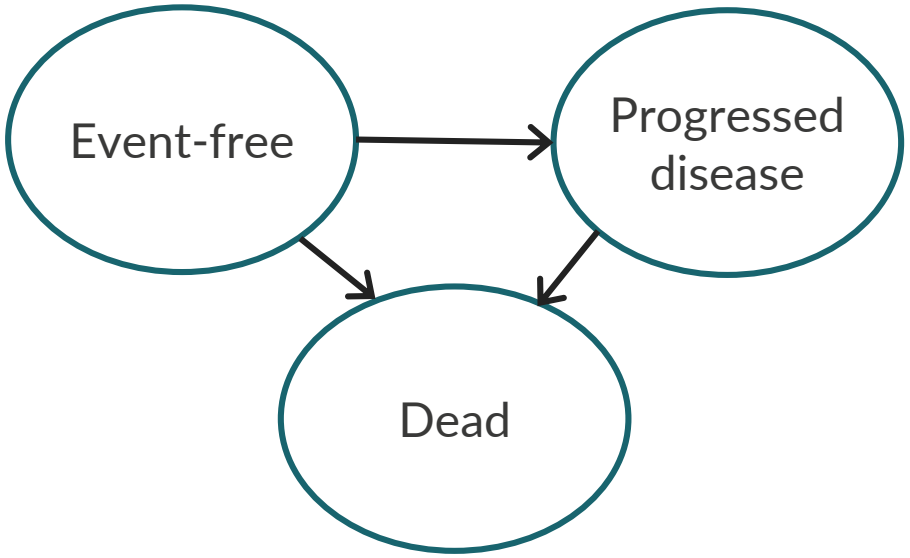
Population	Paediatric and young adult patients up to 25 years of age with B-cell ALL that is refractory, in relapse post-transplant, or in second/later relapse
Intervention	Tisagenlecleucel-T (tis-T)
Comparators	• Salvage chemotherapy (specifically, FLA-IDA [fludarabine, cytarabine and idarubicin]) • Blinatumomab
Outcome	Incremental cost per quality-adjusted life year (QALY) gained
Time horizon	88 years (lifetime)
Cycle length	Monthly
Half cycle correction	Yes
Discount rate	3.5% for costs and utilities (1.5% explored in sensitivity analyses)
Perspective	NHS and PSS
Subgroups	None

Company's model structure

Decision tree (tis-T only)



Partitioned survival model



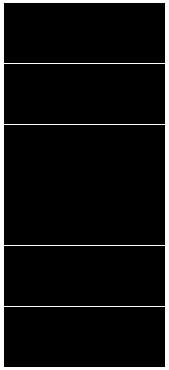
- Hybrid model with initial decision tree (tis-T only) and partitioned survival model (all groups):
  1. Event-free survival (EFS)
  2. Relapsed/progressed disease (PD)
  3. Death
- Naïve indirect comparison:
  - Tis-T – pooling of ELIANA, ENSIGN & B2101J;
  - Blinatumomab – von Stackelberg *et al*;
  - Salvage chemotherapy – Jeha *et al* (assuming clofarabine as proxy)
- Structural assumption that at 5 years, surviving patients enter long-term survival state (general population HRQoL and nominal costs)

Overall survival – company's approach

- **Tis-T** - exponential mixture-cure model with uplifted general population mortality in "cured" population. Approach justified on basis that:
  - Pooled tis-T studies show plateau after 32 months up until latest follow-up of 5 years – suggestive of curative effect
  - Consistent with clinical opinion
  - Similar to NICE TA450 (blinatumomab) and York regenerative medicines report (Hettle, 2017)
- **Blinatumomab** - log normal mixture-cure model with uplifted general population mortality in "cured" population. Approach justified on basis that:
  - Blinatumomab allows patients to receive stem cell transplant (SCT) and to achieve long-term overall survival (OS)
  - Consistent with tis-T modelling approach
  - Similar projected survival to standard Gompertz (used in TA450)
- **FLA-IDA** – standard generalised gamma model with uplifted general population mortality at 5 years (structural assumption). Approach justified on basis that:
  - Estimated cure fractions were too high ([redacted])
  - Clinical opinion suggests few patients would undergo SCT and achieve cure

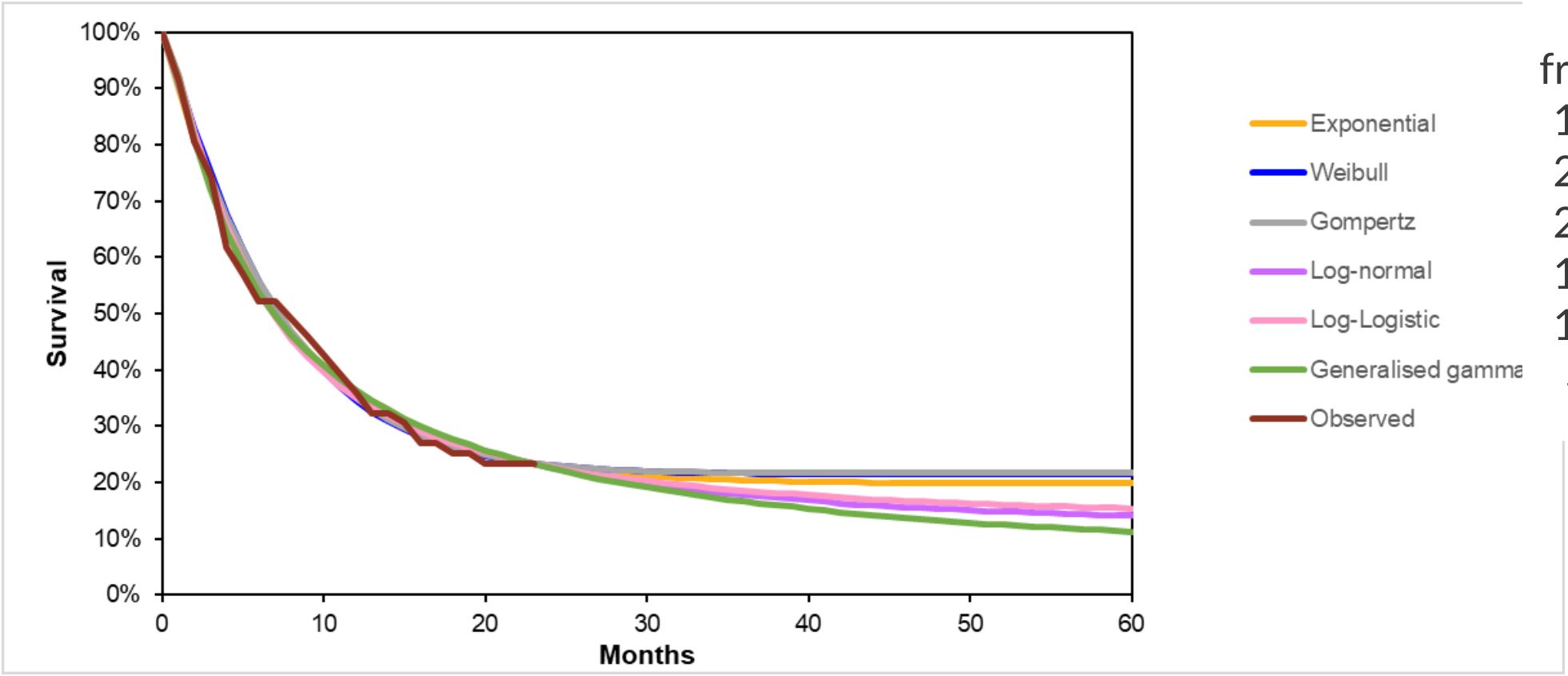
Overall survival – tis-T (pooled studies)

Cure fraction



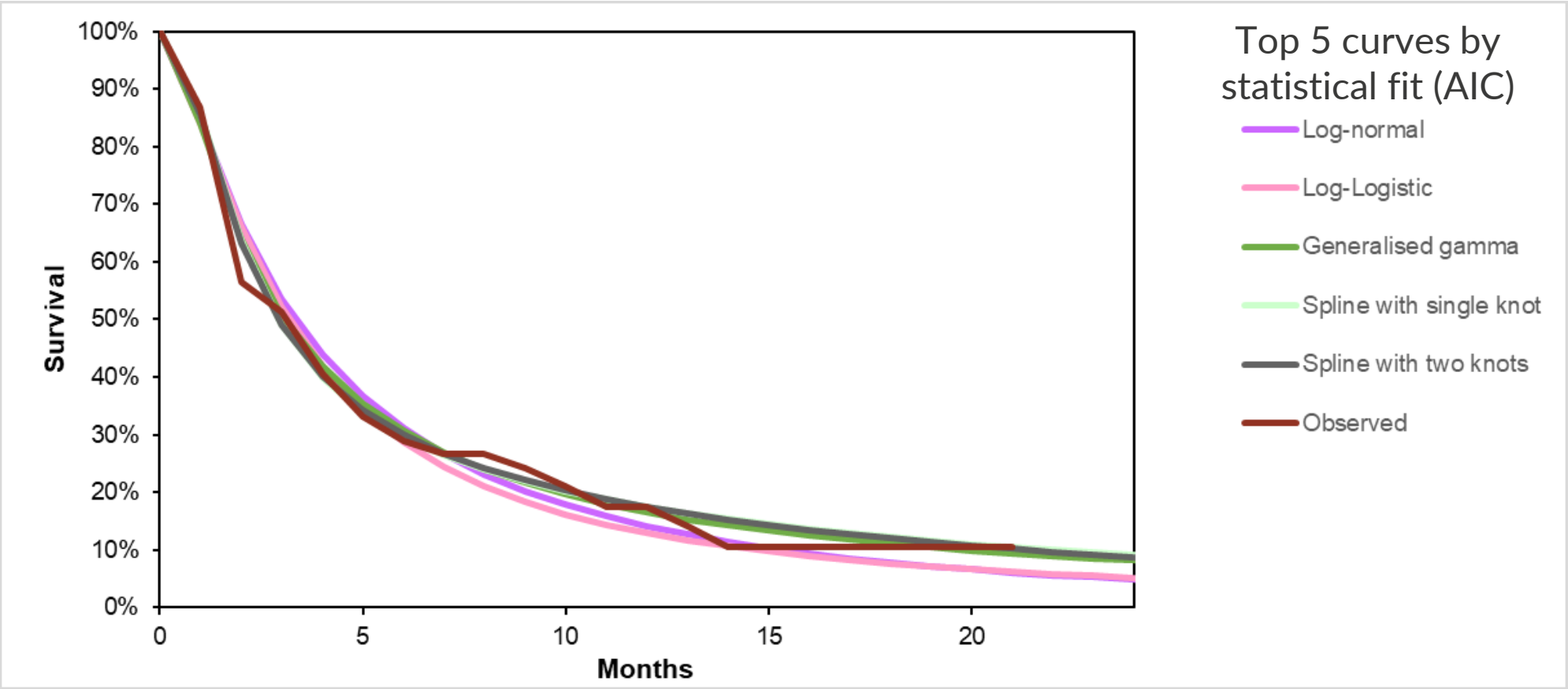
- Base case model - **exponential mixture-cure** (orange).
- Selected on basis of: (a) lowest AIC and BIC and (b) estimated cure fraction is closest to percentage of patients alive after 5 years of follow-up from pooled tis-T efficacy data ([redacted])

Overall survival – blinatumomab (von Stackelberg)



- Base case model – **log normal mixture-cure** (purple).
- Selected on basis of: (a) survival estimates judged to be plausible (b) AIC and BIC superior to log-logistic

Overall survival – salvage chemotherapy (Jeha)



- Base case model – **generalised gamma** (green)
- Selected on basis of: (a) being amongst the best fitting models (AIC and BIC); (b) 3% survival at 5-years was consistent with clinical feedback.

Summary of company's base-case survival curves (naïve indirect comparison)

Event-free survival – company's approach

- **Tis-T** – generalised gamma mixture-cure model with uplifted general population mortality in "cured" population. Approach justified on basis that:
  - None of the standard parametric or spline models provided a good fit to the available data
  - Consistent with OS modelling approach
- **Blinatumomab and salvage chemotherapy**
- No EFS data available for salvage chemotherapy or blinatumomab
- Hazard function for EFS assumed proportional to OS
  - Ratio modelled based on data from UK ALL study (note - patient population does not completely align with appraisal population)
  - Proportional relationship continues until year 5 assuming EFS ≤ OS
  - After year 5, cumulative survival probabilities for EFS assumed flat until EFS=OS

Event-free survival – tis-T

- Base case model - **generalised gamma mixture-cure model** (light blue-grey)
- Selected on basis of: (a) best statistical fit (along with Weibull and Gompertz), and (b) cure rate consistent with overall survival model ([redacted])

Summary of company's base case EFS curves (naïve indirect comparison)

Health-related quality of life

- Utility values from Kelly (2015) used in economic model. Company notes these values were used in Hettle (2017), obtained from large studies. Age-adjusted using Janssen (2014).
- ELIANA has limited EQ-5D data available (scenario analysis only)
- Model includes disutilities for SCT (-0.57), chemotherapy (-0.42) and CRS (-0.91)

State	HRQoL	Source
Health state utility values (base case)		
Event-free	0.91 (SD 0.16)	Kelly *et al* (2015)
Progressed disease	0.75 (SD 0.02)	
Long-term survival	0.91 (SD 0.16)	
Health state utility values (scenario analysis)		
Event-free	0.80 (SD 0.03)	ELIANA (31st Dec 2017 data cut)
Progressed disease	0.63 (SD 0.06)	

Resources and costs (1)

- Model includes costs associated with: pre-treatment for tis-T; drug acquisition & administration; follow-up & monitoring; hospitalisation and ICU; SCT and subsequent follow-up; adverse events (AEs), and terminal care
- PAS discounts available for tis-T, blinatumomab and tocilizumab
- Sourced from eMIT, BNF, NHS Reference Costs 2016/17

Item	Cost*	Notes
Tis-T infusion (total)	[redacted]	Includes transportation, manufacture, delivery, hospitalisation and ICU (includes PAS)
Salvage chemo	£17,208	Includes acquisition and administration. Excludes G-CSF for adult patients.
Blinatumomab	£96,025	Includes acquisition and administration. Assumes up to 5 cycles. Excludes PAS.
Monitoring	£19 to £440/year	Treatment-, time-, and state-dependent.
Terminal care	£7,509	Based on mean non-elective inpatient paediatric admission length of stay ≥1 day

Resources and costs (2)

Item	Cost*	Notes
AEs – Cytokine release syndrome	£18,029	Assumes [redacted] days in ICU and [redacted] doses of tocilizumab
AEs – B-cell aplasia	£11,285	All patients receive IVIG for duration of their aplasia (median treatment duration 11.40 months in ELIANA)
AEs – all	Various	Treatment-dependent
SCT	£116,311	Includes stem cell harvesting, SCT procedure and follow-up

- Rate of subsequent SCT varies by intervention:

Intervention	Rate of subsequent SCT	Source
Tis-T	[redacted]	Pooled tis-T studies
Salvage chemotherapy (FLA-IDA)	16.39%	Jeha *et al*
Blinatumomab	34.29%	Von Stackelberg *et al*

Company's results – deterministic base case (includes PAS for tis-T, excludes PAS for blinatumomab and tocilizumab)

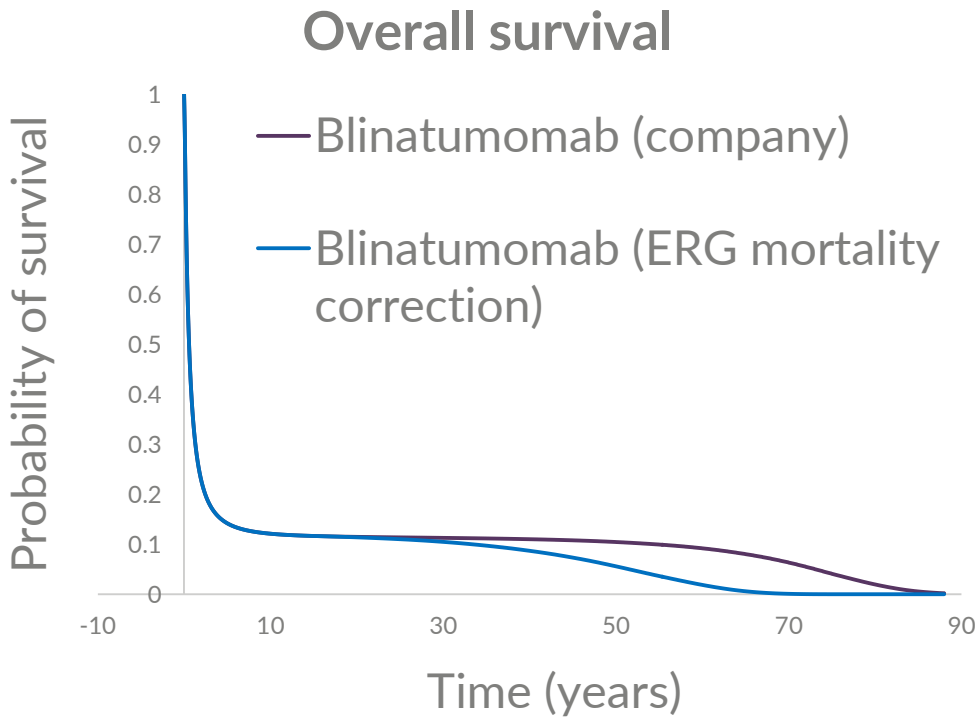
	Absolute			Incremental			
Option	LYGs	QALYs	Costs	LYGs	QALYs	Costs	ICER (£/QALY)
Tis-T	[redacted]	[redacted]	[redacted]			[redacted]	
Salvage chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,404
Blin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,392

ERG's critique - overview

1. Error in modelling long-term mortality
2. Relevance of blinatumomab as a comparator
3. Concerns regarding company's OS extrapolations
   a. Uncertainty regarding cure assumptions for tis-T and blinatumomab
   b. Source of data and modelling approach for salvage chemotherapy
4. Concerns regarding company's EFS extrapolation
5. Concerns regarding health utilities
6. Cost assumptions
   a) Holding beds for CRS events
   b) Patients unlikely to receive >2 cycles of blinatumomab
   c) Rates of SCT
   d) Proportion of patients requiring IVIG for hypogammaglobulinaemia (HGG)

ERG critique (1) - model errors

- ERG corrected an error regarding application of long-term mortality in the mixture cure models whereby the per-cycle mortality risk (the maximum of the cure model and uplifted general population risk) was applied to the cure model rather than the surviving cohort.
- Company states this approach was intended and that it reflects the most relevant survival estimates for the cured and uncured fractions in the mixture cure model



- ERG noted a further possible additional error in application of terminal care costs

ERG critique (2) – relevance of blinatumomab as a comparator

- Blinatumomab increasingly being used earlier in the pathway
- NICE guidance in place for patients who would receive blinatumomab as first-line salvage therapy – these patients would not receive blinatumomab again after 2nd relapse
- Efficacy of tis-T has not been demonstrated in patients previously treated with an anti-CD19 therapy

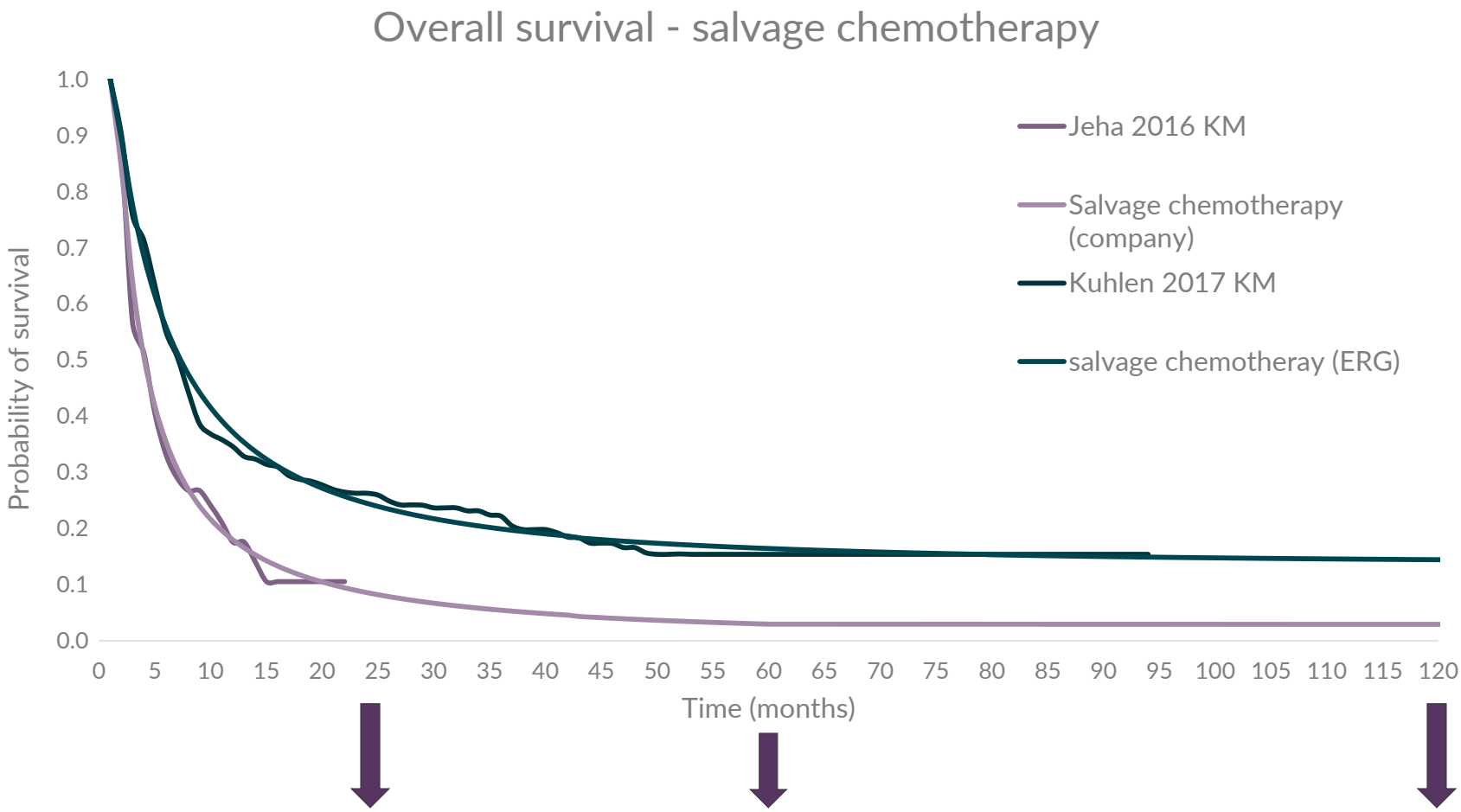
ERG critique (3a) – overall survival extrapolation for tis-T and blinatumomab

- For patients not progressing to tis-T infusion, not appropriate to assume costs and outcomes for comparator therapy – in ELIANA and ENSIGN, no non-infused patients achieved remission and all died within 6 months.
- Uncertainty regarding cure assumption for tis-T given short-term evidence
- Exemplified by wide range of cure rates predicted by modelling ([redacted] for tis-T, 4–22% for blinatumomab)
- Company selected second most optimistic mixture-cure model for tis-T
- Company's scenario analysis of defining a cure-point and then applying an adjusted general population mortality rate may be a more plausible and appropriate alternative given lack of long-term data

ERG critique (3b) – overall survival extrapolation for salvage chemotherapy

- ERG preferred use of mixture-cure model for salvage chemotherapy because of consistency with other modelled interventions and because results were more clinically plausible.
- ERG preferred OS extrapolation for FLA-IDA using data from Kuhlen *et al* (2017) - retrospective analysis of 242 paediatric patients with r/r B-cell ALL in first relapse post SCT. This study has a much larger sample size and longer follow-up.
- ERG notes that Kuhlen only includes patients who have had an SCT, whereas only [redacted] of patients in the tis-T trials had a prior SCT, hence OS may be under-estimated in Kuhlen *et al*.

ERG critique (3b) – overall survival extrapolation for salvage chemotherapy



Proportion of patients alive (%)			
Company base case	8%	3%	3%
ERG base case	24%	16%	14%

ERG critique (4) - company's event-free survival extrapolation

- Same uncertainties regarding use of mixture-cure approach for OS also apply to EFS
- ERG agrees with company's choice of generalised gamma distribution for tis-T
- Given the absence of data, ERG considers the company's approach to modelling comparator group EFS to be appropriate
- EFS data available in Kuhlen → ERG uses extrapolation based on these data for salvage chemotherapy EFS in ERG base case (mixture-cure model with log-normal distribution; cure fraction=4.3%)

ERG critique (5) – health utilities

- Utility value for PD state from Kelly *et al* (0.75) significantly higher than estimate from ELIANA (0.63)
- EFS value from Essig reflects patients cured following relapse and survived ≥5 years. Uncertain whether the utility of cured patients is equivalent to those in short-term EFS. Based on HUI-2 not EQ-5D.
- Health loss associated with SCT (disutility of -0.57 over 1-year) too large and applied for too long
- Health losses for lower grade CRS events and other grade 3/4 AEs excluded
- No health losses applied for AEs occurring beyond 8 weeks post-infusion (applies to [redacted] of patients)
- ERG considered that ELIANA study best reflects impact of tis-T on HRQoL during first 2-years post-treatment as it encompasses AE impacts

ERG critique (6a-b) – costs

- Costs of treatment and pre-treatment generally appropriate, although no training costs included for tis-T
- Assumption that patients not progressing to infusion incur 50% of costs of lymphodepleting chemotherapy and bridging chemo likely to be an underestimate
- ICU may be required to hold “spare bed” in anticipation of CRS event → cost included in ERG base-case
- Patients would be unlikely to receive >2 cycles of blinatumomab before progressing to SCT (marketing authorisation allows maximum of 5 cycles)
- Company should have included cost of G-CSF for adult patients receiving salvage therapy (i.e. FLAG-IDA not FLA-IDA)

ERG critique (6c-d) – costs

- ERG disagrees with evidence source for FLA-IDA – this not only affects EFS and OS, but also SCT rates. Kuhlen *et al* suggests a considerably higher SCT rate than Jeha *et al* (35% vs. 17%).
- 73% patients had not achieved B-cell recovery 2 years post-infusion, hence median time to B-cell recovery likely to underestimate true time and treatment costs. Proportion of patients requiring IVIG likely to have been overestimated.

Technical engagement – B-cell aplasia

Would patients <18 and 18-25 require treatment with intravenous immunoglobulin (IVIG) and for how long?

Company:

- Patients <18 with B-cell aplasia would be treated with IVIG
  - Clinical feedback: duration of [redacted] months assumed in company economic model is plausible
- Patients 18-25 treated with IVIG only if have concurrent severe infection or severe cytomegalovirus (CMV) reactivation (approx. 20% of patients)
  - Duration of treatment 6-12 months

NHSE:

- All patients in ELIANA responding to CAR-T cells developed B-cell aplasia and most of these patients received IVIG
- Until long-term data are available, a pragmatic estimate of IVIG treatment for B-Cell aplasia of up to 50% of responders for a period of 12-24 months would not be unreasonable

ERG exploratory analyses – base case

1. Long-term mortality correction
2. Log normal mixture-cure model fitted to EFS and OS data on salvage chemo from Kuhlen *et al*
3. Log logistic mixture-cure models fitted to OS data for tis-T and blinatumomab (same sources as company)
4. Tis-T EFS modelled using generalised gamma mixture-cure model
5. ELIANA EQ-5D utilities for first 2 years, followed by Kelly *et al* thereafter
6. Lower disutility (-0.13) for SCT 3-12 months post transplant
7. Costs and QALYs for non-infused patients based on OS from ELIANA & ENSIGN
8. IVIG used only in those with hypogammaglobulinaemia
9. Patients receive only 2 cycles of blinatumomab
10. Inclusion of costs of holding beds during CRS risk period

Results – ERG's alternative base case (includes tis-T PAS only)

	Total			Incremental			
Option	LYGs	QALYs	Costs	LYGs	QALYs	Costs	ICER (£/QALY)
ERG's base case (probabilistic)							
Tis-T	[redacted]	[redacted]	[redacted]			[redacted]	
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,265
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,501
ERG's base case (deterministic)							
Tis-T	[redacted]	[redacted]	[redacted]			[redacted]	
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,397
Blinatumomab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,732

Results exclude PAS for blinatumomab and tocilizumab

ERG exploratory analyses – individual analyses (includes tis-T PAS only)

Scenario	Inc. versus blinatumomab			Inc. versus salvage chemo		
	ΔQALYs	ΔCosts	ICER	ΔQALYs	ΔCosts	ICER
Company's base case	[redacted]	[redacted]	£18,392	[redacted]	[redacted]	£25,404
1. Mortality correction	[redacted]	[redacted]	£20,864	[redacted]	[redacted]	£28,806
2. Kuhlen log normal	[redacted]	[redacted]	£18,147	[redacted]	[redacted]	£33,110
3. Blin log logistic	[redacted]	[redacted]	£19,051	[redacted]	[redacted]	£25,368
4. Tis-T log logistic	[redacted]	[redacted]	£21,284	[redacted]	[redacted]	£28,203
5. ELIANA utilities	[redacted]	[redacted]	£18,796	[redacted]	[redacted]	£25,808
6. Lower SCT disutility	[redacted]	[redacted]	£18,572	[redacted]	[redacted]	£25,403
7. Non-infused outcomes from Tis-T studies	[redacted]	[redacted]	£18,108	[redacted]	[redacted]	£25,371
8. IVIG in HGG only	[redacted]	[redacted]	£16,956	[redacted]	[redacted]	£24,359
9. 2 cycles blinatumomab	[redacted]	[redacted]	£20,196	[redacted]	[redacted]	£25,330
10. CRS holding costs	[redacted]	[redacted]	£19,735	[redacted]	[redacted]	£26,382
ERG base case (probabilistic)	[redacted]	[redacted]	£29,501	[redacted]	[redacted]	£48,265

Results exclude PAS for blinatumomab and tocilizumab

ERG exploratory analyses using ERG base case (includes tis-T PAS only)

Scenario	Inc. versus blinatumomab			Inc. versus salvage chemo		
	ΔQALYs	ΔCosts	ICER	ΔQALYs	ΔCosts	ICER
ERG base case (deterministic)	[redacted]	[redacted]	£27,732	[redacted]	[redacted]	£45,397
0% tis-T receive SCT	[redacted]	[redacted]	£23,900	[redacted]	[redacted]	£41,274
100% tis-T receive SCT	[redacted]	[redacted]	£46,133	[redacted]	[redacted]	£65,229
3-year duration IVIG for HGG	[redacted]	[redacted]	£30,695	[redacted]	[redacted]	£48,475
IVIG use for HGG in EFS	[redacted]	[redacted]	£40,192	[redacted]	[redacted]	£58,342
Tis-T OS log normal cure model	[redacted]	[redacted]	£44,299	[redacted]	[redacted]	£74,322

Results exclude PAS for blinatumomab and tocilizumab

Statement from NHS England

Comments on the company's economic model

- The costs of patients having to remain close to treating centres need to be included in the economic analysis
- Hospital costs are challenging to estimate therefore a scenario analyses using the inpatient and follow up costs of a related service such as an allogeneic SCT would be useful

Discount rate

NICE methods guide	Company
• Reference case should use a discount rate of 3.5% for both costs and benefits • Differential discounting should be applied where treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years)	• Costs and benefits discounted at 3.5% annually in base case • Provide scenario analyses of discount rates of 1.5% and 5%

- Applying 1.5% discount rate to costs and benefits decreased company's base case ICER vs both blinatumomab and salvage chemotherapy by 36%.

End of life – Life expectancy

Criterion	Company submission	ERG comments
Life expectancy less than 24 months	**Criterion met** • von Stackelberg et al. (2016) – median OS with blinatumomab =7.5 months. • Jeha et al, (2006) – median OS with clofarabine (proxy for savage chemotherapy) = 13 weeks • Criterion met in previous appraisals of blinatumomab and inotuzumab	**Base case results for mean OS (undiscounted)** Blinatumomab: Company – [redacted] years ERG – [redacted] years Salvage chemotherapy: Company – [redacted] years ERG – [redacted] years **Proportion of patients alive after 2 years** Blinatumomab: 23% in both models Salvage chemotherapy: 8% in company model, 23% in ERG model

- No clinical data for median OS with FLA-IDA in relevant population
- Difference in estimates for salvage chemotherapy driven by use of alternative data source and mixture-cure model by ERG
- <25% of patients alive after 2 years in both company and ERG models
- Mean survival estimates from model driven by long-term survivors (patients alive after 5 years)
  - Blinatumomab: approx. 15% of patients long term survivors in both models
  - Salvage chemotherapy: 3% (company model) or 16% (ERG model) of patients long term survivors

End of life – Life extension

Criterion	Company submission	ERG comments
Extension to life greater than 3 months	**Criterion met** Median OS from the latest data cuts of the three tis-T clinical trials: • ELIANA: [redacted] with a max OS follow-up of [redacted] months • ENSIGN: [redacted] months [redacted] with a max OS follow-up of [redacted] months • B2101J: [redacted] months [redacted] with a max OS follow-up of [redacted] months	**Base case results for mean life extension (undiscounted)** Blinatumomab: Company – [redacted] years ERG – [redacted] years Salvage chemotherapy: Company – [redacted] years ERG – [redacted] years

Equality

- No equality factors identified in company submission
- During scoping it was noted that “Blood support or haematopoietic stem cell transplantation are not acceptable to some religious groups such as Jehovah’s witnesses these patients would receive best supportive care”
- *Population includes children: any additional considerations required?*

Innovation

- **Company considers tis-T to be innovative:**
  - "Represents a paradigm shift" in the management of paediatric and young adult relapsed/refractory ALL
  - Only a single infusion required
  - Potentially curative approach for patients with an otherwise poor prognosis
  - Substantial positive impact on patient and caregiver (for example, allowing return to school/university/employment) has not been captured within the economic analysis
- **Clinical expert statements:**
  - The technology is innovative and can cure new subsets of patients
  - The technology is a 'step-change' in the management of ALL

Key issues – cost effectiveness

- Is it valid to assume a curative effect for tis-T (and comparators) in the model?
- Is blinatumomab an appropriate comparator?
- What is the most appropriate comparator data source for salvage chemotherapy?
- What is the most appropriate overall survival extrapolation?
- Addressing other uncertainties in the model:
  - Prevalence and duration of B-cell aplasia
  - Prevalence of stem-cell transplants
- Are the end of life criteria met?
- Should the 1.5% discount rate be applied?

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