Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554)

For committee and projector – no CON information

Technology appraisal committee C [5 March 2024]

Chair: Steve O'Brien

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External assessment group: SCHARR

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Company: Novartis

Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged 25 and under (MA review of TA554)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary

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Background on B-cell acute lymphoblastic leukaemia (ALL)

ALL is a fast-spreading disease most common in young children

Causes

- ALL is a rare type of cancer affecting the blood and bone marrow, caused by the proliferation of lymphoblasts in the bone marrow and develops rapidly (within months)

Epidemiology

- ~790 people diagnosed each year in UK, most common in children, particularly 0 - 4 years
- Accounts for less than 1% of UK cancer cases and is slightly more common in males

Diagnosis and classification

- ALL can be further categorised according to type of lymphocytes affected (B or T-cell) and the presence or absence of the Philadelphia (Ph) chromosome.
- B-cell ALL represents 80% of cases in children, and 97% of children have Ph negative disease.
- Ph+ disease has a higher risk of relapse and refractory disease, with a different treatment pathway
    - Tisa-cel license covers + and - Ph status (subgroups not considered in this appraisal, in line with TA554).

Prognosis

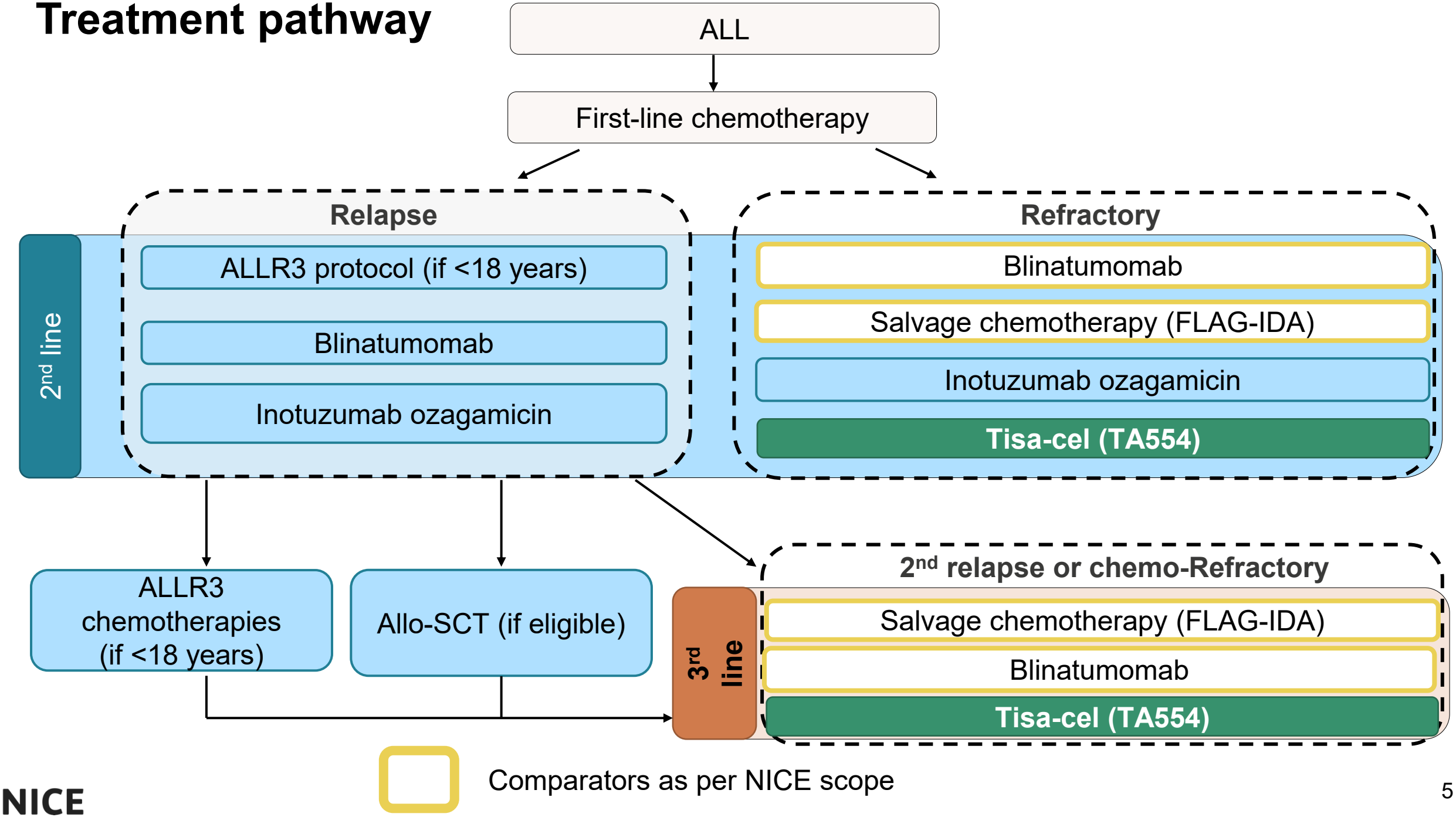
- Five-year survival outcomes vary greatly by age, (from >90% in the under 15s to ~58% in 15-39)
- Survival significantly reduced in relapsed/refractory setting (~10% 5 year survival).

Patient and clinical perspectives

"It is a devastating disease that fundamentally turns everything one knows into chaos and uncertainty." – Blood Cancer UK

- Disease has debilitating impact and wide range of symptoms
- Patients and carers often have to reduce or stop education / work
- Stem cell transplant (SCT) and chemotherapy have significant side-effects
- People with 2nd relapse often only have one curative option, targeted agents followed by an allogenic SCT (allo-SCT)
  - Allo-SCT depends on availability of donor and carries risk of transplant-related mortality (10-20% depending on fitness of patient and donor).
- Tisa-cel improves key outcomes, safety profile preferable compared with SCT
  - Drastically improves quality of life (QoL), allows patients and carers to regain some normalcy
  - Requires inpatient stay typically for 3-4 weeks
  - Side effects include cytokine release syndrome (60%), neurotoxicity (20-30%), prolonged cytopaenias (20-40%)
  - Hypogammaglobulinaemia very common - lack of persistence of CAR T cells occurring within 6 months of infusion is a major cause of treatment failure

Treatment pathway



Tisagenlecleucel (Kymriah, Novartis)

Marketing authorisation	• Tisa-cel is licensed for 'the treatment of paediatric and young adult patients up to and including 25 years of age with B-cell ALL that is refractory, in relapse post-transplant or in second or later relapse'.
Mechanism of action	• Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells
Administration	• Intravenous infusion
Price	• The list price for tisagenlecleucel is £282,000.00 as a one-off cost • There is a confidential patient access scheme • NHSE has a tariff for delivering CAR T-cell therapies

Summary of original appraisal (TA554) and CDF Review

NMA

- Pooled studies for Tisa-cel show curve plateaus around 32 months, suggesting cure
- Tisa-cel improved OS compared with blinatumomab and salvage chemotherapy

TA554

Tisa-cel is 'recommended for use within the CDF as an option for treating relapsed or refractory B-cell ALL in people aged up to 25 years, only if the conditions in the managed access agreement are followed.'

Review of TA554

- Updated study data
- New data collected during CDF use of tisa-cel

Abbreviations: ACM1, first appraisal committee meeting; CDF, cancer drugs fund; OS, overall survival

Issues

Key issues

Issue	ICER impact
1) Choice of comparator studies and extrapolation • In the scenario where tisa-cel is not available, should RIALTO or Von Stackelberg be used to model blinutumomab outcomes?	Moderate
2) Severity weighting for blinutumomab comparison (1.2 vs 1.7)	Large
3) Tariff price for CAR-T	Large
4) IVIg treatment: Proportion having intravenous immune globulin (IVIg) treatment and duration)	Small

Other issues

- ELIANA vs. pooled dataset for tisa-cel effectiveness? (see appendix: Other issue 1)
- Does definition of event free survival (EFS) in tisa-cel studies exaggerate effect? (see appendix: Other issue 2)
- Utility values (see appendix: Other issue 3)
- Minor equalities issues raised (see appendix: Equalities)

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Sources of clinical effectiveness evidence

Key studies for tisa-cel and comparators are single-arm

Single arm open-label clinical studies of **tisa-cel**

ELIANA – phase II
International (no UK centre)
N=97 enrolled, N=79 infused
✓ **in model**
Median follow-up 79.4 months

ENSIGN – phase II
US, multicentre
N=75 enrolled, N=64 infused
✗ not in model
Median follow-up 31.7 months

B2101J – phase I/IIa
US, single centre
N=67 enrolled, N=57 infused
✗ not in model
Median follow-up 47.2 months

ELIANA
Used in economic model for new submission

Pooled analysis
Used in economic model for original submission

SACT dataset (N=121)
Espuelas et al 2022 (N=128)
Real-world use of tisa-cel in UK
✗ not in model

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

Von Stackelberg et al 2016 - phase II
N=70
✓ **models blinatumomab**

Jeha et al 2006 - phase II
N=61
✓ **models FLAG-IDA**

Selected baseline characteristics

	Company	EAG	UK use of tisa-cel	
Characteristic	**ELIANA (N=79)**	**Pooled (N=200)**	**SACT (N=121)**	**Espuelas (N=128)**
Median age, years (range)	11.0 (3-24)	12.0 (1-25)	13 (nor reported)	11.3 (IQR 6.9-16)
≥18 years, n (%)	14 (18%)	30 (15%)	-	-
Ph positive, n (%)	2 (3%)	7 (4%)	16 (13%)	-
Prior haematopoietic SCT, n (%)	48 (61%)	113 (57%)	35% relapsed post SCT, 18% prior SCT (HES data)	52/115 (45.2%)
Primary refractory, n (%)	6 (8%)	16 (8%)	11 (9%)	-
Chemo-refractory or relapsed, n (%)	73 (92%)	184 (92%)	-	Median relapses 2 (IQR 1-2)
Median prior lines (range)	3 (1-8)	3 (1-9)	-	3 (IQR 2-3)
Prior blinatumomab, n (%)	-	-	42 (35%)	34 (26.6%)

Data are for infusion populations

ELIANA disease history, prior therapy from DCO April 2018

Large overlap between studies is likely as both cover real-world use of tisa-cel in UK

EAG

- Pooling data is preferable, original submission noted differences in baseline characteristics was minimal and outcomes were defined the same between studies
- Unclear why SACT data for prior SCT is contradictory

Abbreviations: DCO, data cut off; SCT, stem cell transplant

see appendix for baseline characteristics of studies comprising pooled dataset, ELIANA and Espuelas study design, and suitability of using pooled dataset

Tisa-cel study results – efficacy

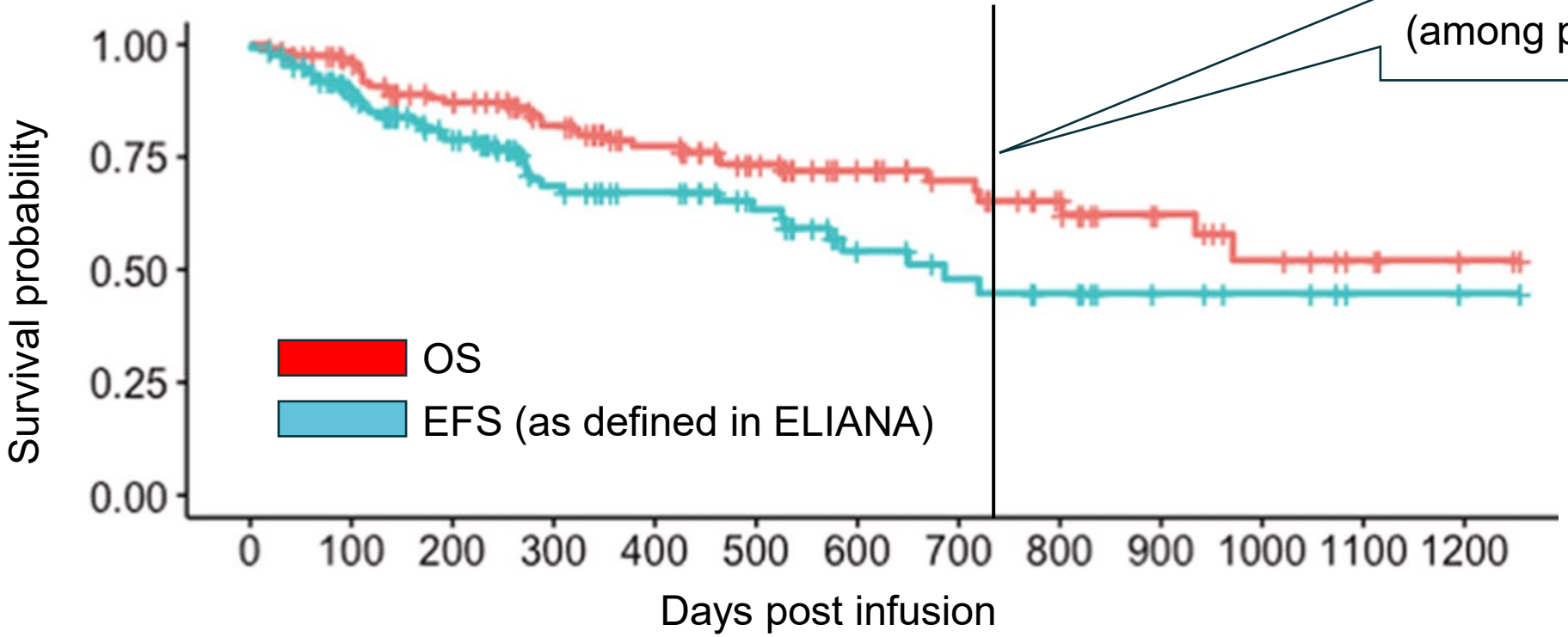
Abbreviations: EFS, event-free survival; OS, overall survival; NE, not estimable *2018 data-cut; ** EFS defined as in ELIANA. See appendix slide on EFS

	Company			EAG		
	ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)	Pooled (N=200)	SACT (N= 121)	Espuelas (N=128)
% complete response (CR) including those with incomplete blood count recovery	82 at 3 months*	70 at 6 months	95 at 28 days	-	-	-
% CR excluding those with incomplete blood count recovery	62	59	74	-	-	-
Duration of remission, median	47 months	NE	28 months	-	-	-
Median EFS	24 months	16 months	25 months	21 months	-	22 months
% EFS, 6 months	72	67	74	72	-	-
% EFS, 12 months	57	54	58	56	-	71**
% EFS, 24 months	50	48	50	49	-	50**
% EFS, 60 months	42	-	43	41	-	-
Median OS	NE	30 months	48 months	48 months	NE	
% died, total	42	47	47	45	24	-
% OS, 6 months	89	84	86	87	90	-
% OS, 12 months	77	65	79	74	81	80
% OS, 24 months	68	55	65	63	72	68
% OS, 60 months	56	-	47	47	67 (36 months)	-

Is pooling of data preferable, or is ELIANA more representative of clinical practice?

OS and EFS in study assessing use of tisa-cel in UK

OS and EFS for 128 patients in Espuelas 2022 (ITT population)



2-year OS 68%
2-year EFS 50%
(among people infused with tisa-cel)

Blood (2022) 140 (Supplement 1): 2408–2410.

NICE Abbreviations: EFS, event-free survival; ITT, intention to treat; OS, overall survival

Blinatumomab evidence base

Sources of blinatumomab effectiveness (both single-arm studies in R/R ALL)

	Von Stackelberg (N=70)	RIALTO (N=110)
Company preferred	✓ (also used in TA554)	✗ (used in TA554 scenario analysis)
EAG preferred	✗	✓
Population	Age <18y, median 8y	Age <18y, median 8y
Location	Europe + US	Europe + US
Line of relapse	• 1st relapse after full salvage induction / SCT • 2nd+ relapse • Refractory (56%) • Prior relapses: 0 (3%), 1 (44%), 2+ (52%)	• Relapse post-SCT (40%) • 2nd+ relapse (55%) • Refractory (15% primary refractory, 21% to reinduction)
Prior allo-SCT	57%	41%
Subsequent allo-SCT	34%	53%
Median OS	7.5 months	14.6 months
Company comments	Was accepted in TA554	Allowed prior blinatumomab, may include people from von Stackelberg
EAG comments	Likely higher risk than NHS: • 71% relapsed in 6m on prior tx • Low subsequent SCT rate	• Only 5% had prior blinatumomab • Clinical advice: sub-sequent SCT rate closer to clinical practice

- Subsequent SCT rate is a key driver of OS
- Von Stackelberg was used in TA554

57% in pooled dataset had prior haematopoietic SCT

EAG and company clinical advisors suggest SCT rate likely ~50%

Abbreviations: OS, overall survival; R/R ALL, relapsed or refractory acute lymphoblastic leukaemia; SCT, stem cell transplant

Salvage chemotherapy evidence base

Sources of FLAG-IDA effectiveness (both single-arm studies in R/R ALL)

	Jeha 2006 (N=61)	Kuhlen 2018 (N=242)
Company preferred	✓ (also used in TA554)	✗
EAG preferred	✗	✓
Population	• <21 years, median 12 years • 79% B-ALL, 21% T/other ALL%	• ≤19 years, median 11 years • 75% B-ALL, 25% other
Location	US	Austria
Intervention	• Clofarabine	• Nelarabine alone; or • Nelarabine+ cyclophosphamide + etoposide (25% palliative only)
Line of relapse	• 38% 2 prior regimens, 62% 3+	• 29% 1st relapse, 57% 2nd, 14% 3rd+
Prior allo-SCT	30% (25% one; 5% two)	100%
Subsequent allo-SCT	15%	26%
Median OS	3 months	~6 months
Company comments	Included	100% prior SCT, 20% extramedullary relapse
EAG comments	• TA554 + clinical advice suggest clofarabine rarely used but likely suitable proxy for FLAG-IDA • Access to SCT less available at time of study; may underestimate outcomes	• TA554 noted limitations with both studies, but concluded both suitable for decision making • Large sample size and long follow-up

Abbreviations: OS, overall survival; R/R ALL, relapsed or refractory acute lymphoblastic leukaemia; SCT, stem cell transplant

Indirect treatment comparison (ITC)

ITC shows tisa-cel improves OS compared to blinatumomab and salvage chemo

Background

- Matching adjusted indirect comparison (MAIC) used to single-arm studies of tisa-cel and comparators
- Single-arm design of studies means only unanchored ITCs are possible, which have a high risk of bias

High priority baseline characteristics adjusted for (yes vs. no)

	Blinatumomab dataset		Salvage chemo dataset	
	Pooled tisa-cel	ELIANA	Pooled tisa-cel	ELIANA
Trisomy 21	✗	✓	✗	✗
Prior lines of therapy	✗	✗	✓	✓
Previous relapses	✓	✓	✗	✗
Prior HSCT	✓	✓	✓	✓

EAG comments

- HRs for MAIC are very similar to naïve comparisons suggests matching had little impact → key treatment effect modifiers and prognostic factors likely not appropriately accounted for

Naïve ITC OS results (company base-case)

	Pooled	ELIANA
HR (95% CIs) Vs. Blinatumomab	0.29 (0.20, 0.44)	0.26 (0.16, 0.43)
HR (95% CIs) Vs. salvage chemo	0.16 (0.11, 0.23)	0.14 (0.09, 0.24)

MAIC results for OS

	Pooled	ELIANA
HR (95% CIs) Vs. Blinatumomab	0.32 (0.21, 0.48)	0.31 (0.18, 0.55)
HR (95% CIs) Vs. salvage chemo	0.20 (0.14, 0.31)	0.19 (0.10, 0.35)

Abbreviations: CI, confidence interval; HR, Hazard ratio; OS, overall survival

Key issue 1 : Effectiveness of tisa-cel versus comparators

EAG: alternative relevant studies may show better outcomes for comparators

Background

- Single-arm design of studies means only unanchored ITCs are possible, which have a high risk of bias

Company

- Von Stackelberg deemed appropriate for decision making in TA554
- Tisa-cel has changed the way blinatumomab is used
  - tisa-cel often used in people for whom allo-SCT is unsuitable e.g. relapse after prior allo-SCT (estimate 50%)
  - blinatumomab typically used to bridge to allo-SCT resulting in higher rates of allo-SCT and improved OS
- If tisa-cel not available, there is less opportunity to use blinatumomab more in those patients who are good candidates for allo-SCT, so would expect lower rates of allo-SCT and poorer OS
- Tisa-cel was licensed during the enrolment period of the RIALTO trial, but not during the von Stackelberg study

EAG comments

- Company's selection of comparator studies neither transparent nor well justified
- Company's advisors estimate 56% subsequent allo-SCT after blinatumomab, 38% after FLAG-IDA
- Allo-SCT rates (and therefore OS) may be more generalisable using other comparator studies:
  - Blinatumomab: RIALTO (53% subsequent allo-SCT; median OS 14.6 months)
  - FLAG-IDA: Kuhlen (subsequent allo-SCT rate 26%; median OS 6 months)

If tisa-cel was not available, which studies would reflect clinical practice for allo-SCT rates and OS outcomes? Which comparator studies should be included?

Abbreviations: ITC, indirect treatment comparison; OS, overall survival; SCT, stem cell transplant

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Extrapolating OS and EFS

Mixture cure models (MCMs) are used to extrapolate data

Background

- MCMs require all studies to have sufficient follow-up and number of events to estimate reliable cure fraction
- Company and EAG prefer different MCMs using different data sources – see Key Issue 1 and 3
- EFS for comparators modelled by applying HR from UK study in ALL and applying to modelled OS function

Company

- Log-logistic for tisa-cel EFS and OS → cure fraction is close to clinician estimates and good fit to ELIANA curves

Company and EAG choices for modelling OS

	Company MCM choice for OS	EAG MCM choice for OS
Tisa-cel	Log-logistic (ELIANA)	Log-logistic (pooled data)
Blinatumomab	Log-normal (von Stackelberg)	Log-logistic (RIALTO)
FLAG-IDA	Log-normal (Jeha)	Log-normal (Kuhlen)

EAG

- If using ELIANA, log-normal better as closer to clinician estimates of OS at all timepoints
- OS in the comparator groups likely to have been underestimated
- Reliance on elicited cure fractions to select preferred survival models not an optimal approach
- All survival models in the company's economic model are reliant on sufficient follow-up and no. of events to estimate a reliable cure fraction → prudent to explore other flexible parametric models, including the structural assumption of a cure timepoint

Abbreviations: ALL, acute lymphoblastic leukamia; EFS, event free survival; ITC, indirect treatment comparison; OS, overall survival; SCT, stem cell transplant

Extrapolating OS and EFS – assuming ELIANA alone

Company make choice based on estimates of cure, EAG on estimates of OS

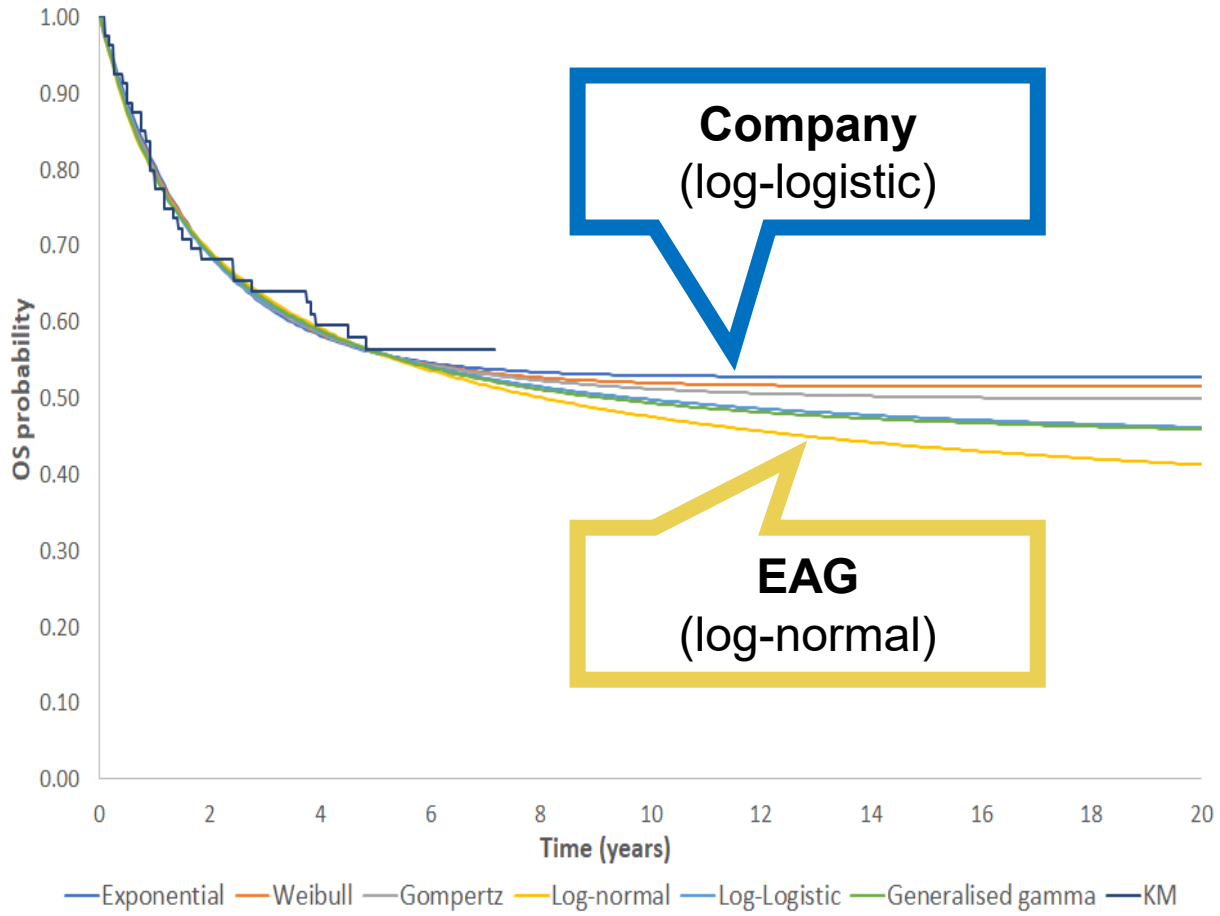
Background

- If using ELIANA alone, company and EAG differ on source of extrapolation method → EAG prefer log-normal (closer to clinician estimate of OS), company prefer log-logistic (closer to estimate of cure)
- EAG's preferred analysis uses pooled data for tisa-cel and alternative studies for the comparators

Tisa-cel cure and OS for key extrapolation methods compared with clinician estimate

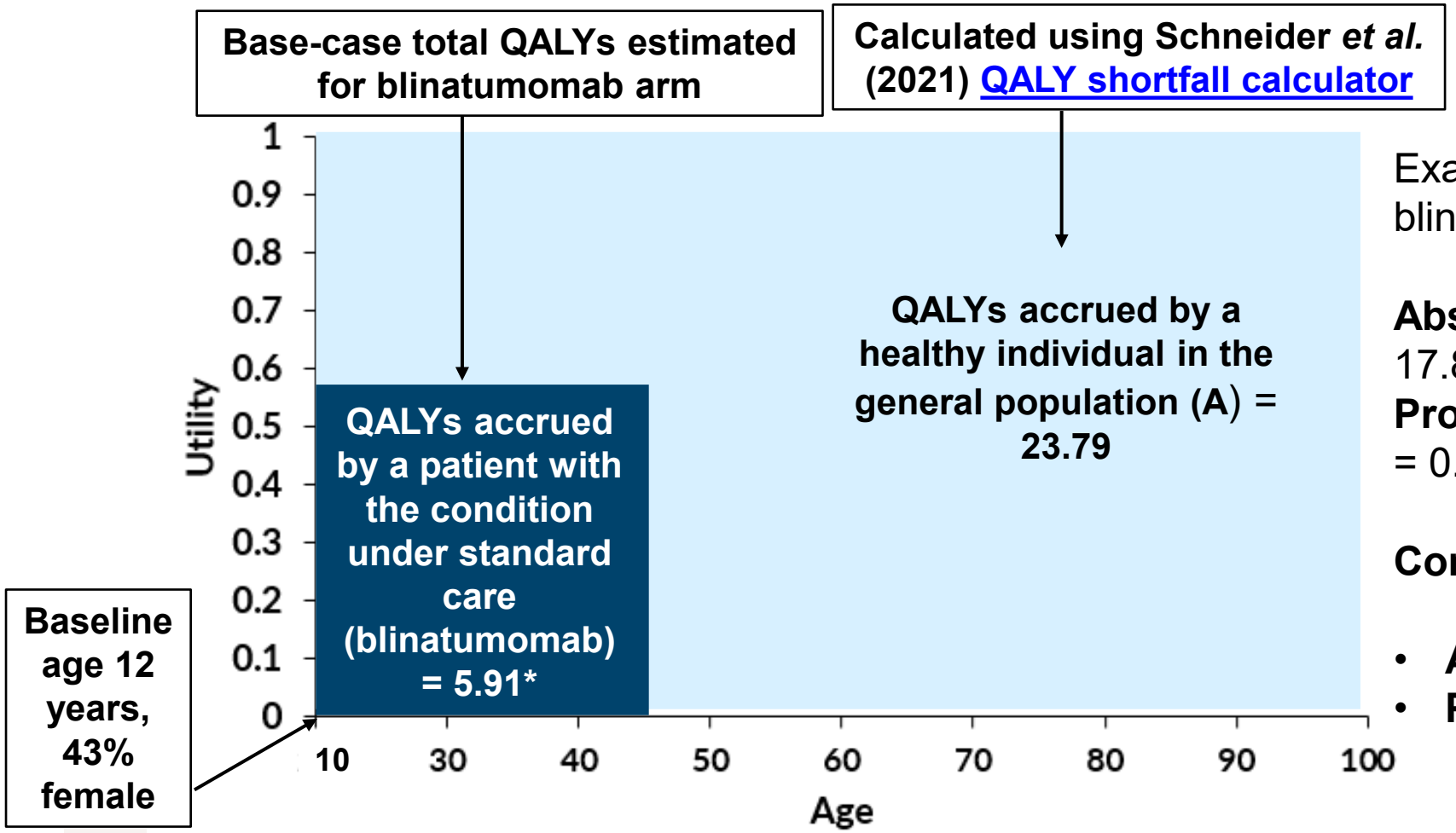
	Log-logistic (ELIANA)	Log-normal (ELIANA)	Log-logistic (pooled)	Clinician estimate
Cure fraction	42.4%	32.8%	34%	40.0%
1 yr OS	79%	79%	77%	76%
5 yr OS	56%	56%	48%	54%
10 yr OS	50%	47%	41%	47%
20 yr OS	46%	41%	37%	42%

Tisa-cel extrapolation choices for OS (ELIANA alone)



QALY weighting for severity

NICE methods now include a QALY weighting system based on disease severity



Example using **EAG estimate** of blinatumomab effectiveness:

Absolute shortfall = 23.79 – 5.91 = 17.88
Proportional shortfall = 17.88 / 23.79 = 0.75

Corresponding QALY weights:

- **Absolute shortfall** = 1.2
- **Proportional shortfall** = 1.2

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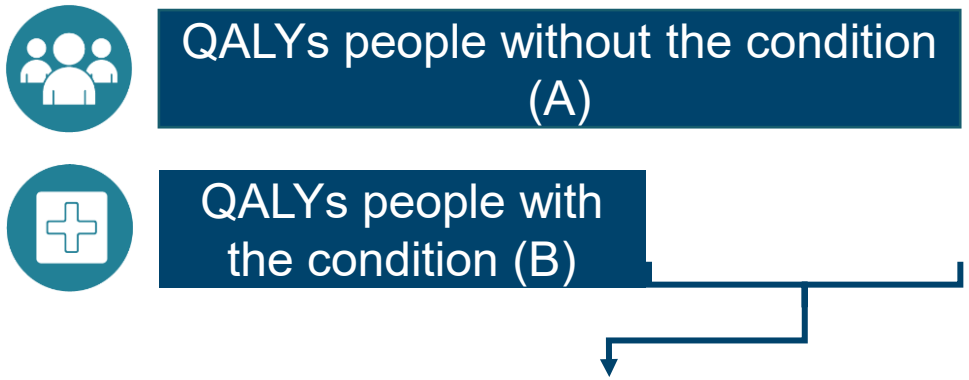
QALY weightings for severity

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: weighting applied according to **whichever of absolute or proportional shortfall implies the greater severity**.

QALY shortfall key

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Company and EAG calculations of shortfall

Source	General Population (QALY)	Treatment	Total QALYs for this population	Absolute Shortfall (AS)	Proportional Shortfall (PS)	Severity modifier
Company	23.79	Salvage-chemo	2.22	21.57	0.91	1.7
		Blinatumomab	3.06	20.73	0.87	1.7
EAG*	23.79	Salvage-chemo	3.69	20.10	0.84	1.7
		Blinatumomab	5.91	17.88	0.75	1.2

*EAG severity weighting dependent on applying their assumption of comparator study

Abbreviations: QALY, quality-adjusted life year

CAR-T tariff costs

NHSE tariff covers costs of administering CAR-T therapies and associated costs

Costs included in tariff (can be excluded from model)

Costs associated with	Included in NHS tariff?
Leukapheresis	Yes
Tisa-cel delivery in hospital	Yes
Adverse events in hospital	Yes
Monitoring for 100 days	Yes
Training	Yes
Conditioning and bridging chemotherapy acquisition, administration and delivery	No
Tisa-cel acquisition	No
Subsequent treatments	No
Subsequent allo-SCT	No

Tariff costs for this appraisal

	Patients treated 2018 - Sept 23			
Age bracket	Patients	%	Tariff	Weighted
18 or under	110	83	£106,504	£88,086
19 or older	23	17	£41,101	£7,108
Total	133	-	-	£95,194

Tariff price appropriate for this appraisal is **£95,194**

Key issue 5: Duration of IVIg treatment

Duration of IVIg treatment differs depending on source and data-cut

Proportion without B-cell recovery in key studies

	Company	EAG	SACT
% of those infused with tisa-cel who get IVIg	30.4%	30.4%	47%
Duration of IVIg, months (per person who get IVIg)	11.4	25.5	18
Duration of IVIg, months (per person infused with tisa-cel)	3.5	7.8	8.5
Expected cost per patient receiving tisa-cel infusion	£6,173	£13,809	£15,081

Company

- Assumptions based on ELIANA
- 40.5% developed hypogammaglobulinemia, of whom 75% get treatment
- Duration based on time to B-cell recovery

Abbreviations: EFS, event-free survival; IVIg, intravenous immunoglobulin; SCT, stem cell transplant

EAG

- 1 clinical adviser said subcutaneous immunoglobulin (SCIg) use is possible → would avoid hospital costs
- Time to B-cell recovery in later datacut of ELIANA ~38 months, much longer than datacut preferred by company
- EAG preferred duration reflects 5-year EFS estimates adjusted for subsequent allo-SCT rate

- What is the most likely duration for B-cell recovery?
- What proportion of people having tisa-cel will require IVIg treatment?
- How long do people have IVIg treatment for?

Discount rate

Company: non-reference case discounting has been included in **scenario analysis**

Background

- Section 4.5.3 of the NICE manual states the "*committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects*" if certain criteria are met

Company

- Believe that criteria are met for non-reference case discounting to be considered:
  - Patients live shortened or impaired life; life expectancy estimated to be less than 24 months
  - Potential for tisa-cel to restore patients to full or near full health
  - Through experience in CDF, evidence suggests 40% patients would be cured following tisa-cel treatment

To note: In TA554, a discount rate of 3.5% was applied for costs and benefits → no robust evidence that tisa-cel was a curative therapy

Abbreviations: CDF, cancer drugs fund

Summary of company and EAG base case assumptions

Key differences focus on choice of data for efficacy of tisa-cel and comparators

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Source of tisa-cel data	ELIANA alone	Pooled dataset of 3 key studies
Blinutumomab data	Von Stackelberg Log-normal for OS Subsequent allo-SCT: 34%	RIALTO Log-logistic for OS Subsequent allo-SCT: 53%
Salvage chemotherapy	Jeha Log-normal for OS Subsequent allo-SCT: 15%	Kuhlen Log-normal for OS Subsequent allo-SCT: 26%
Terminal care costs for people dying prior to infusion	Exclude	Include
IVIg treatment duration	11.4 months	25.5 months
Blinutumomab severity weighting*	1.7	1.2
Salvage chemotherapy severity weighting*	1.7	1.7

*EAG severity weighting dependent on applying their assumption of comparator study

Abbreviations: IVIg, intravenous immunoglobulin; OS, overall survival; SCT, stem cell transplant

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Company base case and EAG scenarios

No.	Scenario (applied to company base case)	ICER (£/QALY) versus blinutumomab	ICER (£/QALY) versus FLAG-IDA
1	**Company base case**		
2	Pooled data for tisa-cel	↑	↑
3	Alternative data sources for comparators and models	↑	↑
4	Terminal care costs for people dying prior to infusion	↑	↑
5	IVIg treatment duration = 25.5 months	↑	↑
6	Inclusion of updated unit costs from eMIT and BNF	↑	↑
7	**EAG base case (2-6 combined)**	↑	↑

Results do not include confidential commercial discounts for comparators

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3) Tariff price for CAR-T	Large
4) IVIg treatment: Proportion having intravenous immune globulin (IVIg) treatment and duration)	Small

Other issues

- ELIANA vs. pooled dataset for tisa-cel effectiveness? (see appendix: Other issue 1)
- Does definition of event free survival (EFS) in tisa-cel studies exaggerate effect? (see appendix: Other issue 2)
- Utility values (see appendix: Other issue 3)
- Minor equalities issues raised (see appendix: Equalities)

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Thank you.

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Back-up slides

Patient and clinical perspectives (1)

Submissions from a clinical expert, 2 patient experts, Anthony Nolan, Blood Cancer UK and Leukaemia Care

Symptoms and impact

- Common symptoms include fatigue, nausea or vomiting, feeling weak or breathless, sleeping problems, headaches, lower backpain and weight loss
- Considerable impact on carers (anxiety, emotional disress, stress, guilt)
- 80% of 16-24-year-olds report having to reduce hours in education/work; nearly half stop completely
- Carers often have to leave jobs too

"It is a devastating disease that fundamentally turns everything one knows into chaos and uncertainty." – Blood Cancer UK

Current treatments

- Typical treatments include stem cell transplant (SCT) and chemotherapy
- Both have significant side effects: Hair loss, fatigue, immunosuppression leading to infections, mucositis, loss of fertility, loss of bone density, increased risk of secondary cancers, graft vs host disease, organ damage
- People who have had second relapse often only have one curative option (targeted agents such a Blinatumomab or Inotzumab) followed by an allogeneic SCT) which carries risk of transplant-related mortality (10-20% depending on fitness of patient and donor).
- Allo-SCT depends on availability of a well-matched donor cell source

Abbreviations: SCT, stem cell transplant

Patient and clinical perspectives (2)

Submissions from a clinical expert, 2 patient experts, Anthony Nolan, Blood Cancer UK and Leukaemia Care

Benefits of tisa-cel

- Improves OS, EFS and RFS - side effects very minor compared to alternative treatments
- *"It has offered unquantifiable hope to patients and families"*
- Patients and their families repeatedly report patient feels better following tisa-cel infusion than they have done since diagnosis
- Improved quality of life for patients and carers: reduced hospital visits, better health of patient
- Patients and carers can return to school/ education/ work
- Improved social and physical development for the patient, improved self-esteem

Drawbacks or side-effects of tisa-cel

- Delivery requires inpatient stay for generally 3-4 weeks
- Short term acute side effects - generally arise in the context of hospital delivery and can persist for up to 4-6 weeks but generally have a duration of days - vast majority lead to complete recovery with no long-lasting effects

- "CAR-T saved my son's life. I wish we could have had it sooner." – patient expert

Abbreviations: OS, overall survival; EFS, event free survival; RFS, relapse-free survival

Equality considerations

Several issues were raised during the scoping consultation exercise:

- People from ethnic minority backgrounds have fewer chances of finding a suitable allogeneic stem cell match → may be disadvantaged if alternative treatments such as tisa-cel are not routinely commissioned.
    - TA893 (where this issue was identified also) acknowledged that a technology appraisal cannot change how suitable matches for allogeneic stem cell transplant are identified

- High unmet need for a CAR-T in people aged up to 25 years → patients aged 26 and over now have access to brexucabtagene autoleucel (TA893) through the Cancer Drugs Fund

Are there any equality issues relevant to the potential recommendations?

Selected baseline characteristics (infused cohorts)

	Company			EAG	
Characteristic*	**ELIANA (N=79)**	**ENSIGN (N=64)**	**B2101J (N=57)**	**Pooled (N=200)**	**SACT (N=121)**
Median age, years (range)	11.0 (3-24)	12.5 (3-25)	11.0 (1-24)	12.0 (1-25)	13 (nor reported)
≥18 years, n (%)	14 (18%)	10 (16%)	6 (11%)	30 (15%)	-
Ph positive, n (%)	2 (3%)	2 (3%)	3 (5%)	7 (4%)	16 (13%)
prior haematopoietic SCT, n (%)	48 (61%)	28 (44%)	37 (65%)	113 (57%)	35% relapsed post SCT, 18% prior SCT (HES data)
Primary refractory, n (%)	6 (8%)	7 (11%)	3 (5%)	16 (8%)	11 (9%)
Chemo-refractory or relapsed, n (%)	73 (92%)	57 (89%)	54 (95%)	184 (92%)	-
Median prior lines (range)	3 (1-8)	3 (1-9)	4 (1-8)	3 (1-9)	-
Prior blinatumomab, n (%)	-	-	-	-	42 (35)

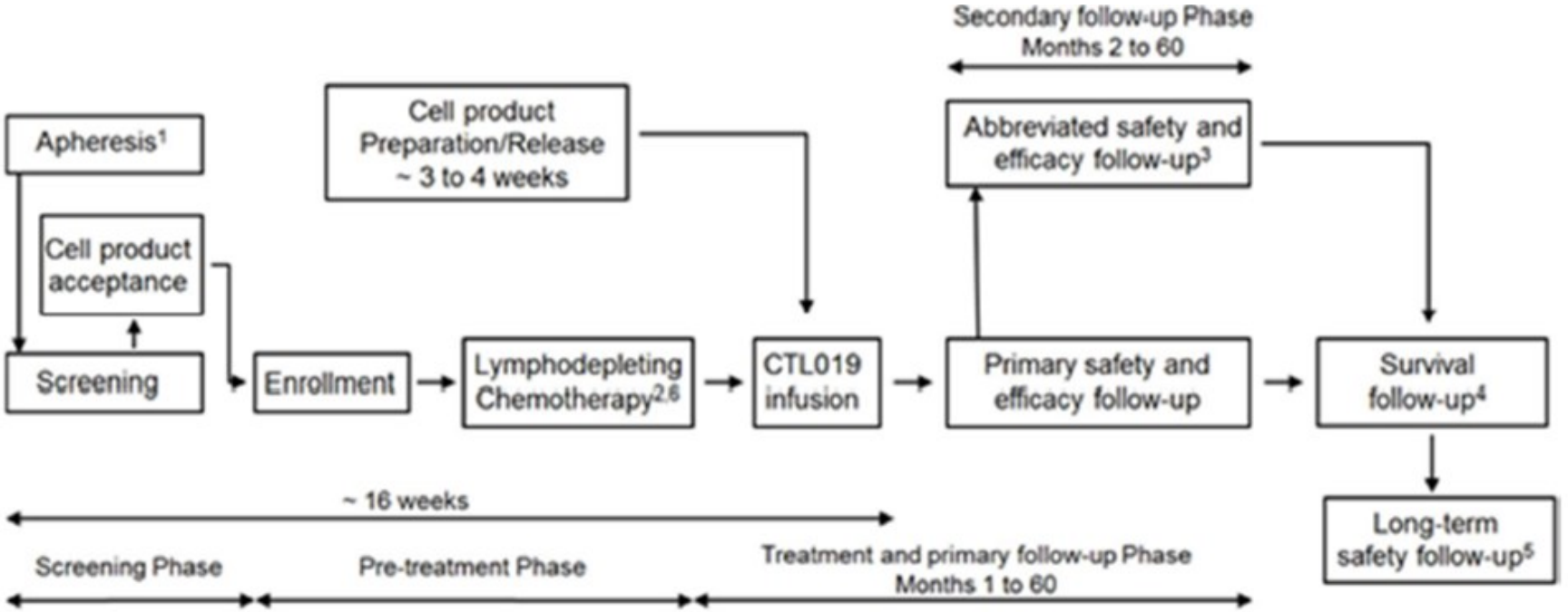
* ELIANA disease history, prior therapy data calculated using DCO April 2018, B2101J data for non-CNS3 only

EAG

- Pooling of data is appropriate and preferable over relying on ELIANA study alone.
- Original company submission noted differences in baseline characteristics was minimal and outcomes were defined the same between studies
- Unclear why SACT data for prior SCT is contradictory

Abbreviations: DCO, data cut-off; SCT, stem cell transplant

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

Primary endpoint

- Overall remission rate (independently-assessed)

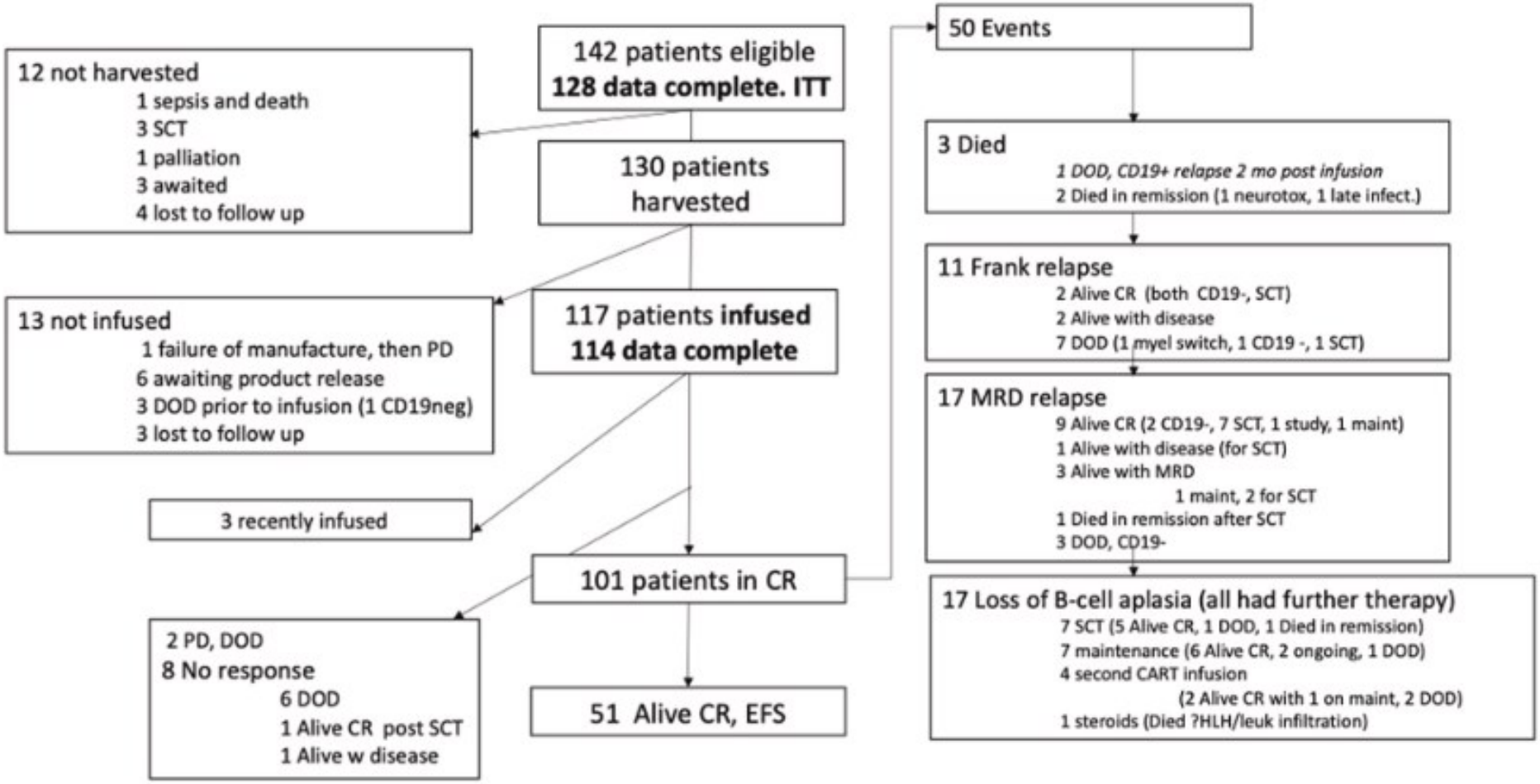
Secondary endpoints used in economic model

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

Abbreviations: ALL, acute lymphoblastic leukaemia; SCT, stem cell transplant

Espuelas et al 2022 – study design

Flow chart for participants included in study of tisa-cel use in UK



Abbreviations: CR, complete remission; ITT, intention to treat; PD, progressed disease; SCT, stem cell transplant

Tisa-cel study results – efficacy

	Company			EAG		
n (%)	ELIANA (N=79)	ENSIGN (N=64)	B2101J (N=57)	Pooled (N=200)	SACT (N= 121)	UK analysis (N=128)
ORR (CR including those with incomplete blood count recovery)	82% at 3 months*	70% at 6 months	95% at 28 days	-	--	-
CR excluding those with incomplete blood count recovery	62%*	59%	74%			
Duration of remission, median	47 months	NE	28 months	-	-	-
Median EFS	24 months	16 months	25 months	21 months	-	-
% EFS, 6 months	72	67	74	72	-	-
% EFS, 12 months	57	54	58	56	-	71** / 45***
% EFS, 24 months	50	48	50	49	-	50** / 38***
% EFS, 60 months	42	-	43	41		-
Median OS	NE	30 months	48 months	48 months	NE	
% died, total	42	47	47	45	24	-
% OS, 6 months	89	84	86	87	90	-
% OS, 12 months	77	65	79	74	81	-
% OS, 24 months	68	55	65	63	72	-
% OS, 60 months	56	-	47	47	67 (36 months)	-

*2018 data-cut; ** EFS defined as in ELIANA; *** EFS defined using stringent criteria

Abbreviations: EFS, event-free survival; OS, overall survival; NE, not estimable

Other issue 1: Preference for ELIANA study vs pooled data

Company prefer using ELIANA alone, EAG prefer pooled data of all 3 studies

Background

- TA554 pooled all 3 key studies to estimate tisa-cel effectiveness
- New submission relies solely on ELIANA (Impact of pooled dataset explored in scenario analyses)

Company

- ELIANA (N=79) has the longest follow-up and is most generalisable to UK clinical practice
- Pooled dataset results comparable to ELIANA but results in shorter median follow-up (48.2 versus 79.4 months)

EAG comments

- Economic model should be informed by the pooled dataset (N=200)
- Company suggests study design and median dose are similar, and differences in baseline characteristic were minor – clinical advice to EAG suggests pooled data is representative of NHS
- Excluding studies enhances uncertainty of tisa-cel effect that were evidenced upon entry to CDF
- Important as ENSIGN and B2101J have comparatively poorer EFS and OS than ELIANA

Is the pooled dataset or the ELIANA study alone more suitable for decision making?

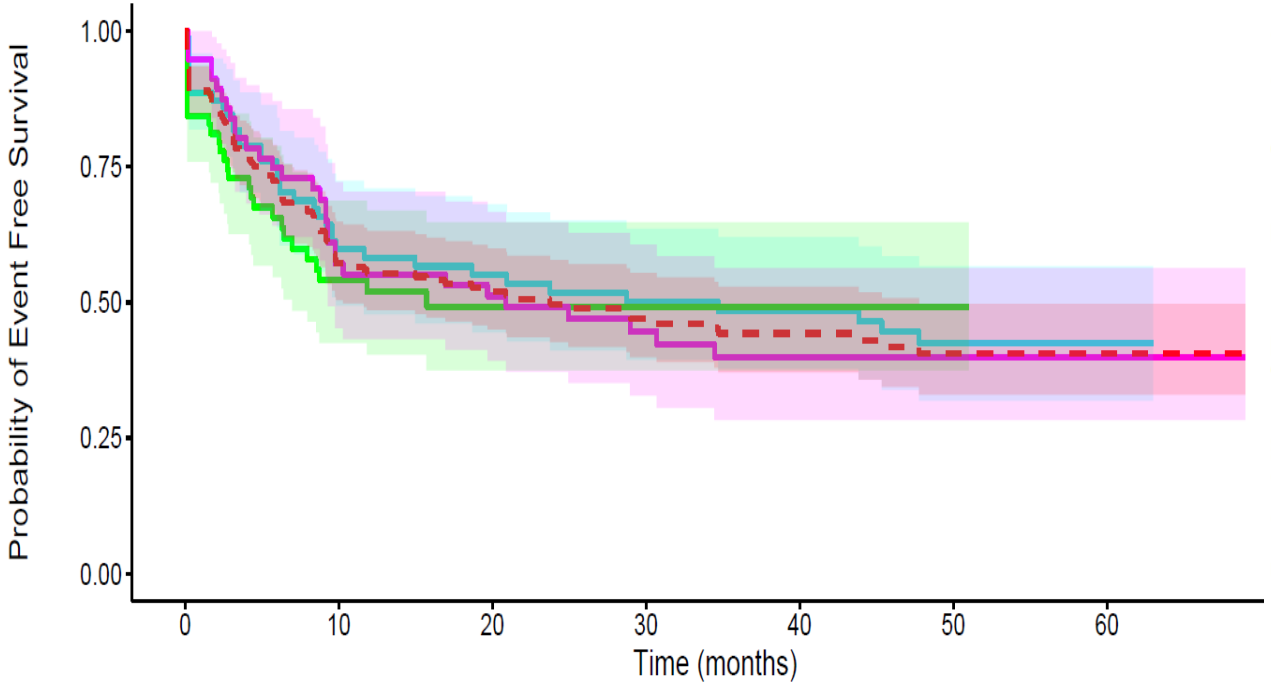
Tisa-cel study results - safety

n (%)	Pooled dataset (n=200)
Grade 3 adverse event	21%
Grade 4 adverse event	73%
Serious adverse event (any grade)	84%
Cytokine release syndrome	81%
Febrile Neutropenia	38%
Haemotological disorders including cytopenia	41%
Infection	73%
Serious neurological adverse reactions	52%
Tumour lysis syndrome	5%

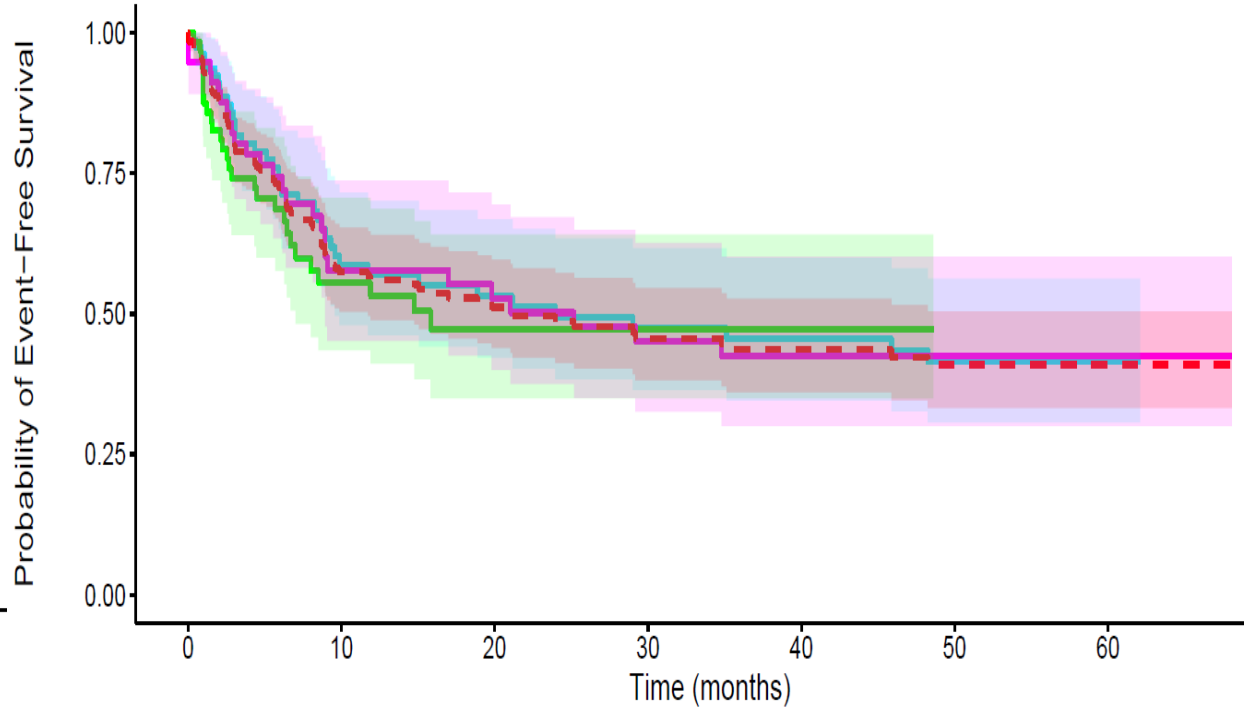
Tisa-cel study results – EFS (with and without allo-SCT censoring)

Definition of EFS in key studies allows censoring for allo-SCT and further anticancer therapy

EFS without censoring for allo-SCT, but censored for other subsequent treatments)



EFS censoring for allo-SCT and subsequent treatments



ELIANA (median 24m*)

ENSIGN (median 16m*)

B2101J (median 25m*)

Pooled (median 21m*)

* Median value when censoring for allo-SCT. Abbreviations: Abbreviations: EFS, event-free survival; SCT, stem cell transplant

Other issue 2: Definition of EFS

EAG: EFS definition in the tisa-cel studies may exaggerate benefits

Background

- EFS definition in ELIANA, ENSIGN and B2101J censors for allo-SCT and further anticancer therapy
- Excludes other clinically relevant events including MRD relapse and early loss of B-cell aplasia
- 16 /18 patients with subsequent allo-SCT in ELIANA had the transplant whilst in CR

Company

- Censoring for allo-SCT is more appropriate as it reflects the intended use of tisagenlecleucel as a curative treatment and averts any biases in treatment effect resultant of subsequent allo-SCT

EAG comments

- Scenario analyses without censoring for allo-SCT suggests it has minimal impact on EFS
  - However, results without censoring for further treatment not reported
- Excluding key events may exaggerate the absolute benefits of tisagenlecleucel
  - UK real-world analysis of 128 patients (Espuelas, 2022) found much shorter median EFS using stringent definition (7 months) than ELIANA definition (22 months)
  - Stringent definition may lower tisa-cel EFS and in turn, mean utility gains in the first 5 years
- Bias may be particularly pronounced if subsequent allo-SCT was due to MRD-positivity or loss of B-cell aplasia → may be indicative of treatment failure but this will be masked by the censoring mechanism

Is the company definition or stringent definition of EFS preferable?

Abbreviations: EFS, event-free survival; SCT; stem-cell transplant

Company's model overview

People accrue different costs and QALYs depending on whether they receive infusion

Modelled tisa-cel treatment course

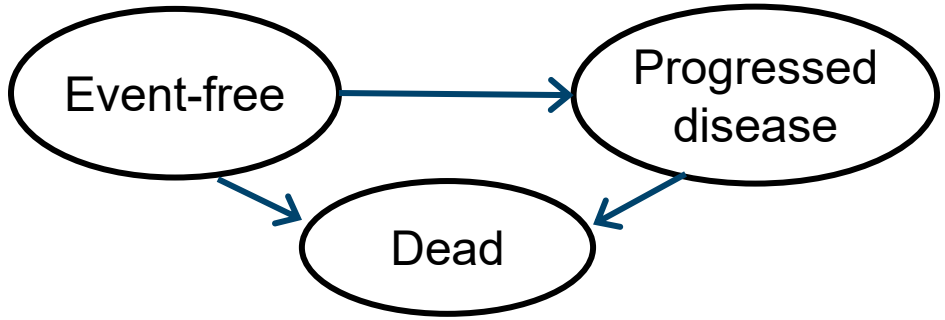
Assigned to tisa-cel

- **81.4% received infusion:** Incur costs and benefits as usual
- **11.3% discontinue before infusion:** 50% blinatumomab, 50% FLAG-IDA (cost and QALY according to subsequent treatment) 100% leukapheresis costs, 50% bridging, 50% lymphodepleting chemo costs
- **7.2% die before infusion:** accrue 0 life years, treatment costs and QALYs. 100% incur leukapheresis costs, 50% bridging chemo and 50% lymphodepleting chemo

EAG

- TA554 EAG stated that in NHS people who discontinue likely receive palliative therapy not intensive therapy.
- Pooled data OS for people not-infused is 5 months; model assumes 3.9 years.
- Only 5.1% received lymphodepleting chemo in pooled dataset

Partitioned survival model, 88-year time horizon



Abbreviations: OS, overall survival; QALY, quality adjusted life years

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline	At model entry, patients assumed to be 12 years old and 43% female
Intervention efficacy	ELIANA
Comparator efficacy	• OS: taken from von Stackelberg and Jeha studies • EFS: by applying HR from UK ALL study to modelled OS function for each comparator
Utilities	• Determined by health-state and time since receiving treatment, same for all treatments • Patients alive for 5 years have utility equal to EF state prior to this timepoint • Short-term QALY loss for Grade 3/4 treatment-related AEs (for 1st monthly cycle of model) • Subseqeuent allo-SCT results in disutility for 12 months (based on Sung et al, Hettle et al). • CRS and non-CRS ICU stay based on assumptions
Costs	• Bridging chemotherapy and lymphodepleting chemotherapy (tisa-cel group only) • Treatment (procedure/drug acquisition costs, administration costs and hospitalisation costs) • Health state resource use (applied in each monthly cycle)* • Management of AEs (applied in first model cycle) and subsequent allo-SCT • terminal care (once-only cost at point of death, if died within 5 years of model entry)* * In the company's base case analysis: health state and terminal care costs associated with death <100 days post-infusion are assumed to be captured within the NHSE CAR-T tariff.
Allo-SCT	Model assumes 22.8% of people receiving tisa-cel, 14.8% of those having salvage chemo and 34.3 % of those having blinatumomab go on to receive subsequent allo-SCT.

Other issue 3: Utility values

Company base-case sources utility values from Kelly et al instead of ELIANA

Background

- Previous tisa-cel economic models used values from ELIANA or Kelly, along with long-term survivor assumption
- People assumed 'cured' after 5 years – have utility of EF health state and SMR of 4.0 (TA554 SMR = 9.05)

Previous economic model identified in company's review

Study	EF value	PD value	Long-term survivor utility	Sources
Carey (2022)	0.80	0.63	become EF value after 5 yrs	ELIANA (EQ-5D-3L)
Moradi-Lakeh (2021)	0.91	0.75	Not reported	Kelly (EF mapped to HUI-2, PD mapped to EQ-5D)
Thielen (2020)	0.83	0.68	Not reported	ELIANA (EQ-5D-3L, Dutch tariff)
Ribera Santasusana (2020)	0.91	0.75	Not reported	Kelly (EF mapped to HUI-2, PD mapped to EQ-5D)
NoMA (2018)	0.80	0.63	become EF value after 5 yrs	ELIANA (EQ-5D-3L)
TA554 + current model	0.91	0.75	become EF value after 5 yrs	Kelly (EF mapped to HUI-2, PD mapped to EQ-5D)

Company

- Base-case did not use data from EQ-5D-3L estimates from ELIANA due to limited sample size.
- Since TA554, clinicians have gained more experience using CAR-Ts, lower SMRs applied in recent appraisals

EAG comments

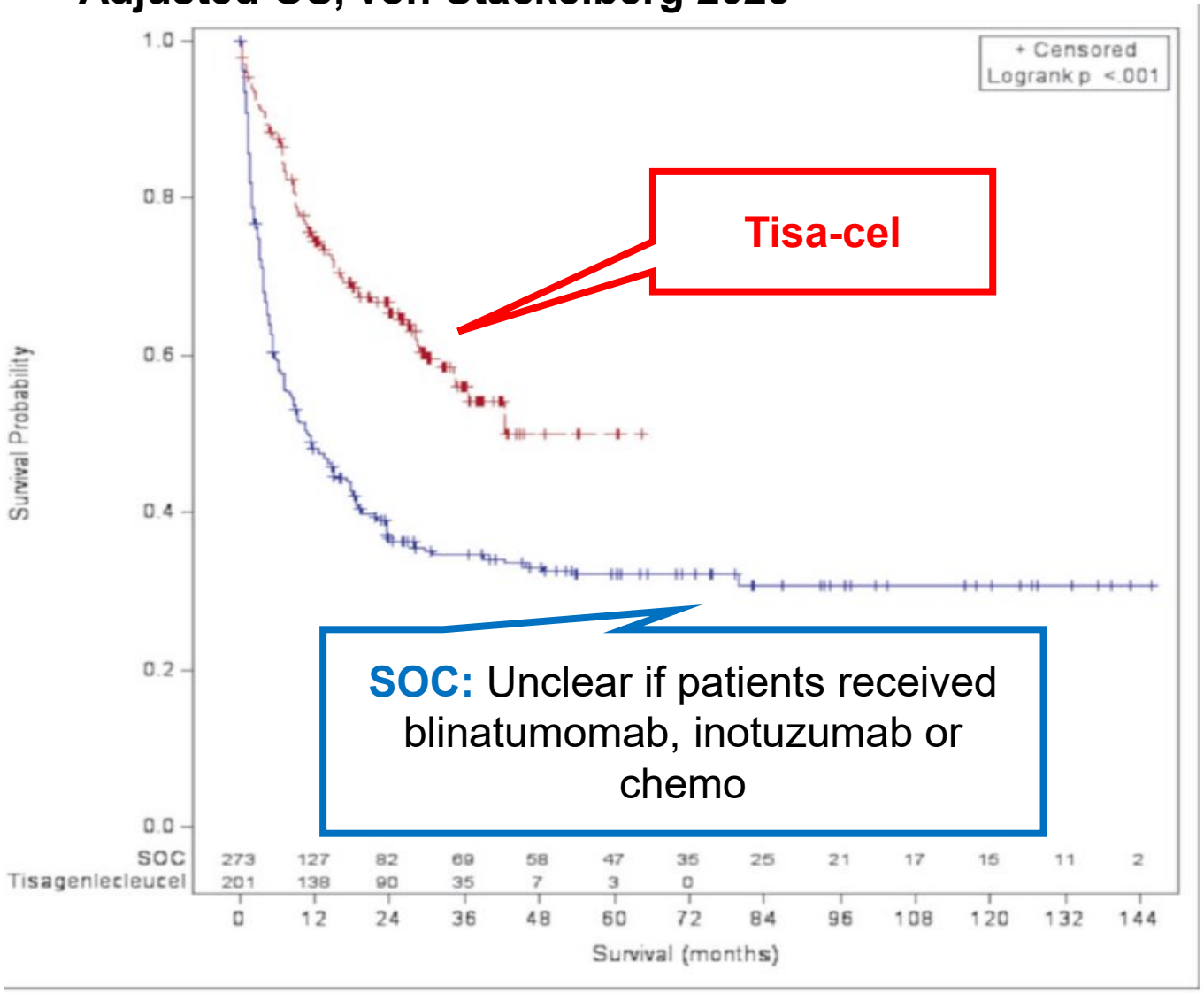
- Neither ELIANA nor Kelly is ideal, TA554 guidance does not comment on appropriateness of different values
- Company also applies -0.57 disutility for 1 year following allo-SCT (based on Sung), NHSE agreed that assumed duration was excessive given age of target population – not key ICER driver

Which utility values are more plausible?

Additional real-world evidence – von Stackelberg 2023

Tisa-cel vs. historical standard of care in children/young adults with relapsed/refractory B-cell ALL

Adjusted OS, von Stackelberg 2023



Patient-level data from 3 real-world registry studies in German/Austrian speaking countries used for ITC.

EAG: Long term OS (5-years onwards) is around 30%, much closer to EAG extrapolations, using RIALTO (cure fraction 23.4%), than company extrapolations (cure fraction 11.4%).