For committee, contains confidential information

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults

Technology appraisal committee C 4th October 2022

Chair: Stephen O'Brien

Lead team: Rob Forsyth, Nigel Langford, and Stella O'Brien

Evidence review group: ScHARR, The University of Sheffield

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Company: Kite (a Gilead company)

NICE National Institute for Health and Care Excellence

KTE-X19 for R/R B –precursor ALL

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- ❑ Modelling
- ❑ Points to consider (5)
- ❑ End-of-life criteria
- ❑ ICERs
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ❑ Summary

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Abbreviations: ALL, acute lymphoblastic leukaemia; ICER: incremental cost-effectiveness ratio; R/R, relapsed/refractory

Background on acute lymphoblastic leukaemia

The condition

- A malignant disorder derived from white blood cells (lymphocytes)
- 75% of ALL is derived from precursor B-cells (B-cell ALL)

Epidemiology

- Incidence of ALL has two peaks. First peak occurs in childhood; second at approx. 50 years of age
- Rare in adults: 0.2 % of new cancers in UK
- 790 new cases each year in the UK

Classification

- Classification based on presence of Philadelphia-chromosome (PH+ or PH-)

Symptoms

- Signs of bone marrow failure (anaemia, leukopenia and thrombocytopenia)
- Non-specific symptoms such as fever, weight loss, night sweats, propensity to bruise or bleed, fatigue, weakness, dyspnoea, bone and joint pain, dizziness and frequent infection

Prognosis

- Prognosis in adults is poor. <40% achieving long-term remission
- Estimated 5-year survival for ALL in England: age 25-64 is 4 in 10; people over 65 years old is 15 in 100
- Philadelphia positive (PH+) has poor prognosis despite targeted treatments

Abbreviations: ALL, acute lymphoblastic leukaemia; PH, Philadelphia chromosome

Autologous anti-CD19 transduced CD3+ cells* (Tecartus; Kite, a Gilead company)

Marketing authorisation	• CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients 26 years of age and above with relapsed or refractory B- cell precursor acute lymphoblastic leukaemia (ALL) • Licensed in the EU since September 2022
Mechanism of action	• CAR-T therapy • Manufactured from patient's own T-cells, returned to patient, treatment targets CD 19-expressing tumour cells
Administration	• Single intravenous infusion; dose: 1 million anti-CD19 CAR T-cells per kg of body weight • Leukapheresis, conditioning therapy and bridging chemotherapy are needed prior to one-off infusion with the technology
Price	• List price per infusion is £316,118 • A confidential patient access scheme has been agreed

*KTE-X19 will be used in this presentation

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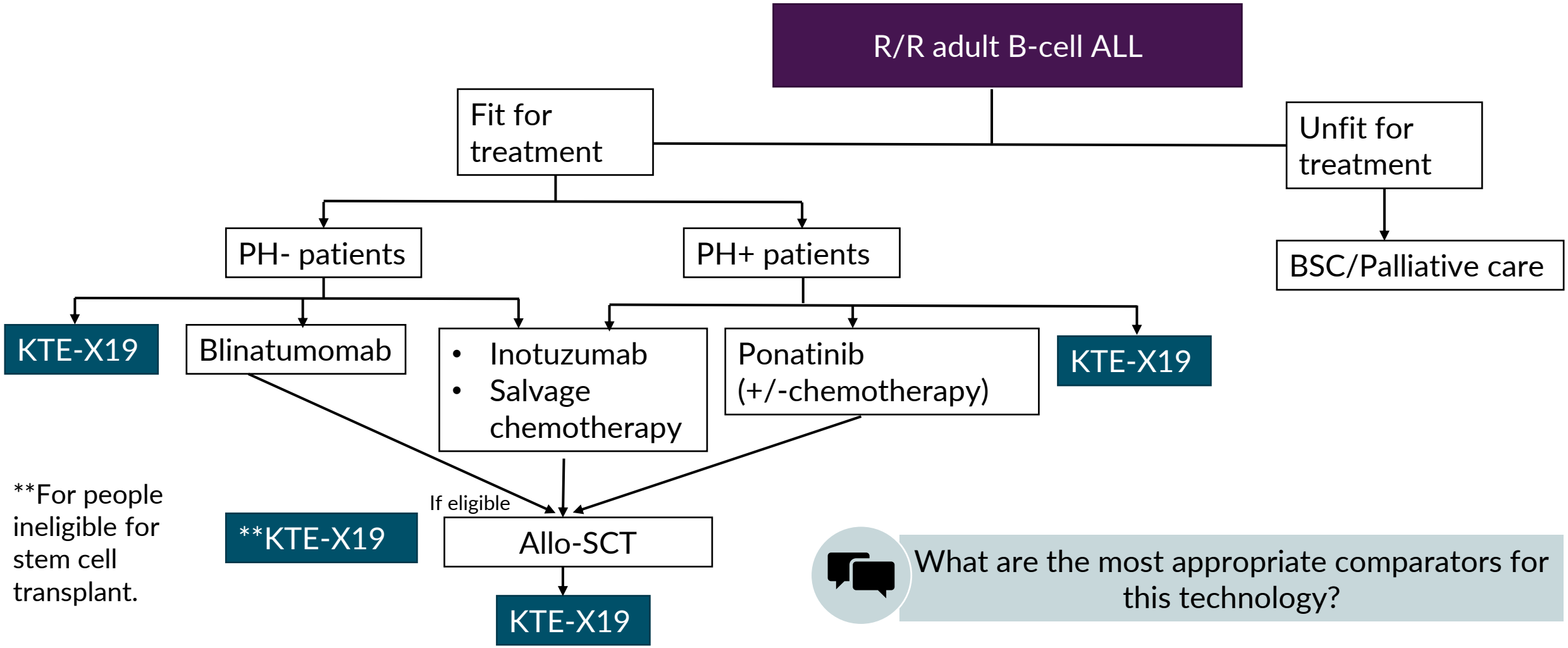
Abbreviations: CAR-T therapy, chimeric antigen receptor T-cell therapy

Treatment pathway and proposed position of KTE-X19



Source: Company submission, Treatment pathway, figure 7

Abbreviations: ALL, acute lymphoblastic leukaemia; Allo-SCT, Allogeneic-stem cell transplant ;BSC, Best supportive care; KTE-X19, autologous anti-CD19-transduced CD3+ cells; R/R, relapsed/refractory

Patient expert perspectives

Submission from Leukaemia Care

- ALL is aggressive with severe symptoms, rapid progression and very poor prognosis. A diagnosis has a significant impact on quality of life of patients and their families
- ALL has a high relapse rate of 50%. People with relapsed ALL are more likely to experience anxiety (74%) and report a negative impact in their finances as patients need to stop working (70%)
- Current treatments are insufficient as they're not curative. In this setting, salvage chemotherapy is often prescribed which extends people's lives by months
- CAR-T therapy licensed for < 25 years old with R/R ALL. Strong unmet need for adults ≥ 25 years old
- Patients experienced less severe short-term and more manageable side effects with CAR-T compared to allo-SCT
- CAR-T only administered in a few centres in the UK (12 adult centres)
- CAR-T does not guarantee a cure in every patient although is a significant improvement compared to best supportive care or death

"my consultant said to my sister "how old are you"… I think she said "oh I'm 29" and he said "see if it was you, you wouldn't be able to have this treatment", which was like woah"

"It all just felt so quick"

"A month after my discharge, I was travelling to London on my own for my clinic visits. It was tiring but there is no way that I could have done that so soon after my transplant"

Abbreviations: ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic-stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy

Clinical expert perspectives

Submission from clinical expert

- Patients with relapsed or refractory ALL typically have “a dismal prognosis”: 1 year OS post 1st salvage regimen is approximately 25%
- Considerable unmet clinical need. Blinatumomab and inotuzumab are licensed for this indication with OS of 8 months
- Currently only potentially curative option for relapsed adults over 25 is allo-SCT
    - majority do not receive it because of stringent eligibility requirements
    - eligibility compromised for age, fitness levels, donor availability or lack of remission
    - may offer improved outcomes for patients from minority ethnic heritage who have less chance of finding a match for a curative allo-SCT
- Patients ineligible for allo-SCT may be eligible for CAR-T therapy
    - plausible patient preference as response and remission may be durable without risk of allo-SCT toxicity
- KTE-X19 delivered in a CAR-T approved FACT-JACIE centres. Patients may need to travel and stay within an hour of the centre for 4 weeks after infusion which may add complexity

Abbreviations: ALL, acute lymphoblastic leukaemia; allo-SCT, allogeneic-stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy; FACT-JACIE, Foundation for the Accreditation of Cellular Therapy-Joint Accreditation Committee; OS, overall survival

Key issues

Model driver

Issue #	Issue for discussion	Resolved?	ICER impact
2	Uncertainty around the appropriateness of the company's naïve comparison approach	No	
5	Concerns with life expectancy of cured patients compared to general population	No	
6	Concerns with cured patients having the same utility values as general population	No	
9	Uncertainty of the costs associated with delivering KTE-X19 infusion	No	
4	Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19	No	
	End-of-life		

The issues below have been reviewed by the chair and have been moved to the back up slides.

Issue 7: Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab ozogamicin
Issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA
Issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib

Abbreviations: AE, adverse events; Allo-SCT, Allogeneic-stem cell transplant; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

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Abbreviations: ALL, acute lymphoblastic leukaemia; ICER: incremental cost-effectiveness ratio; R/R, relapsed/refractory

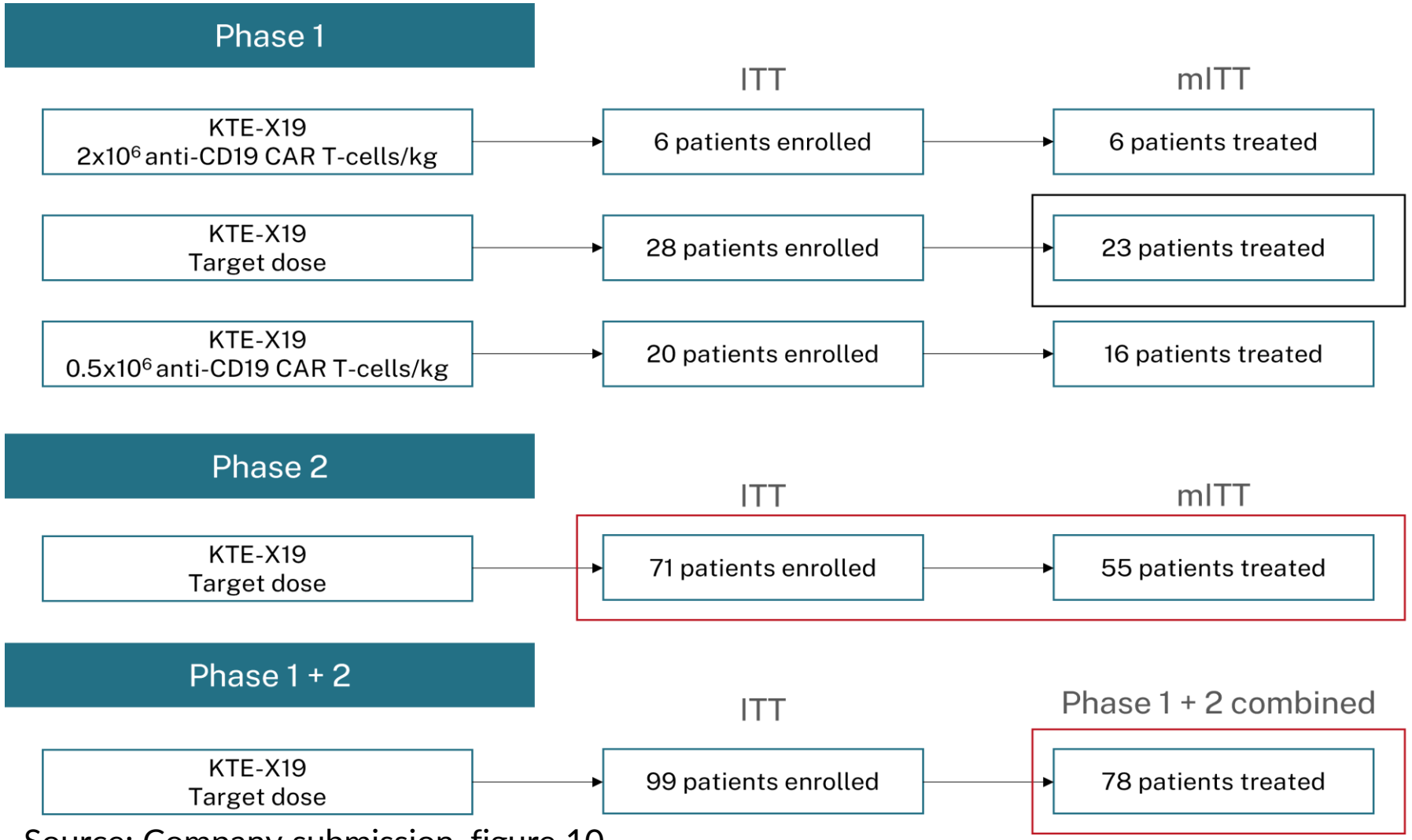
Key clinical trial-ZUMA 3

ZUMA-3 is currently ongoing (final completion date expected September [redacted])

Trial name	ZUMA-3
Design	Phase 1/2 , multicentre, open-label, single arm study, non-randomised
Population	Adult patients with R/R ALL defined as: • First relapse following a remission lasting ≤12 months • R/R after second-line or higher therapy • R/R after allo-SCT (transplant >100 days prior to enrolment and no immunosuppressive medication in previous month)
Intervention	KTE-X19 (n=78)
Duration	Median follow-up [redacted](Latest data cut: 23/07/21)
Primary outcome	Overall complete remission (Combined measure of patients achieving complete remission and complete remission with incomplete haematological recovery)
Secondary outcomes	MRD-rate, DoR, OCR, allo-SCT rate, OS, RFS, incidence of AE and EQ-5D
Locations	No data from UK centres United states: 21; Canada: 1; France 4; Germany 3; Netherlands 3
Used in model?	OS, EFS, AE frequency, HRQoL

Abbreviations: AE, adverse event; ALL, acute lymphoblastic leukaemia; allo-SCT, Allogeneic-stem cell transplant; DoR, duration of remission; EFS, event-free survival; EQ-5D-5L, EuroQol 5 Dimensions 5 level; HRQoL, health related quality of life; KTE-X19, autologous auto-CD19-transduced CD3+ cells; MRD, Minimal residual disease negativity; OS, overall survival; R/R, relapsed/refractory

Clinical trial: ZUMA-3 patient cohorts
Clinical effectiveness informed from Phase 1 & 2 datasets



The mITT populations in each phase received target dose and the opportunity to complete 6-month disease assessment

Source: Company submission, figure 10.

Abbreviations: CAR T-cell, chimeric antigen receptor T-cell; ITT, intent-to-treat; mITT, modified intent-to-treat

Latest data cut: 23 Jul 21

ZUMA-3 (Phase 1+2 combined, >25 years): Overall response

Response Category, N (%)	Phase 1 (N = [redacted])	Phase 2 (N = [redacted])	Phase 1+2 (N = [redacted])
Number of OCR (CR + CRi)	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]
CRi	[redacted]	[redacted]	[redacted]
CRh	[redacted]	[redacted]	[redacted]
BFBM	[redacted]	[redacted]	[redacted]
PR	[redacted]	[redacted]	[redacted]
NR	[redacted]	[redacted]	[redacted]
Unknown or not evaluable	[redacted]	[redacted]	[redacted]
Source: Company response to technical engagement, additional supportive evidence, table 3.			

Abbreviations: BFBM, blast-free hypoplastic or aplastic bone marrow; CR, complete remission; CRh, complete remission with partial haematologic recovery; CRi, complete remission with incomplete haematologic recovery; N, number; NR, no response; PR, partial response; OCR, overall complete remission

Latest data cut: 23 Jul 21

ZUMA-3 (Phase 1+2 combined, >25 years): Overall survival and relapse free survival

Source: Company response to technical engagement, additional supportive evidence, figure 5 and 7.

Abbreviations: CI, confidence interval; OS, overall survival; RFS, relapse free survival

Indirect treatment comparison methodology

	Indirect comparison methods		ERG approach
Comparison	Naïve comparison	MAIC	
KTE-X19 vs blinatumomab • (TOWER) - AD • (SCHOLAR -3) – IPD	Preferred by company and used in economic model Company prefers SCHOLAR-3 study	Scenario analysis	• Also prefers SCHOLAR-3 study • NC high risk of bias • MAIC informative • Suggests applying transportable HR to ZUMA-3 data with HR estimated using MAIC and STC adjustments to get a more accurate midpoint if company believes ZUMA-3 population is appropriate
KTE-X19 vs inotuzumab • (INO-VATE) – AD	Preferred by company and used in economic model	Scenario analysis	
KTE-X19 vs FLAG IDA • **pooled TOWER and INO-VATE - AD**	Preferred by company and used in economic model	Scenario analysis	
KTE-X19 vs ponatinib • **(PACE)-AD**	Preferred by company and used in economic model	Not feasible	• Accepts NC for ponatinib as MAIC not feasible

Source: ERG report, Critique of indirect comparison, section 3.4

Company
- Prefers NC since SCHOLAR-3 (IPD) provided HR similar to NC against blinatumomab whereas MAIC diverged
- ZUMA-3 aligned to UK population but TOWER and INO-VATE not . MAIC would not adjust to the population of interest.

ERG
- Agreement of 2 models does not mean they are correct
- Naïve comparisons of TOWER and INO-VATE are at high risk of bias.
- Regulatory subgroup >25 years old is different from population in comparison trials >18 years old

Abbreviations: AD, aggregated data; CRi, complete remission with incomplete haematologic recovery; HR, hazard ratio; IPD, individual patient data; MAIC, matched-adjusted indirect comparison; NC, naïve comparison; STC, simulated treatment comparison.

Latest data cut: 23 Jul 21

Indirect treatment comparison results: Overall survival

Updated indirect treatment comparison results (phase 1+2 combined, >25 years)

	Full population			>25yrs (21 months data cut)		
Comparison	Naïve comparison HR (CI)	ESS	MAIC HR (CI) 3 salvage status*	Naïve comparison HR (CI)	ESS	MAIC HR (CI) 3 salvage status*
KTE-X19 vs blinatumomab (TOWER)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs inotuzumab (INO-VATE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs FLAG-IDA pooled chemo (TOWER +INO-VATE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to technical engagement, additional supportive evidence, table 4.

*Note: 3-level salvage means salvage status was in one of three categories: first salvage, second salvage, third or higher salvage, 2-level salvage means two categories: first salvage, second or higher salvage.

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Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio

Latest data cut: 23 Jul 21

Indirect treatment comparison results: Event-free survival

Updated indirect treatment comparison results (phase 1+2 combined, >25 years)

	Full population			>25yrs, (21 months data cut)		
Comparison	Naïve comparison HR (CI)	ESS	MAIC HR (CI) 3 salvage status*	Naïve comparison HR (CI)	ESS	MAIC HR (CI) 3 salvage status*
KTE-X19 vs Blinatumomab (TOWER)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs Inotuzumab (INO-VATE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs FLAG-IDA pooled chemo (TOWER +INO-VATE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company response to technical engagement, additional supportive evidence, table 5.

*Note: 3-level salvage means salvage status was in one of three categories: first salvage, second salvage, third or higher salvage, 2-level salvage means two categories: first salvage, second or higher salvage.

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Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio.

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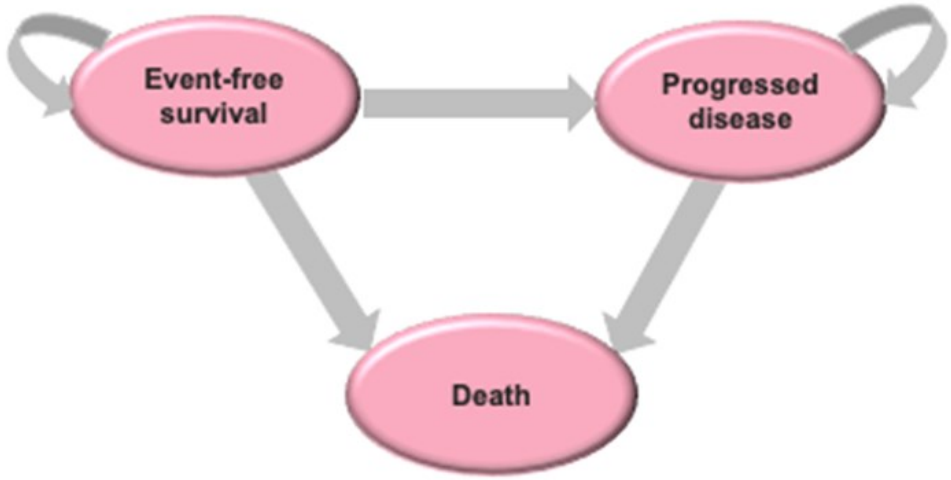
Economic model

Partitioned survival model comprising 3 mutually exclusive health states: event-free, progressed disease, and death



Source: company submission, document B, figure 33.

Parameter	Assumption and evidence source
KTE-X19	ZUMA-3
Comparators	INO-VATE, TOWER, PACE, SCHOLAR-3
Time horizon; Cycle length	57-year time horizon; weekly cycles without half-cycle correction
Discount rate	3.5% per annum
Utility values	Health state utility, ZUMA-3
Costs and resource use	PSSRU, NHS reference costs, electronic market information tool and assumption in previous appraisals TA554, TA450 and TA541

Abbreviations: PSSRU, Personal Social Services Reference Unit

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Key issues

Model driver

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2	Uncertainty around the appropriateness of the company's naïve comparison approach	No	
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9	Uncertainty of the costs associated with delivering KTE-X19 infusion	No	
4	Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19	No	
	End-of-life		

The issues below have been reviewed by the chair and have been moved to the back up slides.

Issue 7: Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab ozogamicin
Issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA
Issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib

Abbreviations: AE, adverse events; Allo-SCT, Allogeneic-stem cell transplant; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach [1]

Background

- Company's economic model uses treatment effect estimates from naïve indirect comparisons instead of MAIC. ZUMA-3 population healthier than those in comparator studies

Company

- SCHOLAR-3 most appropriate ITC for blinatumomab and naïve comparisons for the rest of comparators
- ZUMA-3 population generalisable to UK clinical practice likely to receive treatment. Eligible patients must have ECOG PS 0 or 1
- Disagrees with ERG that only using phase 2 data from ZUMA-3 in matching to SCHOLAR-3 compromises results

Stakeholder technical engagement response

- In absence of randomised comparison data, it is not possible to have confidence when comparing across studies

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; MAIC, Matching-adjusted indirect comparison.

Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach [2]

ERG comments

- Requested exploratory analysis of ICERs using results from MAIC to estimate efficacy in ZUMA-3. Concerns that naïve comparison does not reflect the true relative treatment effect of KTE-X19
- Might be differences in populations and implies that naïve analysis is not appropriate → populations should be adjusted
- If populations are similar, then the MAIC would have little impact
- The comparison versus blinatumomab using SCHOLAR-3 should use phase 1 + 2 dataset and not only phase 2. ERG notes potential meaningful differences in allo-SCT exposure between the two groups
- Company did not present analysis using the inverse of HRs to match comparators to KTE-X19 population*

Are the naïve comparisons presented by the company appropriate to inform decision making?

*Analysis included in updated economic model but not referenced by the company. The ERG had insufficient time to critique this analysis once it had been identified

Abbreviations: Allo-SCT: Allogeneic-stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance score; MAIC, Matching-adjusted indirect comparison; TE, technical engagement.

Key issue 5: Concerns with the life expectancy of cured patients compared to general population [1]

Background

- Company's model assumes a SMR of 1.09 to model mortality risk of patients considered cured compared to that of age- and sex- matched UK population. (Source Maurer et al. conducted in R/R DLBCL)
- ERG considers underestimate as this population has higher mortality rate. It applied a SMR of 4 based on TA541 Inotuzumab ozogamicin for R/R B-cell ALL. (Source Martin et al.)

Company

- SMR proposed by ERG relates to long-term survival following SCT and not a CAR-T
- SCT is more burdensome and has longer-term treatment requirements
- TA450 Blinatumomab for previously treated PH- ALL assumed an SMR of 1

Stakeholder technical engagement response

- Disagree life expectancy declines when people are cured. Risk of relapse reduces over time and people can live a normal life
- Evidence is weak for both the company's and ERG's SMR. No data for patients surviving post CAR-T therapy
- In absence of evidence it should be assumed to be the same as other patients cured of ALL by other means

Abbreviations: ALL, acute lymphoblastic leukaemia; DLBCL, diffuse large B-cell lymphoma; PH-, Philadelphia negative chromosome; R/R, relapsed/refractory; SMR, standardised mortality rate

Key issue 5: Concerns with the life expectancy of cured patients compared to general population [2]

ERG comments

- Company's SMR sourced from different population (R/R DLBCL patients)
- Martin et al states mortality risks are 4-9 times higher than general population after 25 years→ ERG's SMR is conservative compared to the 4.5 midpoint value of this study
- Noted that [redacted]

Which is the most appropriate SMR to use in the model – the company's or the ERG's?

Source: ERG response to TE, figure 3.

Abbreviations: ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell therapy; EFS, event-free survival; R/R, relapsed/refractory; SMR, standardised mortality rate

Key issue 6: Concerns with cured patients having the same utility values as general population

Background

- After 3 years, all surviving patients are assumed to have no residual disease or treatment related HRQoL decrement. Uncertain assumption given that patients had an increased risk of death

Company

- HRQoL of cured patients would be same or close to general population; patients will recover over time from ALL and its treatment
- Increased mortality risk in cured patients does not equal to patients scoring low on self-reported HRQoL compared to the general population
- Appraisals which used general population utility applied to cured patients are TA559, TA554, and TA450

ERG comments

- ERG utility value (0.92) between post-infusion pre-relapse and general population
- No precedence where general population utility was applied to a population with SMR >1
- Clinical advice was compelling that HRQoL would be reduced due to cumulative drug toxicities.

Stakeholder technical engagement response

- Disutilities in this population likely related to previous treatments. Lack of evidence after CAR-T therapy
- Patients live a near-normal life after CAR-T therapy and can return to daily activities sooner

Should people treated with KTE-X19 have the same utility values as the general population?

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; HRQoL, health related quality of life

Key issue 9: Uncertainty of the costs associated with delivering KTE-X19 infusion [1]

Background

- NHS tariff available for the delivery of CAR-T therapy [redacted] → uncertainty about true costs to the NHS
- Committee recognised lack of transparency about what is included in tariff in on-going appraisals

Company

- Lack of transparency for NHS Tariff figure, value is unfair and unreasonable→ Company submitted a freedom of information request for an itemised breakdown of the costs and assumptions
- Company calculated costs of delivering infusion at xxx from an average of [redacted] in hospital per patient → NICE methods followed
- Tariff not used in previously appraisals including XTE-X19 for mantle cell lymphoma (TA677)
- Propose collect healthcare resource use data after CAR-T infusion through CDF

ERG and NICE technical team comments

- ERG uses company's value [redacted] in its base case and undertook a scenario analysis using £50,000 and [redacted] (the cost with management of AE equals to xxx
- AE costs, costs for leukapheresis, conditioning and bridging chemotherapies, and administration costs are now additional to the costs of delivering the infusion (£7,152)
- In on-going ID1684/1685/3980 & this appraisal NICE suggests that the NHS Tariff should not be used

Abbreviations: AE, adverse events; CAR-T, chimeric antigen receptor T-cell therapy; CDF, cancer drugs fund

Key issue 9: Uncertainty of the costs associated with delivering KTE-X19 infusion [2]

NHS England

- In ID1684 & 1685: agreed that the tariff may have been an overestimate, but company's estimate is an underestimate
- NHS England are undertaking urgent analysis to calculate true costs
- Note: NICE has received this analysis, but further clarification on-going – work is not yet complete, and not shared with committee, company, ERG, or other stakeholders yet

Stakeholder technical engagement response

- Urge committee to ask NHS England as to how this figure was derived and clarify the calculation uncertainty.
- Current estimates are serious overestimate. Patients now stay on average 10 days in hospital and receive tocilizumab to reduce complications

Should the cost-effectiveness analyses include the NHS tariff for the delivery of CAR-T therapy?

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy

Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19 [1]

Background

- In ZUMA-3, 14/78 patients received allo-SCT post treatment with KTE-X19→ not accounted in cost calculation nor QALY impacts in company's model
- Post hoc analysis of OS adjusting for allo-SCT→ Weak (neither planned nor sufficiently powered)

Company

- Patients would not receive allo-SCT as subsequent treatment option in clinical practice. In ZUMA-3 performed exclusively in patients who achieved remission given investigational nature of KTE-X19
- Recent data cut supports a cured population and sensitivity analysis demonstrates standalone cure not dependent on allo-SCT
- UK clinicians stated they would not use an allo-SCT following CAR-T

ERG comments

- Uncertain if people who receive allo-SCT in ZUMA-3 had a survival benefit due to the procedure
- Given allo-SCT was used in the trial, costs were incurred and QALYS were affected, it should be considered
- Noted that [redacted]

Stakeholder technical engagement response

- Agrees with company assertions. KTE-X19 will be delivered as definitive therapy with no plan for allo-SCT.
- In ZUMA-3, 18% had a transplant→ a similar percentage may be seen in clinical practice.

Is it appropriate to include costs and QALY losses for people who could potentially receive allo-SCT?

Abbreviations: Allo-SCT, Allogeneic-stem cell transplant; CAR-T, chimeric antigen receptor T-cell therapy; EFS, event-free survival; OS, overall survival; EFS, event-free survival

Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19 [2]

Latest data cut: 23 Jul 21

Months	KM estimates of OS
12	[redacted]
18	[redacted]
24	[redacted]
Months	**KM median OS**
	[redacted]

Source: Company response to technical engagement; additional supportive evidence, Table 1

Company comments: ZUMA-3 data supporting cured fraction of patients.

[redacted]

Source: Company response to technical engagement, additional supportive evidence, Figure 1

ERG comment: Reminder that [redacted].

Abbreviations: Allo-SCT, Allogeneic-stem cell transplant; CI, confidence interval; EFS, event-free survival; KM, Kaplan-Meier; NE, not estimable; OS, overall survival

Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19 [3]

Latest data cut: 23 Jul 21

Company comments: Sensitivity analysis of median OS stratified by censoring allo-SCT supporting survival is independent of transplant

[redacted]

Source: Company response to technical engagement, additional supportive evidence, Figure 2.

Abbreviations: Allo-SCT, Allogeneic-stem cell transplant; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; OS, overall survival

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End-of-life

Latest data cut: 23 Jul 21

Criterion	Data available
Treatment indicated for patients with a short life expectancy, normally less than 24 months	Current 'standard of care' median OS: 4-8 months Median OS: Inotuzumab: 7.7 months (INO-VATE) FLAG-IDA: 5.3 months (INO-VATE/TOWER) Blinatumomab: 7.7 months (TOWER) Ponatinib: 8.0 months (PACE)
	Company economic model output: Median OS: % alive at 2 years: Inotuzumab: 7.6 months 22% FLAG-IDA: 5.3 months 13% Blinatumomab: 7.8 months 19% Ponatinib: 7.1 months 20%
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	Clinical data: Median OS KTE-X19: [redacted] months (95% CI: [redacted]) (ZUMA-3, phase 1+2 combined, >25 years)
	Company economic model output: Median OS KTE-X19: 19.09 months
Source: Adapted from company response to TE 2.1, company submission end-of-life table 34 and ERG report section 5.	

Does KTE-X19 meets NICE's end-of-life criteria?

KTE-X19 for R/R B –precursor ALL

- ❑ About
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider (5)
- ❑ End-of-life criteria
- ✓ **ICERs**
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ❑ Summary

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Abbreviations: ALL, acute lymphoblastic leukaemia; ICER: incremental cost-effectiveness ratio; R/R, relapsed/refractory

Cost-effectiveness results

CONFIDENTIAL

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

Assumptions in company and ERG base-case:

Company base-case	ERG base-case	ERG scenarios
• Uses naïve indirect comparisons • Excludes allo-SCT associated costs and QALY loss for KTE-X19 patients • Applies a SMR of 1.09 • Assumes same HRQoL than general population • Does not accept NHSE CAR-T delivery tariff. Company's proposed tariff [redacted]	• Uses MAIC comparisons and accepts naïve comparison for ponatinib • Includes allo-SCT associated costs and QALY loss for KTE-X19 patients • Applies a SMR of 4 • Assumes lower HRQoL than general population • Assumes CAR-T delivery tariff calculated by company [redacted]	• **Testing individual ERG changes** • **Using MAIC methodology for comparisons** • **Sensitivity analysis using different values for NHSE CAR-T delivery tariff**

Abbreviations: allo-SCT, allogeneic-stem cell transplant; CAR-T, chimeric antigen receptor T-cell; HRQoL, health related quality of life; SMR, standardised mortality rate

Impact of ERG scenario analysis on company base case ICER PH– subgroup

Deterministic results

Scenario (applied to company base case)	Incremental costs (£) versus SoC	Incremental life years versus SoC	Incremental QALYs versus SoC	ICER (£) versus SoC
Company base case using naïve indirect comparison				
Issue 4: Including allo-SCT costs and QALY loss	↑	=	↓	↑
Issue 5: Using SMR 4 applied to general population mortality for cured patients	↑	↓	↓	↑
Issue 6: Assuming cured patients have lower HRQoL than the general population	=	=	↓	↑
Issue 7: Assuming the management costs of AEs with KTE-X19 equivalent to those of inotuzumab	↑	=	=	↑
Exploratory analysis (4-7)	↑	↓	↓	↑

Arrow indicates direction and scale of change in costs, LYs, QALYs or ICER **compared to company base case**

Abbreviations: ICER, incremental-cost effectiveness ratio; LY, life years; QALY, quality-adjusted life year; SOC, standard of care

Impact of ERG scenario analysis on company base case ICER PH+ subgroup Deterministic results

Scenario (applied to company base case)	Incremental costs (£) versus SoC	Incremental life years versus SoC	Incremental QALYs versus SoC	ICER (£) versus SoC
Company base case using naïve indirect comparison				
Issue 4: Including allo-SCT costs and QALY loss	↑	=	↓	↑
Issue 5: Using SMR 4 applied to general population mortality for cured patients	↑	↓	↓	↑
Issue 6: Assuming cured patients have lower HRQoL than the general population	=	=	↓	↑
Issue 7: Assuming the management costs of AEs with KTE-X19 equivalent to those of inotuzumab	↑	=	=	↑
Issue 10: Assuming no adjunctive chemotherapy with ponatinib	↑	=	=	↑
Exploratory analysis (4-7, 10)	↑	↓	↓	↑

Arrow indicates direction and scale of change in costs, LYs, QALYs or ICER **compared to company base case**

Abbreviations: ICER, incremental-cost effectiveness ratio; LF, life year; QALY, quality-adjusted life year; SOC, standard of care

Impact of ERG exploratory analysis on base case ICER Overall population applicable to PH– and PH+

Probabilistic results

Scenario (applied to company base case)	Incremental costs (£) versus SoC	Incremental life years versus SoC	Incremental QALYs versus SoC	ICER (£) versus SoC
Company base case naïve comparison against FLAG-IDA				
ERG base case - MAIC adjusted to FLAG-IDA (1 knot normal)	↑	↓	↓	↑
ERG base case- MAIC adjusted to FLAG-IDA (log-normal)	↑	↓	↓	↑
Company base case naïve comparison against Inotuzumab				
ERG base case - MAIC adjusted to inotuzumab (1 knot hazard)	↑	↓	↓	↑
ERG base case - MAIC adjusted to inotuzumab (log-normal)	↑	↓	↓	↑

Arrow indicates direction and scale of change in costs, LYs, QALYs or ICER **compared to company base case**

NICE Abbreviations: ICER, incremental-cost effectiveness ratio; LF, life year; QALY, quality-adjusted life year; SOC, standard of care

KTE-X19 for R/R B –precursor ALL

- ❑ About
- ❑ Clinical evidence
- ❑ Modelling
- ❑ Points to consider (5)
- ❑ End-of-life criteria
- ❑ ICERs
- ✓ **Other considerations: Equality; innovation; Cancer Drugs Fund**
- ❑ Summary

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Abbreviations: ALL, acute lymphoblastic leukaemia; ICER: incremental cost-effectiveness ratio; R/R, relapsed/refractory

Other considerations

Equality considerations

(Patient expert response)

- "Approving CAR T in the relapsed/refractory setting for adults with ALL would solve the inequality that arises from this therapy currently being approved only for under 25's. People of any age deserve the equal opportunity to have a potential cure."

(Professional organisation response)

- "This technology would potentially improve equality. Individuals from non-Caucasian backgrounds are less likely to have a matched unrelated donor on the international stem cell transplant registries. According to Anthony Nolan, white Caucasians have 71% chance of finding the best match from an unrelated donor. By contrast, patients from minority ethnic backgrounds only have a 37% chance. Stem cell transplant was previously the only potentially curative treatment for individuals with relapsed refractory ALL, individuals from minority ethnic backgrounds are disadvantaged."

Innovation

(Professional organisation response)

- "The technology is offering potentially curative option for patients who would otherwise be palliative."

Abbreviations: ALL, acute lymphoblastic leukaemia; CAR-T, chimeric antigen receptor T-cell therapy.

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

- ZUMA-3 is ongoing and will complete in September [redacted]
- Patients will be followed up to 15 years after receiving KTE-X19

KTE-X19 for R/R B –precursor ALL

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- ❑ ICERs
- ❑ Other considerations: Equality; innovation; Cancer Drugs Fund
- ✓ **Summary**

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Abbreviations: ALL, acute lymphoblastic leukaemia; ICER: incremental cost-effectiveness ratio; R/R, relapsed/refractory

Key issues

Model driver

Issue #	Issue for discussion	Resolved?	ICER impact
2	Uncertainty around the appropriateness of the company's naïve comparison approach	No	
5	Concerns with life expectancy of cured patients compared to general population	No	
6	Concerns with cured patients having the same utility values as general population	No	
9	Uncertainty of the costs associated with delivering KTE-X19 infusion	No	
4	Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19	No	
	End-of-life		

The issue below have been reviewed by the chair and have been moved to the back up slides.

Issue 7: Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab ozogamicin
Issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA
Issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib

Abbreviations: AE, adverse events; Allo-SCT, Allogeneic-stem cell transplant; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

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Thank you.