For public observers: all ACIC redacted

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in people 26 years and over

Technology appraisal committee C

14th February 2023

Chair: Stephen O'Brien

Evidence review group: ScHARR, The University of Sheffield

Technical team: Albany Chandler, Sally Doss, Chris Griffiths, Jasdeep Hayre

Company: Kite (a Gilead company)

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KTE-X19 for R/R B –precursor ALL

❑ Background

- ACM 1 conclusions overview
- Clinical evidence
- Economic model
- Consultation responses
- Issues to consider
  - Methods for indirect treatment comparison
  - Long-term mortality risk in cured population
  - Long-term quality of life in cured population
  - Inclusion of allo-SCT costs and QALYs
  - NHSE CAR-T cost estimate
  - Equalities issues
  - Cancer Drugs Fund
- Summary

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Abbreviations: ALL, acute lymphoblastic leukaemia; R/R, relapsed/refractory; ACM, appraisal committee meeting; allo-SCT, allogenic-stem cell transplant; QALY, quality-adjusted life year

Background on acute lymphoblastic leukaemia (ALL)

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

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

Autologous anti-CD19 transduced CD3+ cells (KTE-X19) (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

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

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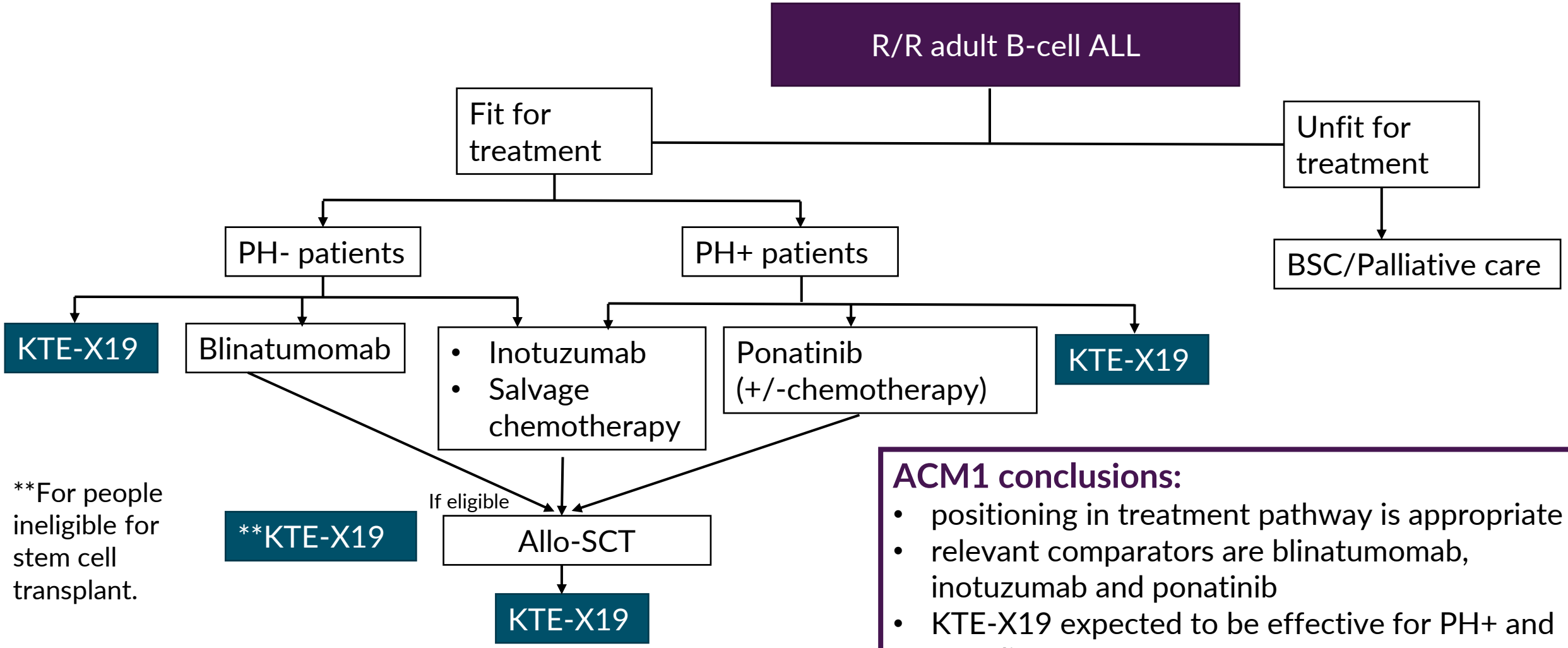
Treatment pathway and proposed position of KTE-X19



**For people ineligible for stem cell transplant.

ACM1 conclusions:

- positioning in treatment pathway is appropriate
- relevant comparators are blinatumomab, inotuzumab and ponatinib
- KTE-X19 expected to be effective for PH+ and PH- disease

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

ACM1 company and ERG base case and committee preferred assumptions

Assumption	Company base case	ERG base case	Committee preferred assumption ACM1
Method for ITC (inotuzumab)	Naïve indirect comparison	MAIC inverse hazard ratio	Differences in populations across trials should be accounted for: **use MAIC inverse hazard ratio approach**
Long-term mortality	Applies SMR 1.09	Applies SMR 4.0	Likely higher risk of mortality after KTE-X19 than in general population: **apply SMR 4.0**
Long-term quality of life	General population mortality after 3 years	0.92 utility multiplier applied after 3 years	Likely lower QoL after KTE-X19 than in general population: **apply 0.92 utility multiplier after 3 years**
Allo-SCT costs and QALYs	Excludes costs and QALYs associated with allo-SCT after KTE-X19	Includes costs and QALYs associated with allo-SCT after KTE-X19	Some people may have allo-SCT after KTE-X19: **include costs and QALYs associated with allo-SCT after KTE-X19**
CAR-T cost estimate	[redacted]	Uncertain – various scenarios ran	£60k – but **should be reviewed if new evidence is presented**

Other committee conclusions at ACM1

- ZUMA-3 suggests KTE-X19 could be clinically effective, but curative treatment effect is uncertain
- End of life criteria is met
- Not suitable for CDF: further evidence from ZUMA-3 will not address uncertainty in comparative clinical-effectiveness evidence or uncertainty around mortality rate and utilities for people who have had KTE-X19

Abbreviations: ACM, appraisal committee meeting; MAIC, matching-adjusted indirect comparison; SMR, standardised mortality rate; allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year

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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

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, relapse-free survival and cure assumption

ACM1 conclusions

- KTE-X19 could be clinically effective but curative treatment effect is uncertain as analysis includes some people who have had prior allo-SCT – unclear if benefits from allo-SCT or KTE-X19

ERG comment

- RFS probability is [redacted], suggesting no cure with KTE-X19

Stakeholder comments

- Clinical expert and patient expert experience indicates KTE-X19 can be curative
- Cure after 3 years considered appropriate for tisagenlecleucel for ALL

Abbreviations: CI, confidence interval; OS, overall survival; RFS, relapse free survival; ALL, acute lymphoblastic leukaemia

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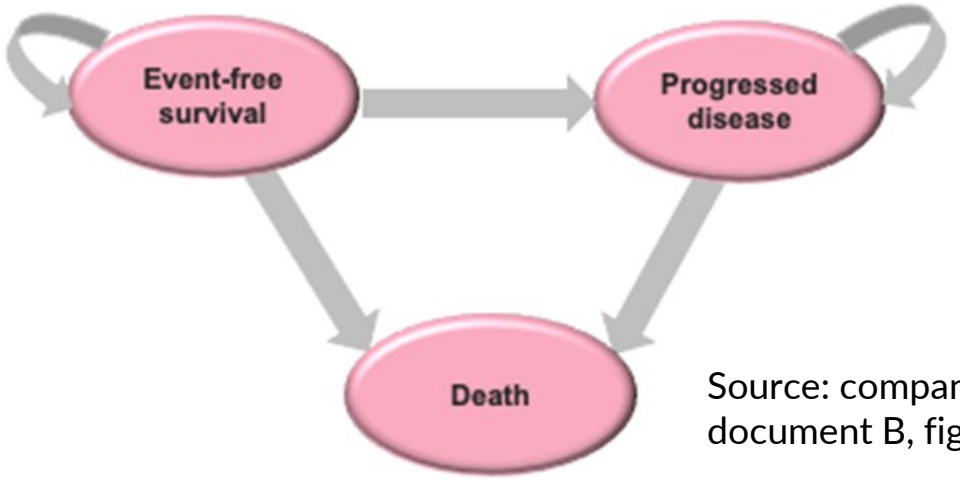
Economic model

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

ACM1 conclusion:

- Company's economic model is appropriate for decision making

Abbreviations: PSSRU, Personal Social Services Reference Unit

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Consultation responses

Responses received from:

- Company (Kite, a Gilead company)
- Leukaemia Care
- Patient expert
- Clinical expert

Summary of Leukaemia Care, patient expert and clinical expert consultation responses:

KTE-X19 efficacy and cure assumption:

- Cure accepted at 3 years for tisagenlecleucel and efficacy results for KTE-X19 similar; relapses after 12 months very unlikely and curative outcomes seen in real-world evidence
- ACD uses equal efficacy of tisagenlecleucel in PH- and PH+ subgroups to justify assumption of equal KTE-X19 efficacy across subgroups – unreasonable not to apply other clinical similarities such as cure assumption
- Clinical expert opinion that KTE-X19 is an effective treatment

Long-term quality of life

- Negative impact of early treatment with KTE-X19 far outweighed by ability to return to near-normal life after treatment, including ability to perform daily activities, complete education, work and socialise

Inequalities

- Age inequality not addressed by draft recommendation – tisagenlecleucel recommended in CDF for people aged under 26 and unfair to limit CAR-T to under 26s only
- People not able to receive a SCT do not currently have a potentially curative treatment option

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Several key issues remain after consultation

Issue	Resolved?	ICER impact
Uncertainty around the appropriateness of the company's naïve comparison approach	No – for discussion	Moderate
Life expectancy of cured patients compared to general population	No – for discussion	Large
Long-term utility value of cured population compared with the general population	No – for discussion	Moderate
Inclusion of allo-SCT related costs and QALY loss for people receiving KTE-X19	No – for discussion	Large

Abbreviations: ACD, appraisal consultation document; Allo-SCT, Allogeneic-stem cell transplant; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

Methods for indirect treatment comparison (1)

ACM1 conclusions

- ZUMA-3 was a single arm trial, so ITC needed to estimate KTE-X19 efficacy compared with comparators
- Inverse hazard ratio from MAIC applied to the ZUMA-3 baseline arm was preferred method of ITC for inotuzumab
- Matched comparison via SCHOLAR-3 accepted method of ITC for blinatumomab
- Naïve comparison for ponatinib deemed reasonable due to lack of data to inform MAIC

Company ACD response

- ERG approach using inverse hazard ratio from MAIC flawed:
  - HR derived from unanchored MAIC at high risk of bias with small sample size
  - HR does not align with HRs calculated from other ITCs and transitivity assumption does not hold
  - Survival curves generated provide unrealistically high OS rate and cure fraction compared with INO-VATE (inotuzumab trial) data, given prognostic factors in ZUMA-3 are more unfavourable than in INO-VATE
- Naïve comparison more appropriate – median from this is better aligned with median survival in INO-VATE

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Abbreviations: MAIC, matching-adjusted indirect treatment comparison; ITC, indirect treatment comparison; HR, hazard ratio; OS, overall survival

Methods for indirect treatment comparison (2)

ERG comments

- Concerned that naïve comparisons don't reflect treatment effect of KTE-X19 due to key differences in populations across studies
- Prefers to use inverse HR from unanchored MAIC to model KTE-X19 vs inotuzumab
- Appropriate to adjust for observed and known prognostic factors with unanchored MAIC and acknowledge risk of bias, rather than use naïve ITC which does not address known differences in the populations
- Disagrees with company assertion that unanchored MAIC HR is inconsistent with results produced from other ITCs of KTE-X19 vs blinatumomab and inotuzumab vs blinatumomab (company has not considered results from an updated analysis of inotuzumab vs blinatumomab ITC with baseline covariate adjustments)
- Inappropriate to compare survival curve for inotuzumab with INO-VATE as results include population adjustment
- Company matched SCHOLAR-3 to ZUMA-3 phase 2 data only for blinatumomab comparison – ERG would have preferred matching with pooled phase 1 and 2 data

Which method for indirect treatment comparison with inotuzumab is appropriate?

Abbreviations: MAIC, matching-adjusted indirect treatment comparison; ITC, indirect treatment comparison; HR, hazard ratio; OS, overall survival

Long-term mortality risk in cured population (1)

ACM1 conclusions

- Cured population after KTE-X19 treatment likely to be at higher risk of mortality than general population
- Committee preferred ERG's approach, assuming a standardised mortality ratio (SMR) of 4 (sourced from Martin et al. 2010), rather than company's approach of SMR of 1.09
- Increased risk of death is linked to allo-SCT and risk of graft vs host disease before KTE-X19 treatment

Company ACD response

- Maintain base case approach of applying SMR of 1.09
- Martin et al. selected on assumption that all people receiving KTE-X19 have allo-SCT – not all people will have prior allo-SCT in clinical practice and [redacted]% had prior allo-SCT in ZUMA-3
- Only 11% of 5-year survivors in Martin et al. have acute lymphoblastic leukaemia
- People with active graft vs host disease cannot receive KTE-X19 in line with SmPC – so population with prior allo-SCT receiving KTE-X19 at lower risk of death than population in Martin et al.
- Increase in SMR above 1.09 should be based on % of prior SCT in ZUMA-3 (=2.2); provided scenario using SMR 2.2

Abbreviations: allo-SCT, allogenic stem cell transplant; SmPC, summary of product characteristics; GvHD, graft-vs-host disease

Long-term mortality risk in cured population (2)

ERG comments

- Mortality data in Martin et al. for people 5-years relapse free, so prominence of GvHD less important
- Likely to be long term impact on health due to cumulative drug toxicities
- Company's preferred SMR source conducted in population with 0% acute lymphoblastic leukaemia
- SMR of 4 is reasonable but conducts scenarios using company's suggested value of 2.2 and a threshold analysis

Previous technology appraisals

TA541: inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

- Committee preferred assumption was to apply SMR of 4 for people still alive after 3 years who had received haematological SCT, based on lower end of estimate in Martin et al. 2010
- Note: not all people in model in current appraisal have received SCT

- Other appraisals in untreated acute myeloid leukaemia have used SMRs after stem cell transplant (committee preference: TA552, SMR 2.34; TA523, SMR 2 plausible but may be higher)

What is the appropriate mortality adjustment for people who are considered cured following KTE-X19?

Abbreviations: allo-SCT, allogenic stem cell transplant; SmPC, summary of product characteristics; GvHD, graft-vs-host disease

Long-term quality of life in cured population (1)

ACM1 conclusions

- People who are considered cured after KTE-X19 likely to have reduced HRQoL compared with the general population due to cumulative toxicity from previous treatments, risks of KTE-X19 and the disease itself
- Committee preferred ERG's approach of applying utility multiplier of 0.92 to general population utilities (calculated using ratio between value after infusion in ZUMA-3 and general population), to adjust for lower HRQoL for cured population after 3 years

Company ACD response

- ERG's rationale that mortality and HRQoL are correlated is flawed; even if ERG's rationale correct, midpoint between HRQoL of responders in ZUMA-3 and general population is disproportionate to mortality risk of someone considered cured
- Disagree that mortality and HRQoL are correlated as mortality can be driven by acute events not impacting QoL
- Cured population will have HRQoL of general population in long term, which includes large proportion of people with weakened immune systems and cancer survivors
- Precedent from previous appraisals which use general population utility for cured population

Abbreviations: HRQoL, health-related quality of life; CDF, cancer drugs fund

Long-term quality of life in cured population (2)

Stakeholder comments

- People can return to near normal life after CAR-T therapy
- Benefits of extended life far outweighs the QoL implications
- May be emotional and financial impact in early stages of treatment, but doesn't prevent normal daily activities after treatment
- Routine hospital appointments can help alleviate health-related anxiety as disease is being monitored

ERG comments

- Prefers to apply utility multiplier of 0.92
- Proportion of people with weakened immune system or cancer survivors in general population, but this will be much lower than proportion of people in the R/R ALL population
- Disagrees that there is TA precedent for using general population utility in cured population
- No precedent using general population utility when SMR applied
- Clinical expert feedback indicates cumulative drug toxicity will impact QoL for life

Is it appropriate to adjust general population utility estimates for people who are considered cured following KTE-X19?

Abbreviations: QoL, quality of life; R/R ALL, relapsed/refractory acute lymphoblastic leukaemia; TA, technology appraisal

Inclusion of allo-SCT related costs and QALYs (1)

ACM1 conclusions

- Costs and QALYs associated with allo-SCT should be included in the model for people having KTE-X19

Company ACD response

- Sensitivity analysis censoring for allo-SCT found no difference in overall survival – although not powered, analysis is informative
- Allo-SCTs in ZUMA-3 (14/78) were pre-planned due to investigational nature of trial; no survival advantage expected in people who received allo-SCT whilst in remission in ZUMA-3; [redacted]
- Survival greater for people with allo-SCT and KTE-X19 than people who received SCT and other treatment
- Use of subsequent allo-SCT not anticipated in clinical practice

Abbreviations: allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year; CDF, cancer drugs fund

Inclusion of allo-SCT related costs and QALYs (2)

Stakeholder comments

- ACD states that sensitivity analysis not powered but that allo-SCT could have provided a survival advantage – if no evidence that allo-SCT provides advantage, fair to assume there isn't one

ERG comments

- Unclear that all allo-SCT in ZUMA-3 were pre-planned
- People who received allo-SCT in ZUMA-3 may have benefited, costs were incurred and HRQoL was affected, which should be accounted for
- Clinical expert feedback that allo-SCT would be considered for people with relapsed disease who were fit

Is inclusion of costs and QALYs associated with allo-SCT appropriate?

Abbreviations: allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year; CDF, cancer drugs fund

NHS England CAR-T cost estimate

Background

- NHSE confirmed CAR-T costs to be used is £41.1k (updated since ACM1)

Company ACD response

- "Believe that the tariff issue is resolved at 41.1k when appropriate like for like changes have been made"
- £41.1k remains an overestimate based on available real-world evidence on costs and resource use of CAR-T delivery
- Applied £41.1k CAR-T costs in updated model but excluded from model all healthcare resource costs up to 100 days other than KTE-X19 acquisition, subsequent treatment and subsequent allo-SCT costs

Stakeholder comments

- Fewer staff needed for CAR-T compared with SCT

ERG comments

- Applied £41.1k CAR-T cost but amended company model to also separately include costs excluded by company but not covered by overarching CAR-T cost estimate
  - ERG separately model costs for conditioning and bridging chemotherapy acquisition, administration and delivery and adverse events after treatments other than KTE-X19

Abbreviations: allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year; CDF, cancer drugs fund

Equalities issues

ACM1 conclusions

- The marketing authorisation for KTE-X19 specifies use only for people aged 26 years and over
- For people up to age 25 with relapsed or refractory ALL, another CAR-T treatment is available within the CDF
- The availability of CAR-T for different age groups cannot be addressed within a technology appraisal, which make decisions within the marketing authorisation (MA for KTE-X19 specifies people aged 26 years and older)

Stakeholder comments

- Committee has not addressed the age inequality issue - if KTE-X19 not recommended, people aged 26 years and older are not eligible for a CAR-T therapy but people under 26 years are
- Some people are not eligible for SCT (e.g. older people) or are less likely to find a suitable stem cell donor ("white Caucasians have a 71% chance of finding the best match from an unrelated donor. This drops to a 37% chance for patients from minority ethnic backgrounds." [professional organisation submission])
    - KTE-X19 access could improve equality as otherwise SCT is the only potentially curative treatment which some people don't have access to due to age or family background

Have equalities issues been adequately considered in the recommendations?

Abbreviations: ALL, acute lymphoblastic leukaemia; allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year; CDF, cancer drugs fund; MA, marketing authorisation

Cancer Drugs Fund

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

ACM1 conclusions

- Not suitable for CDF: further evidence from ZUMA-3 will not address uncertainty in comparative clinical-effectiveness evidence or uncertainty around mortality rate and utilities for people who have had KTE-X19

Company ACD response

- Uncertainty around allo-SCT rate, mortality rate and quality of life in long-term survivors could be addressed in CDF

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

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Abbreviations: CDF, Cancer Drugs Fund; allo-SCT, allogenic stem cell transplant

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Company and ERG base case assumptions post-consultation

Assumption	Company base case	ERG base case
Comparison method (inotuzumab)	Naïve indirect comparison	MAIC inverse hazard ratio
Comparison method (blinatumomab)	SCHOLAR-3 data adjusted to ZUMA-3	SCHOLAR-3 data adjusted to ZUMA-3
Long-term mortality	SMR 1.09	SMR 4.0
Long-term quality of life	General population mortality after 3 years	0.92 utility multiplier applied after 3 years
Allo-SCT costs and QALYs	Excludes costs and QALYs associated with allo-SCT after KTE-X19	Includes costs and QALYs associated with allo-SCT after KTE-X19
CAR-T cost estimate	£41.1k - excludes other healthcare resource costs for 100 days other than KTE-X19 acquisition, subsequent treatment and allo-SCT	£41.1k - excludes other healthcare resource costs for 100 days other than KTE-X19 acquisition, subsequent treatment, allo-SCT, conditioning and bridging chemotherapy and adverse events after other treatments
Adjunctive chemotherapy with ponatinib (PH+ subgroup only)	15% receive adjunct chemotherapy	0% receive adjunct chemotherapy

ERG also corrected an error in the company's model which increased the ICER

Abbreviations: allo-SCT, allogenic stem cell transplant; QALY, quality-adjusted life year; SMR, standardised mortality rate; MAIC, matched-adjusted indirect comparison; IVIg, intravenous immunoglobulin

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential discounts for comparators and other treatments in the pathway

ACM1 conclusions

- KTE-X19 meets the end-of-life criteria

Summary

- Company's base case for the PH- and PH+ populations are within the range of what would usually be considered cost-effective use of NHS resources
- ERG's base case the PH- and PH+ populations are not within the range of what would usually be considered cost-effective use of NHS resources

Impact of ERG exploratory analysis on company base case

Description of ERG exploratory and scenario analysis
2: Inverse HRs from MAIC to model inotuzumab
4: Including allo-SCT costs and QALYs
5: SMR of 4 applied after 3 years
6: Applying utility multiplier 0.92 after 3 years
9: Amending NHS CAR-T cost estimate
10: No adjunctive chemotherapy with ponatinib
Scenario: ERG base case plus SMR 2.2 after 3 years
Threshold analysis: ERG base case with varying SMRs

PH- subgroup:
ERG base case includes exploratory analysis 2, 4-6 and 9

PH+ subgroup:
ERG base case includes exploratory analysis 2, 4-6 and 9-10

ERG exploratory analysis impact on company base case	Incremental costs (£) versus SoC	Incremental life years versus SoC	Incremental QALYs versus SoC	ICER (£) versus SoC
ERG base case	↑	↓	↓	↑

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

Company also provided scenario analyses for:
- Applying a SMR of 2.2
- Assuming 50% allo-SCT costs and QALY loss

Abbreviations: allo-SCT, allogenic stem cell transplant; ICER, incremental-cost effectiveness ratio; LY, life years; QALY, quality-adjusted life year; SOC, standard of care; HR, hazard ratio; MAIC, matched-adjusted indirect treatment comparison; SMR, standardised mortality rate

Key issues

Issue	Resolved?	ICER impact
Uncertainty around the appropriateness of the company's naïve comparison approach	No – for discussion	Moderate
Life expectancy of cured patients compared to general population	No – for discussion	Large
Long-term utility value of cured population compared with the general population	No – for discussion	Moderate
Inclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19	No – for discussion	Large

Abbreviations: ACD, appraisal consultation document; Allo-SCT, Allogeneic-stem cell transplant; ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

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Thank you.