NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people 26 years and over [ID1494]

Contents:

The following documents are made available to consultees and commentators:

Access the **final scope** and **final stakeholder list** on the NICE website.

Pre-technical engagement documents

1. **Company submission** from Kite, a Gilead company

2. **Clarification questions and company responses:**
   a. Main response
   b. Updated cost-effectiveness analyses appendix

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Leukaemia Care
   b. NCRI-ACP-RCP-RCR
   c. NHSE CAR-T tariff summary
   d. Gilead response to NHSE CAR-T tariff documents

4. **Evidence Review Group report** prepared by ScHARR

5. **Evidence Review Group report – factual accuracy check**

Post-technical engagement documents

6. **Technical engagement response from company:**
   a. Response form
   b. Additional evidence appendix
   c. Updated cost-effectiveness results

7. **Technical engagement responses and statements from experts:**
   a. Professor David Marks, Director Bristol BMT Unit/Head ALL program – clinical expert, nominated by Kite
   b. Sophie Wheldon, Advocacy Officer – patient expert, nominated by Leukaemia Care

8. **Technical engagement responses from consultees and commentators:**
   a. Leukaemia Care
   b. NCRI-ACP-RCP-RCR

9. **Evidence Review Group post-technical engagement documents** prepared by ScHARR:
    a. ERG critique of company response to technical engagement
    b. ERG addendum post-committee meeting
    c. ERG additional analysis post-committee meeting, including NHSE CAR-T delivery costs

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

KTE-X19 for previously treated B-precursor adult acute lymphoblastic leukaemia [ID1494]

Document B

Company evidence submission

November, 2021

File name	Version	Contains confidential information	Date
ID1494_KTEX19 RR ALL_Document B_FINAL 23.11. 21 [ACIC]	1.0	Yes	23/11/21

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List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
ALL	Acute lymphoblastic leukaemia
allo-SCT	Allogeneic-stem cell transplant
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BFBM	blast-free hypoplastic or aplastic bone marrow
BIC	Bayesian information criterion
BSC	Best supportive care
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CI	Confidence interval
CNS	Central nervous system
CR	Complete remission
CRh	Complete remission with partial haematologic recovery
CRi	Complete remission with incomplete haematologic recovery
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CSR	Clinical study report
DLTs	Dose-limiting toxicities
DOR	Duration of remission
DSU	Decision support unit
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFS	Event-free survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
ESS	Effective sample size
FLAG	Fludarabine, cytarabine (Ara-C), granulocyte-colony stimulating factor
GvHD	Graft versus host disease
HR	Hazard ratio
HRQoL	Health-related quality of life
IDA	Idarubicin
IL	Interleukin
IP	Investigational product
IPD	Individual patient-level data
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous

KM	Kaplan Meier
MAIC	Matching-adjusted indirect comparison
MCM	Mixture cure model
MedDRA	Medical Dictionary for Regulatory Activities
MEDS	Medidata Enterprise Data Store
MeSH	Medical Subject Headings
mITT	Modified intent-to-treat
MRD	Minimal residual disease
NE	Not estimable
NHS	National health service
NR	Not reached
OCR	Overall complete remission
OS	Overall survival
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PD	Progressed disease
PEG-Asp	Pegylated asparaginase
PETHEMA	Spanish Programa Español de Tratamiento en Hematologia
PFS	Progression-free survival
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome-positive
Ph-	Philadelphia chromosome-negative
PR	Partial remission
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life
R/R	Relapsed/refractory
RFS	Relapse-free survival
SCA	Synthetic control arm
SCT	Stem cell transplant
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SoC	Standard of care
SRT	Safety Review Team
TKI	Tyrosine kinase inhibitor
TSD	Technical Support Document
VAS	Visual Analogue Scale
VOD	Veno-occlusive disease
WBC	White blood cell

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission appraises the clinical and cost-effectiveness of KTE-X19 within its anticipated European Medicines Agency (EMA) marketing authorisation, namely, [redacted]. This submission is consistent with the NICE final scope and the NICE reference case.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia	Adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia	
Intervention	Autologous anti-CD19-transduced CD3+ cells	Autologous anti-CD19-transduced CD3+ cells (KTE-X19)	
Comparator(s)	• Philadelphia-chromosome-negative ALL ○ Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy ○ Inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ Blinatumomab • Philadelphia-chromosome-positive ALL ○ Inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ A tyrosine kinase inhibitor (such as imatinib, dasatinib, or ponatinib), alone or in combination with FLAG-based combination chemotherapy	• Philadelphia-chromosome-negative ALL ○ Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy ○ Inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ Blinatumomab • Philadelphia-chromosome-positive ALL ○ Inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ Ponatinib + chemotherapy (FLAG-IDA)	• Imatinib: used as the first-line tyrosine kinase inhibitor of choice in the UK for treatment of Philadelphia-chromosome-positive ALL. Clinical expert feedback was that it therefore has no place in the R/R treatment pathway • Dasatinib: not reimbursed for use in the UK, and lacks approval from NICE (TA714) • Ponatinib: based on feedback from clinical experts, we understand

	• Best supportive care	○ Inotuzumab ozogamicin (CD22-positive B-precursor ALL) ○ FLAG-based combination chemotherapy	that ponatinib is typically used in combination with chemotherapy in the UK • Best supportive care: people unable to tolerate chemotherapy or targeted treatments would not be eligible for KTE-X19
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • treatment response rate (including minimal residual disease, haematologic responses and complete remission) • rate of allogeneic stem cell transplant • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • treatment response rate (including minimal residual disease, haematologic responses and complete remission) • rate of allogeneic stem cell transplant • adverse effects of treatment • health-related quality of life	

Subgroups to be considered		• Philadelphia chromosome status (positive or negative)	The model distinguishes between Philadelphia-chromosome status to allow comparison with blinatumomab (Ph-) and ponatinib (Ph+)

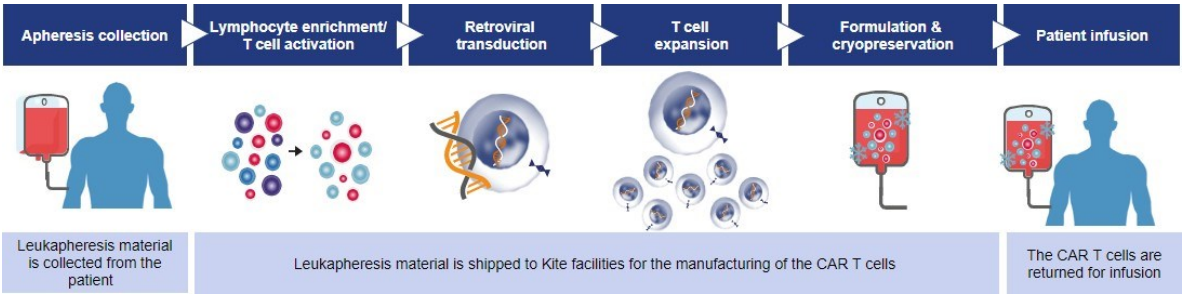
Key: ALL, acute lymphoblastic leukaemia; FLAG-IDA, Fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin; Ph-, Philadelphia chromosome-negative; Ph+, Philadelphia chromosome-positive; SCT, stem cell transplant.

B.1.2 Description of the technology being appraised

The draft Summary of Product Characteristics (SmPC) is presented in Appendix C.

KTE-X19 is a chimeric antigen receptor (CAR) T-cell therapy directed against CD19 – a B-cell-specific cell surface antigen that is expressed in most B-cell malignancies, including acute lymphoblastic leukaemia (ALL). KTE-X19 is manufactured from patients' own T-cells, which are engineered *ex-vivo* to target the CD19-expressing tumour cells when they are returned to the patient. Figure 1 depicts the steps involved in the manufacturing and administration of CAR T-cell therapy.

Figure 1: Overview of the CAR T-cell Administration Process



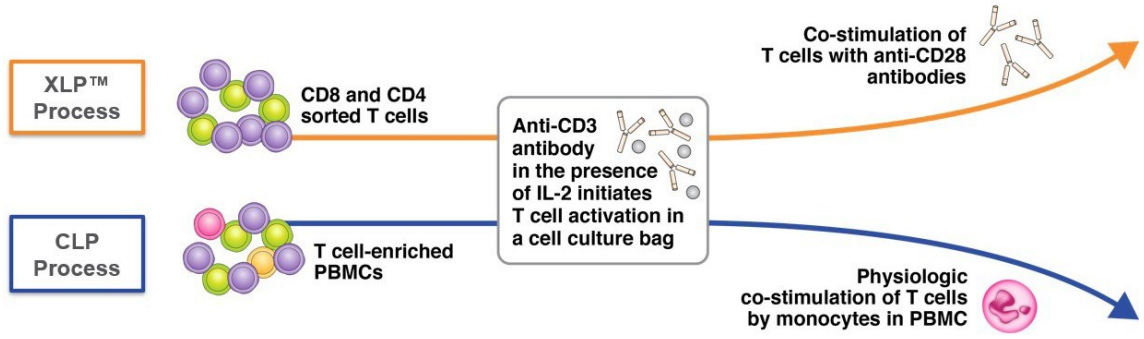
Key: CAR, Chimeric antigen receptor
Source: adapted from (1).

The KTE-X19 CAR construct and mode of action is displayed in Table 2. Following engagement of KTE-X19 with CD19-expressing target cells, the CD3ζ domain activates the downstream signalling cascade that leads to T-cell activation, proliferation, and acquisition of effector functions, such as cytotoxicity. The intracellular signalling domain of CD28 provides a co-stimulatory signal that works in concert with the primary CD3ζ signal to augment the T-cell function, including IL-2 production (2). Together, these signals result in proliferation of KTE-X19 CAR T-cells and direct killing of target cells. Furthermore, the activated T-cells secrete cytokines and other molecules that can recruit and activate additional anti-tumour immune cells (3).

Unique to the production of KTE-X19 within the Kite CAR T-cell product franchise are the T-cell enrichment and activation stages within the manufacturing process, which is internally referred to as the XLP™ process compared with the CLP process

used to manufacture axicabtagene ciloleucel (Yescarta®). Differences between the two are depicted in Figure 2.

Figure 2: Enrichment and activation of T-cells via the XLP™ or CLP process



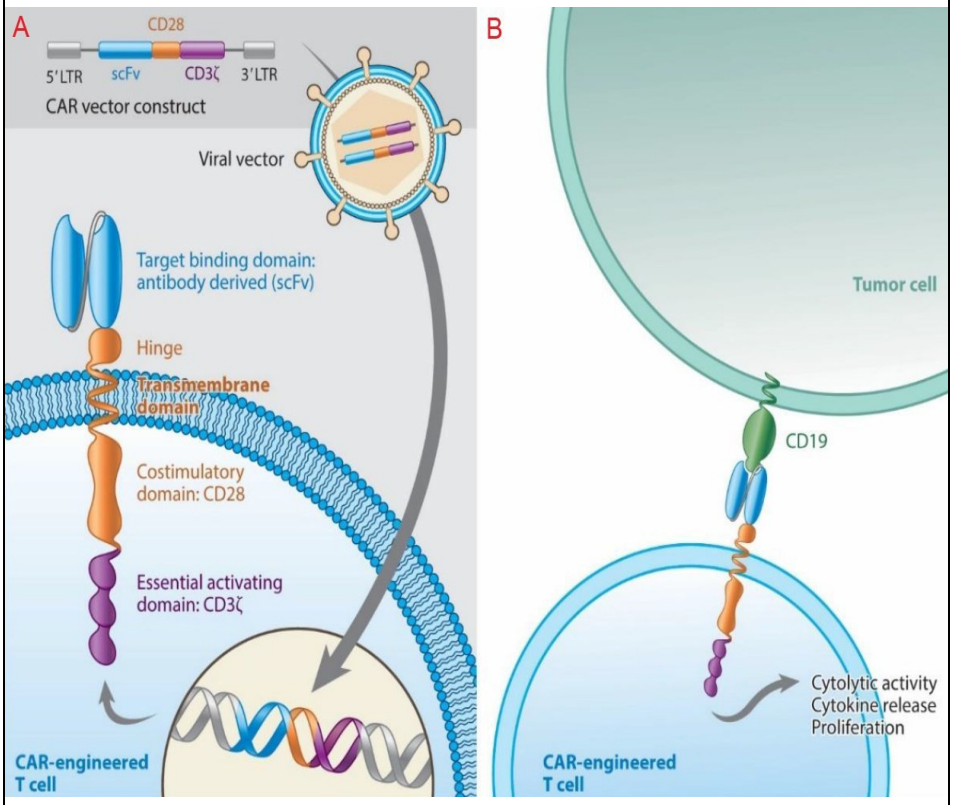
Key: IL-2, interleukin-2; PBMC, peripheral blood mononuclear cell.

The XLP™ process was introduced to minimise hypothetical product quality issues (and is the process used to manufacture KTE-X19 in the ZUMA-3 study). By positively selecting CD4+ and CD8+ cells during enrichment and activating the enriched T-cells with exogenous antibodies, circulating tumour cells are removed from the leukapheresis product, eliminating the risk of premature activation and exhaustion of CAR T-cells during the *ex-vivo* expansion step of the manufacturing process (which can occur if tumour cells are present in the leukapheresis product).

Table 2 provides summary information regarding the KTE-X19 technology. The draft SmPC is provided in Appendix C.

Table 2: Technology being appraised

UK approved name and brand name	Autologous anti-CD19-transduced CD3+ cells (KTE-X19)
Mechanism of action	KTE-X19 is a second-generation, CD19-directed CAR consisting of four main components: • an extracellular domain consisting of an scFv from the heavy and light chains of the antibody variable region, directed against CD19 • A hinge region to optimize the accessibility of the epitope, and a transmembrane region derived from the co-stimulatory molecule CD28 • The intracellular CD28 domain

	• The CD3ζ signalling domain, working together with the CD28 domain to aid T-cell activation The KTE-X19 CAR construct and mode of action is depicted below. 
Marketing authorisation/CE mark status	The application for a Type II variation was submitted to the EMA on [redacted] and is currently ongoing. Positive opinion from the CHMP is expected on [redacted] and anticipated regulatory approval is expected [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated marketing authorisation in adult ALL: [redacted] KTE-X19 is also approved for the treatment of mantle cell lymphoma, with the following EMA marketing authorisation: • KTE-X19 is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor
Method of administration and dosage	KTE-X19 is provided as cells dispersion for intravenous infusion. The anticipated approved dose for adults with R/R B-cell ALL is 1 x 10^6 anti-CD19 CAR T-cells/kg body weight, aligned to the ZUMA-3 Phase 2 dose. This is a lower target dose than recommended for the R/R MCL indication (which is 2 x 10^6 anti-CD19 CAR T-cells/kg body weight).

	The anticipated conditioning chemotherapy for adults with R/R B-cell ALL is aligned to the ZUMA-3 conditioning regimen: • Fludarabine (25 mg/m^2/day) administered via IV over 30 minutes on Days -4, -3, and -2 prior to KTE-X19 treatment • Cyclophosphamide (900 mg/m^2/day) administered over 60 minutes on Day -2 prior to KTE-X19 treatment Paracetamol 500 – 1,000mg oral and diphenhydramine 12.5 – 25mg intravenous or oral (or equivalent) is also recommended approximately 1 hour prior to infusion.
Additional tests or investigations	No additional tests or investigations are anticipated, beyond what is already performed in clinical practice, to identify the patients eligible to receive KTE-X19.
List price and average cost of a course of treatment	List price: £316,118 Average cost of a course of treatment with PAS applied is [redacted] Total costs including leukapheresis, bridging therapy, conditioning chemotherapy and administration: [redacted]
Patient access scheme (if applicable)	A patient access scheme has been approved by PASLU for NHS England. This patient access scheme involves a simple [redacted] discount from list price

Key: ALL, acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; MCL, Mantle cell lymphoma; PASLU, Patient Access Schemes Liaison Unit; R/R, relapsed/refractory

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

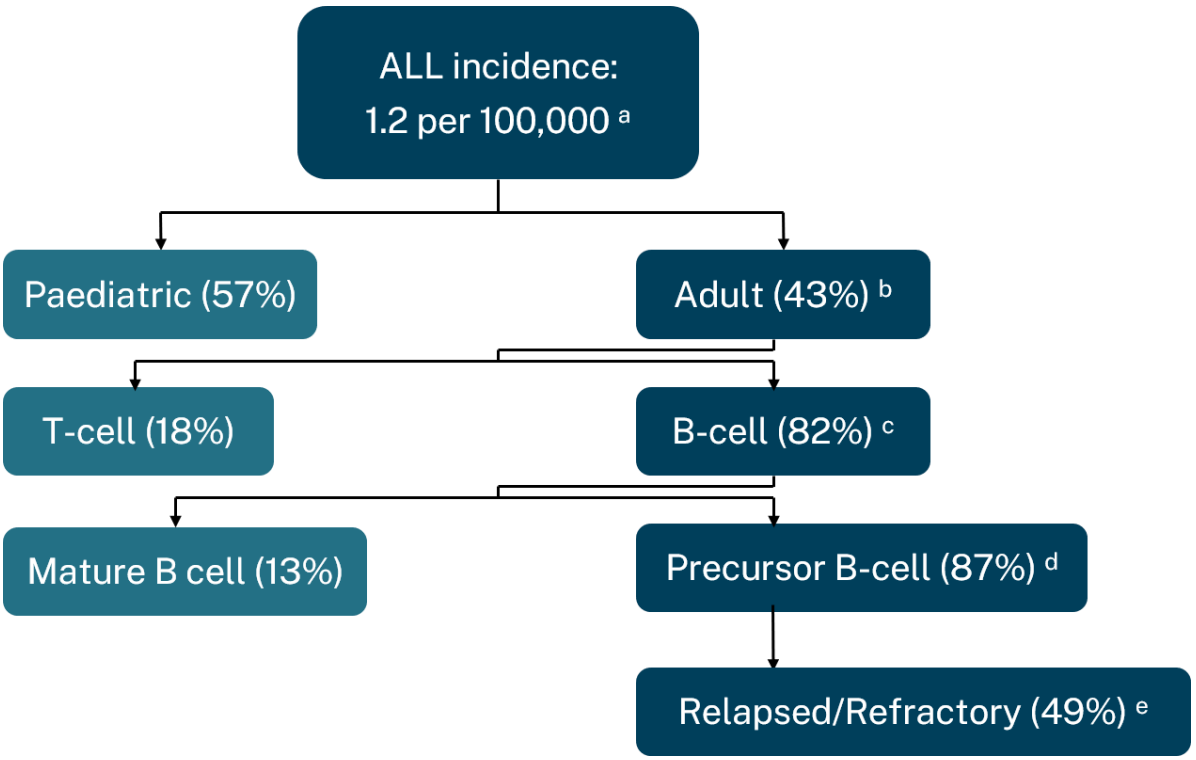
ALL is a rare haematological malignancy characterised by the abnormal proliferation and accumulation of lymphoblasts, and represents approximately 10% of all leukaemia cases (4,5).

Lymphoblasts are immature cells that normally differentiate into white blood cells (WBCs) including B lymphocytes (B-cells) and T lymphocytes (T-cells). In ALL, there is an accumulation of malignant, poorly differentiated lymphoblasts in the bone marrow, blood and extramedullary sites such as the lymph nodes, liver, spleen and central nervous system (CNS) (4).

ALL occurs in a bimodal age distribution and is most commonly diagnosed in people younger than 20 years of age; people over 20 years of age account for approximately 40% of ALL cases in the UK based on data from 2015-2017 (6).

Adult ALL cases normally develop from progenitors of the B-cell lineage with 82% of adults with ALL diagnosed with B-cell ALL in the UK; 87% of these are B-precursor cell ALL (Figure 3).

Figure 3: ALL sub-classifications



Key: ALL, acute lymphoblastic leukaemia
[a] Based on Cancer Research UK data 2015-2017 (6).
[b] Calculated based on UK age-specific ALL incidence data reported by Cancer Research UK (2015-2017) (6).
[c] Weighted average based on i) UK population-based cytogenetic study of 349 patients (≥15 years of age) with ALL diagnosed between 1983-2001 (7) ii) analysis of cytogenetic data from 1522 patients (15-65 years of age) with ALL encoded on the MRC UKALLXII/ECOG 2993 study (8).
[d] Based on data from a UK population-based cytogenetic study of 349 patients (≥15 years of age) with ALL diagnosed between 1983-2001. Of 240 B-cell ALL cases, 208 were precursor B-cell (7).
[e] Based on UKALLV12/ECOG data including 1508 newly diagnosed ALL patients (15-60 years of age). 136 patients were refractory to induction therapy, with a further 609 patients relapsing after achieving a remission (9).

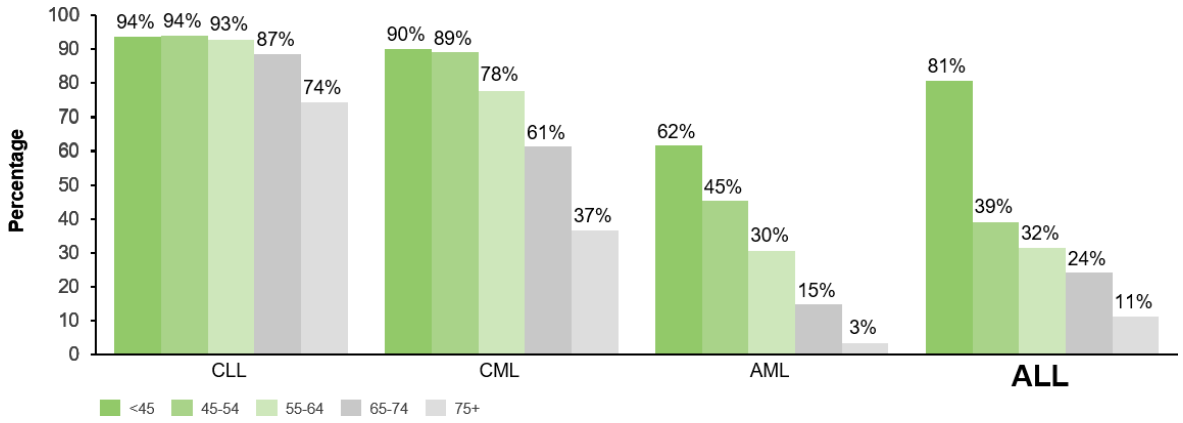
The clinical presentation of patients with ALL can be non-specific, involving a combination of constitutional symptoms and signs of bone marrow failure (anaemia, leukopenia and thrombocytopenia) (4). Many patients are diagnosed after an emergency admission with symptoms that have developed quickly (10). Common B-precursor ALL symptoms include fever, weight loss and night sweats (collectively known as ‘B symptoms’), easy bleeding or bruising, fatigue, dyspnoea, dizziness, weakness, joint or bone pain, and frequent infection (11).

ALL cells are fast growing (hence the ‘acute’ nomenclature), and the disease has an aggressive course; leukaemic cells can quickly accumulate and if left untreated, ALL

would cause death within a few weeks or months (4,12). This aggressive disease results in low survival rates for ALL relative to chronic leukaemia types, particularly in older populations. Age at diagnosis has a striking impact on prognosis and most deaths occur in adults. Five-year survival rates in patients diagnosed before they reach 45 years of age are as high as 81%, whereas in patients diagnosed at or over 65 years of age, the 5-year survival rate is approximately 18% (Figure 4).

Whilst survival rates in children and younger adults have dramatically improved over time, older adults have not seen that same improvement. Pulte *et al.,* (2009) found 5-year survival in 15–19-year-olds had increased from 41.0% to 61.1% between 1980-1984 and 2000-2004. Conversely, during that same time period, 5-year survival in adults ≥60 years of age only increased by 4.3%, from 8.4% to 12.7% (13).

Figure 4: 5-year relative survival of leukaemia types, stratified by age at diagnosis



Key: ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; SEER, Surveillance, Epidemiology, and End Results Program. The SEER databased reports survival rates between 2010 to 2016.
Source: (14).

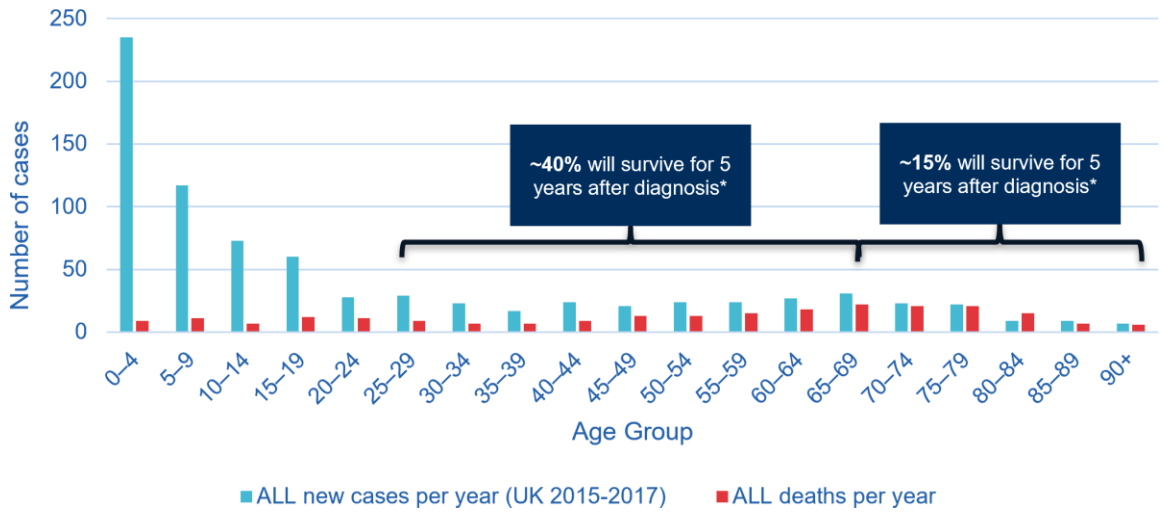
This reduced survival expectation is primarily driven by higher relapse rates following initial treatment for ALL in the adult population with cure rates estimated at 20–40% for adult ALL compared with over 80% for paediatric ALL (15–17). Several factors are thought to feed into the higher relapse rates in adult ALL, including better tolerance of younger patients to more aggressive first-line treatment approaches (chemotherapy-based myeloablative treatments) (16–18). The reduced survival expectation is even further pronounced in older adults, primarily due to a prevalence of adverse-risk disease biology, comorbidities, and reduced tolerance that may

preclude intensive curative modalities, as well as increased prevalence of poor-risk disease factors in older patients (17).

One of the most prominent ALL subtypes in adults is Philadelphia-chromosome-positive (Ph+) ALL, an abnormality resulting from a t(9;22) (q34;q11) translocation that results in a *BCR-ABL1* fusion gene. While the Ph+ genetic abnormality is rare in children, frequency increases with age, and it is the most common single genetic mutation in adult ALL (17). Ph+ ALL has historically been associated with poor disease prognosis, and is still considered a poor risk cytogenetic group despite the introduction of targeted treatment with tyrosine kinase inhibitors (TKIs) (16,19).

Summary survival data reported by the National Health Service (NHS) England estimate 5-year survival rates of 40% in adult ALL patients aged 25 to 64, reducing to 15% in adult ALL patients aged 65 or older (20). These data are depicted alongside ALL incidence data from Cancer Research UK in Figure 5.

Figure 5: ALL new cases and deaths, stratified by age group per year (2015–2017, UK)



Key: ALL, acute lymphoblastic leukaemia
Source: (6,20).

B.1.3.2 Outcomes for adult ALL patients

The core goal of ALL therapy, as with any life-threatening disease, is to extend patients life expectancy while preserving their quality of life (QoL) and minimising the toxicity of treatment. This remains particularly exigent for the adult ALL population,

for whom survival outcomes are considerably worse than for the paediatric population (Figure 4).

Alongside survival extension, complete remission (CR) and complete remission with incomplete haematological recovery (CRi) provide a well-defined metric of disease control that can be used to monitor and determine response to treatment in patient management as well as in a clinical trial setting. Minimal residual disease (MRD) is also an important outcome measure considering its proven link to prognosis and patient QoL (21). These key treatment objectives are defined in Table 3.

Table 3: Definitions of key treatment objectives in ALL

Treatment objective	Abbreviation	Definition
Complete remission	CR	≤5% blasts in the bone marrow and the absence of blood leukaemic blasts, and recovery of peripheral blood counts with neutrophils greater than 1 × 10^9/L and platelets counts greater than 100 × 10^9/L
Complete remission with incomplete haematologic recovery	CRi	≤5% blasts in the bone marrow and the absence of blood leukaemic blasts, partial recovery of peripheral blood counts and resolution of any extramedullary disease[a]
Minimal residual disease negativity	MRD-	The presence of leukemic cells not detectable by microscopy and may be measured by standardized methods with a sensitivity of less than 1 x 10^{-4} (<0.01%[b]) detectable leukemic cells in bone marrow samples

Notes: a) the definition of CRi does vary across clinical trials. b) Blinatumomab NICE reimbursement criteria in Philadelphia-chromosome negative adult ALL requires minimal residual disease of at least 0.1%.
Source: (19,22,23).

Adult ALL has historically had a dismal prognosis, with limited treatment options and cure rates less than 40%, even with 1st line treatment (17). Despite a high rate of response to first-line induction chemotherapy, only 30–40% of adult patients with ALL will achieve long-term remission (15). Following relapse to front-line therapy, prognosis is poor with most R/R adult ALL patients unlikely to live beyond a year (24). For example, median OS in the pivotal trials of blinatumomab and inotuzumab ozogamicin (hereafter inotuzumab) was 7.7 months (25,26). Considering the average age of adult R/R ALL adult patients is 40–50 years, this disease is starkly reducing peoples life expectancy (25,26).

B.1.3.3 Burden of disease

Due to the aggressive nature of R/R ALL combined with side effects of current treatments, adults with R/R ALL have a reduced QoL compared with both the general population and patients with other types of cancer (4).

In a comprehensive cancer centre survey conducted in Canada, adults with ALL reported the lowest QoL of all adult cancer patients surveyed, with a mean EQ-5D score of 0.70 and a mean visual analogue scale (VAS) score of 66.7, compared with EU5 population norms of 0.86-0.92 and 75-83 respectively (27,28).

B.1.3.4 Clinical Care Pathway

Formal treatment guidelines used to inform the most appropriate management of both newly diagnosed ALL and R/R ALL in Europe come from the European Society for Medical Oncology (ESMO) guidelines (19). Whilst NICE do not provide full guidelines on the treatment of ALL, they do provide a pathway for the treatment of lymphoid leukaemias (29).

*B.1.3.4.1 **ESMO Guidelines***

Since the release of the ESMO guidelines in 2016, several new targeted therapies have been approved for use in the EU. The targeted therapy inotuzumab gained European approval for the treatment of adult ALL in June 2017 (30). Blinatumomab, another targeted therapy, gained approval in Europe in November 2015 (31). While blinatumomab was approved before the publication of the ESMO guidelines, the approval occurred during the development of the article; as such, it was listed as ‘under investigation’.

As described in section B.1.3.2, the goal of treatment is to induce CR whilst limiting toxicity of treatment, as both of these factors are correlated with overall survival (OS) (32). First line treatment begins with an induction phase, which generally consists of pegylated asparaginase (PEG-Asp) in combination with antineoplastic chemotherapy. Eligible patients with a suitable donor may receive a potentially curative stem cell transplant (SCT) at this stage. However, limitations with induction therapies (that is, the low CR rates) subsequently restrict the use of allo (allogeneic) -SCT, the main potentially curative treatment option available to adults with R/R ALL

in current practice. Of note is that in the UK, most patients are entered into clinical trials in first line, with the aim of evaluating different treatment approaches (33).

For those patients who do achieve CR with induction therapy, the potential benefits of allo-SCT still need carefully considering alongside the potential risks. ESMO guidelines recommend allo-SCT in first CR for Ph+ patients and all patients with poor early MRD response. However, the guidelines state that use of SCT in first CR is not defined in a satisfactory way and requires continuous update, with this partly due to the improving results with conventional and targeted chemotherapy regimens.

No specific recommendations have been made by the ESMO for the treatment of adult patients with R/R Ph- ALL, other than treatment with allo-SCT. Similarly, no specific recommendations have been made for the treatment of R/R Ph+ ALL in adults, except for the use of a different TKI to that given during the induction phase of treatment, preferably 2nd or 3rd generation TKIs. Where patients have relapsed post-allo-SCT or are ineligible/unlikely to achieve allo-SCT, ESMO provides no specific recommendations, perhaps in acknowledgement of the limited options available.

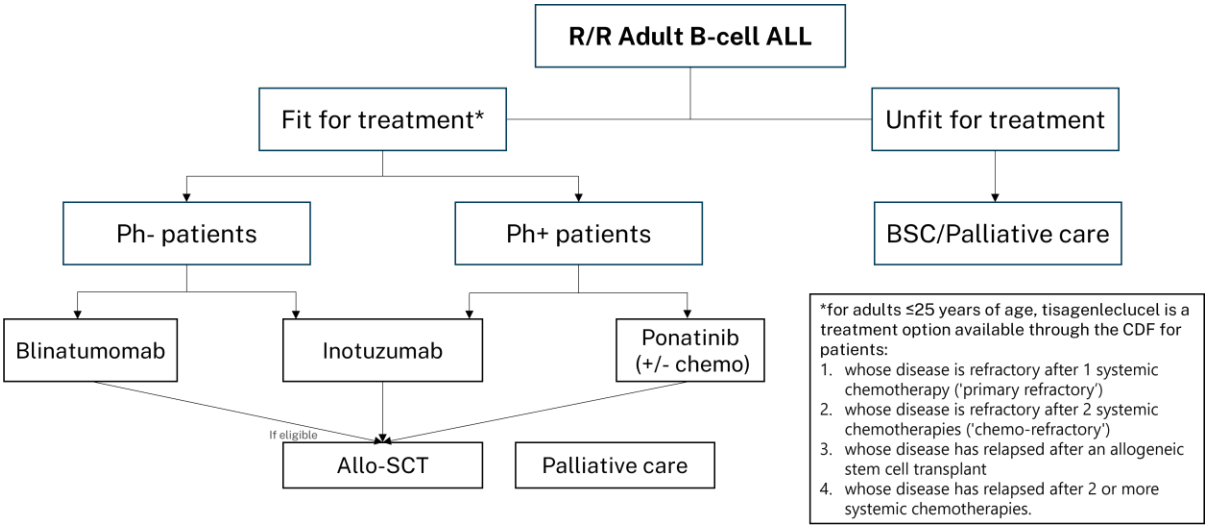
*B.1.3.4.2 **NICE lymphoid leukaemia treatment pathway***

The NICE treatment pathway for lymphoid leukaemia has recently been updated (September 2020), providing an overview of recommendations for first-line treatment, treating complete remission with MRD, and treating R/R ALL in the UK (29).

Pegaspargase is recommended by NICE (TA408) as part of antineoplastic combination therapy for the treatment of newly diagnosed ALL (34). In Ph- patients in first CR with MRD (>0.1%), blinatumomab is recommended as a treatment option (TA589).

The NICE recommendations for the treatment of ‘fit’ R/R adult ALL are in part determined by the presence of the Philadelphia chromosome) as depicted in Figure 6.

Figure 6: Treatment algorithm for R/R adult B-cell ALL



Key: ALL, acute lymphoblastic leukaemia; BSC, best supportive care; CDF, Cancer Drugs Fund; Ph, Philadelphia chromosome; SCT, stem cell transplant
Source: adapted from the NICE lymphoid leukaemia pathway (29).

The reimbursement conditions for the four treatment options approved by NICE for R/R adult ALL are provided in Table 4. Of note is that tisagenlecleucel is recommended only in patients up to the age of 25 years who fulfil specific criteria, whilst blinatumomab is recommended only for Ph- patients and ponatinib is recommended only in specific Ph+ patients. Based on discussion with clinical experts, it is our understanding that ponatinib is not commonly given as a monotherapy in clinical practice in England, but instead as part of combination with chemotherapy (35).

Table 4: NICE treatment guidance for R/R adult ALL

TA	Recommendations
TA554	Tisagenlecleucel therapy is recommended for use within the CDF as an option for treating R/R B-cell ALL in patients up to the age of 25 years, and only if the conditions in the managed access agreement are followed.
TA541	Inotuzumab ozogamicin is recommended, within its market authorization, as an option for treating relapsed or refractory CD22-positive B-cell precursor B-cell ALL in adults. Individuals with R/R Ph+ ALL should have had prior treatment with at least one TKI. Inotuzumab ozogamicin is recommended only if the company provides it according to the commercial arrangement.
TA450	Blinatumomab is recommended, within its marketing authorization, as a treatment option for R/R Ph- precursor B-cell ALL in adults, only if the company provides it with the discount agreed in the PAS.

TA451	Ponatinib is recommended as a treatment option for adults with Ph+ ALL when: • The disease is resistant to dasatinib • Dasatinib cannot be tolerated or is not clinically appropriate for the patient • the T315I gene mutation is present Ponatinib is only recommended when the company provide the drug at the discounted rate agreed in the PAS.

Key: ALL, acute lymphoblastic leukaemia; CDF, cancer drugs fund; CR, complete remission; NICE, National Institute for Clinical Excellence; PAS, patient access scheme; R/R, relapsed/refractory; TA, technology appraisal; TKI, tyrosine kinase inhibitor
Source: NICE lymphoid leukaemia pathway (29).

B.1.3.4.3 Unmet needs with current treatment

The introduction of novel treatment options such as biological targeted therapies (blinatumomab and inotuzumab) and TKI therapies has improved the prognosis of adult R/R ALL in recent years. However, in their pivotal clinical trials, blinatumomab and inotuzumab only yielded CR rates of 34% and 36%, respectively, and median OS times of 7.7 months (for both treatments) (25,26). Median OS for ponatinib in the pivotal Phase 2 trial (n=32) was 8.0 months (36). As a result, feedback received from UK clinical experts was that none of these options are considered curative, and that long-term outcomes for blinatumomab, inotuzumab, and ponatinib in UK clinical practice are largely contingent on subsequent SCT (35).

However, a significant proportion of patients cannot proceed to transplant, and post-transplant morbidity and mortality remain high, underlining a substantial unmet need. For example, in the pivotal blinatumomab TOWER study, only 24% of subjects in both arms went on to receive allo-SCT. Among these patients, 10/38 in the blinatumomab group (26%) and 3/12 in the chemotherapy group (25%) died during a median follow-up period of 206 and 279 days, respectively (25). In addition, high risk patients in the first line setting will have already received a SCT.

Five-year survival rates in adult ALL patients receiving SCT in the R/R setting remain below 25%, and allo-SCT can result in severe side effects such as graft versus host disease (GvHD), serious infection and veno-occlusive disease (VOD) (9,37,38). In a structured literature review of allo-SCT-related complications in leukaemia, long-term side effects included chronic GvHD (43% at 5 years post SCT), secondary tumour (21% at 20 years post SCT), hypothyroidism (11% at 15 years post-SCT), bronchiolitis obliterans (9.7% at 122 days post-SCT), cardiovascular disease (7.5%

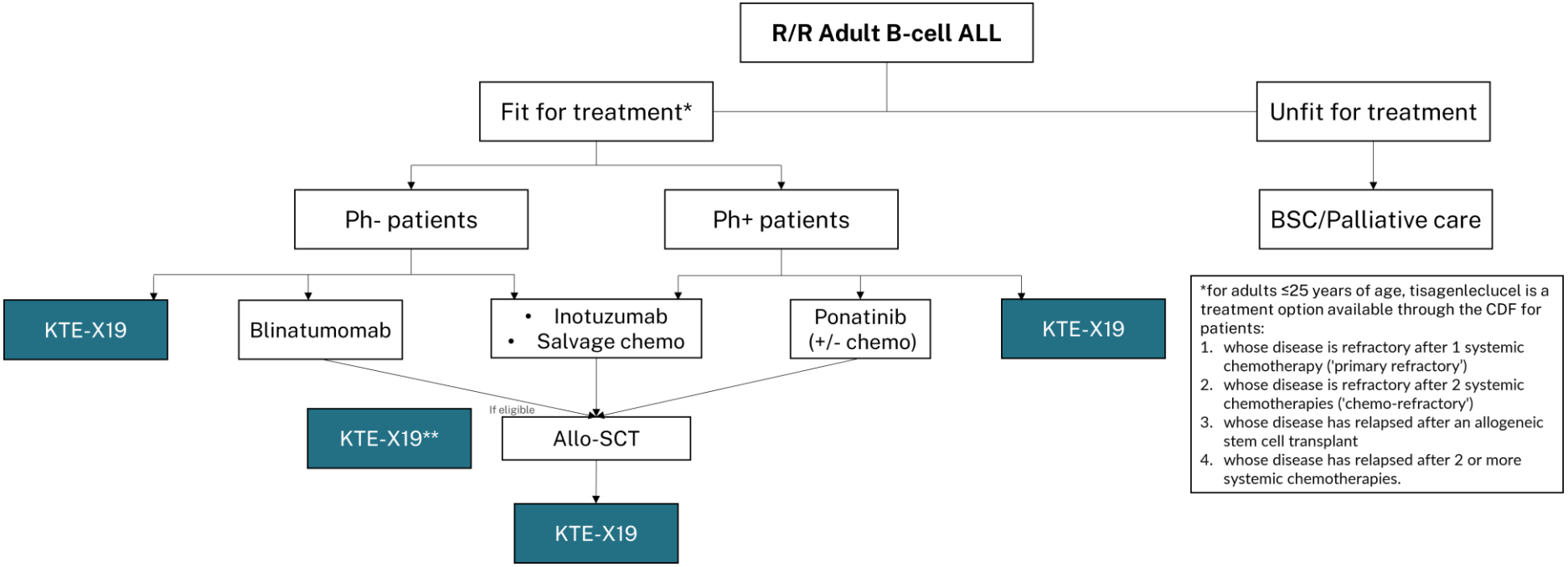
at 15 years post-SCT) and avascular necrosis (5.4% at 10 years post-SCT). Not only do such side effects put patients' lives at risk, but they can also be complicated and costly to manage, with a significant impact on QoL (27,38,39).

Tisagenlecleucel is approved only for the treatment of R/R B-ALL in paediatric and young adult patients up to 25 years of age. In the ELIANA trial, a CR/CRi rate of 83% was achieved. Notably, subgroup analysis in the subjects who were aged ≥ 10 years of age and < 18 years demonstrated a CR/CRi rate of 88% (95% CI: 69%, 97%), whereas the CR/CRi rate declined to 75% (95% CI: 43%, 95%) in subjects ≥ 18 years. The benefit-risk profile of tisagenlecleucel is not well established in the adult population (40).

B.1.3.4.4 Proposed positioning of KTE-X19 in the R/R adult ALL pathway

The proposed positioning of KTE-X19 aligned to the decision problem is displayed schematically in Figure 7.

Figure 7: Proposed positioning of KTE-X19 in the adult ALL treatment pathway



Key: ALL, Acute lymphoblastic leukaemia; BSC, best supportive care; CDF, cancer drug fund; Chemo, chemotherapy; Ph, Philadelphia chromosome; R/R, relapsed/refractory; SCT, stem cell transplant.
Notes: **where ineligible for stem cell transplant.

Clinical experts felt that KTE-X19 was likely to be positioned in clinical practice for use in adults with R/R B-cell ALL who:

- Have relapsed post-SCT;
- Are ineligible for SCT (on the basis of age, frailty, comorbidities or other criteria);
- Are unlikely to achieve SCT via existing bridging therapies (primary refractory, relapsed within 12 months, failed ≥2 lines of prior therapy).

This is in line with the inclusion criteria of the pivotal trial evaluating KTE-X19 in R/R B-cell ALL: ZUMA-3 (41,42).

The addition of a potentially curative treatment option for these patients for whom allo-SCT is either not an option or not recommended would provide a valuable addition to the treatment armamentarium. The following text provides more detail on the unmet need that exists in the anticipated positioning of KTE-X19 in UK clinical practice.

R/R adult ALL: relapsed post-allo SCT:

As a potentially curative option, allo-SCT has 5-year OS rates of 23% in R/R adult ALL (9). Following relapse to allo-SCT, survival expectations remain poor. In a retrospective analysis of 465 ALL patients from European Group for Blood and Marrow Transplantation (EBMT) centres who had relapsed following allo-SCT, the median survival post-relapse was 5.5 months, and the estimated post-relapse 5-year survival rate was only 8% (with salvage treatments including chemotherapy, cytoreductive therapy, supportive care, donor lymphocyte infusion and second SCT) (43). Based on discussion with clinical experts practicing in England, although a second allo-SCT is permitted in certain circumstances (i.e. where the patient achieved a CR lasting ≥12 months with first SCT), clinicians do not perceive it to be a viable therapeutic option (35). Therefore, patients who relapse post-allo-SCT pose a significant unmet need. Treatment options for these patients include salvage chemotherapy, or blinatumomab/ inotuzumab (if these have not already been tried), outcomes of which are largely contingent on consolidation with SCT.

R/R adult ALL: ineligible for SCT

A number of factors affect eligibility for allo-SCT, including donor availability, remission status, depth of remission, and comorbidities (19). The EBMT group previously estimated between 5–30% of adults with R/R ALL would be eligible for allo-SCT consolidation due to the low CR rates observed with salvage chemotherapy (44). Eligibility has increased with the introduction of targeted treatments to the ALL treatment pathway and associated increase in CR rates for adult R/R ALL patients, but still remains low (25,26).

R/R adult ALL: unlikely to achieve SCT

Given the requirement to achieve CR prior to SCT, a number of groups are unlikely to achieve SCT, specifically:

- Adult R/R ALL that has relapsed within 12 months of first remission

The Spanish Programa Español de Tratamiento en Hematologia (PETHEMA) group analysed prognostic factors after first relapse in adult ALL patients enrolled in risk-adapted PETHEMA trials (n = 263) Relapse within a year of first remission was associated with a particularly poor prognosis, with a 5-year survival probability of only 1.8% for these patients, compared with 15% for patients relapsing between 1–2 years of first remission and 31% for patients relapsing more than 2 years after first remission (45).

- Adults with primary refractory ALL

Adults with primary refractory ALL have a similarly poor prognosis, with median OS of 4-5 months and only ~30% CR on salvage chemotherapy (24). Primary refractory adult ALL has a 1-year survival rate of only 15% (46).

- Adults with R/R ALL that have failed ≥2 lines of prior therapy

Survival rates for patients with R/R B-ALL 1 year after the second, third, and fourth or higher lines of therapy are 26%, 18%, and 15%, respectively (24). Furthermore, CR rates decline with each subsequent line of treatment (CR rates of ≤ 47% with second-line and higher chemotherapy vs ≤ 21% with third-line and higher

chemotherapy), with associated reduction in likelihood of reaching allo-SCT (24,47–52).

Therefore, the anticipated positioning of KTE-X19 in clinical practice addresses a considerable unmet medical need where no potentially curative option exists with current approved treatments associated with median OS of only 4-8 months (25,26).

B.1.3.5 Summary of Unmet Medical Need

R/R B-ALL in adult patients continues to represent an unmet medical need, as demonstrated by the low response rates and limited outcomes observed in recent studies of novel therapies. Complete response is required in order to receive a potentially curative SCT, which is associated with ~23% OS at 5 years (9,53). As described in section B.1.3.4.4, there are a number of groups within the R/R adult ALL population that have a particularly dismal prognosis. Among those with primary relapsed ALL, patients with short first remissions (< 12 months) have worse outcomes than patients who relapse after a longer first remission (CR rates of 22% vs 41%, respectively) (52). CR rates decline with each subsequent line of treatment (CR rates of ≤ 47% with second-line and higher chemotherapy vs ≤ 21% with third-line and higher chemotherapy) (24,47–52). Furthermore, survival rates for patients with R/R B-ALL 1 year after the second, third, and fourth or higher lines of therapy are 26%, 18%, and 15%, respectively (24).

Novel treatment strategies are also needed for older patients with R/R B-ALL, a population who remain challenging due to the high morbidity and mortality associated with intensive chemotherapy regimens and SCT and many are too frail to withstand these treatments, as well as the increased incidence of high-risk factors such as Ph+ disease among older patients with ALL (24,54).

Collectively, these results highlight the need for additional therapies such as KTE-X19 that can induce more durable responses with potentially long-term survival in adult patients with R/R B-ALL. This is particularly true in those with the highest unmet need, including those who have relapsed post-SCT or are ineligible for SCT, or those with particularly poor prognostic indicators such as primary refractory

disease or first relapse within 12 months that make them unlikely to be able to achieve SCT.

B.1.4 Equality considerations

No equality issues related to the use of KTE-X19 have been identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

A systematic literature review (SLR) was conducted to identify all relevance clinical evidence associated with the decision problem outlined in section B.1.1. Full details are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

See Appendix D1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to KTE-X19.

One Phase 1/2 trial was identified in the clinical SLR that provides direct clinical evidence for the efficacy and safety of KTE-X19 for the treatment of adult R/R B-cell ALL: ZUMA-3 (NCT02614066) (55). Eight records were retrieved relating to ZUMA-3, including two publications relating to the Phase 1 results, one publication relating to the Phase 2 results, and 5 conference abstracts (Table 96).

ZUMA-3 is an ongoing Phase 1/2, multicentre, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with R/R B-ALL (55). Phase 1 results were published by Shah *et al.,* (2021) (41). Phase 2 results are provided by the Shah *et al*., (2021) publication in *The Lancet* (42). The data cut-off for the Phase 2 publication is 9th September 2020, and this is the same as the data cut-off for the clinical study report (CSR) (56). Therefore, where possible, the publicly available Shah *et al*., (2021) publications for Phase 1 and Phase 2 published in *Blood* and *The Lancet*, respectively, will be the primary sources for information in this section, with data from the CSR used to supplement where deemed appropriate (41,42,56).

Patients from both Phase 1 and Phase 2 will be followed up to 15 years after the last patient received KTE-X19. Preliminary results from the most recent analysis with data cut-off 23/07/21 provide longer-term data on the durability of KTE- X19. Whilst

more detail will be made available through the evaluation process, key results of this most recent data cut-off are presented in Section B.2.6.

Table 5: Clinical effectiveness evidence

Study	ZUMA-3 (NCT02614066)				
Study design	A Phase 1/2 Multi-Center Study Evaluating the Safety and Efficacy of KTE-X19 in Adult Subjects with Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia (R/R ALL)				
Population	Adults with relapsed/refractory B-ALL				
Intervention(s)	KTE-X19				
Comparator(s)	None (ZUMA-3 is a single-arm trial)				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	ZUMA-3 presents the pivotal, regulatory, clinical evidence in support of KTE-X19 for the treatment of adult R/R ALL				
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival (including relapse-free and event-free survival)** • **Treatment response rate (including minimal residual disease, haematologic responses and complete remission)** • **Rate of allogeneic stem cell transplant** • **Adverse effects of treatment** • **Health-related quality of life**				
All other reported outcomes	N/A				

Key: ALL, acute lymphoblastic leukaemia; N/A, not applicable; R/R, relapsed/refractory.
Notes: outcomes in bold are those directly used in the economic modelling.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial design

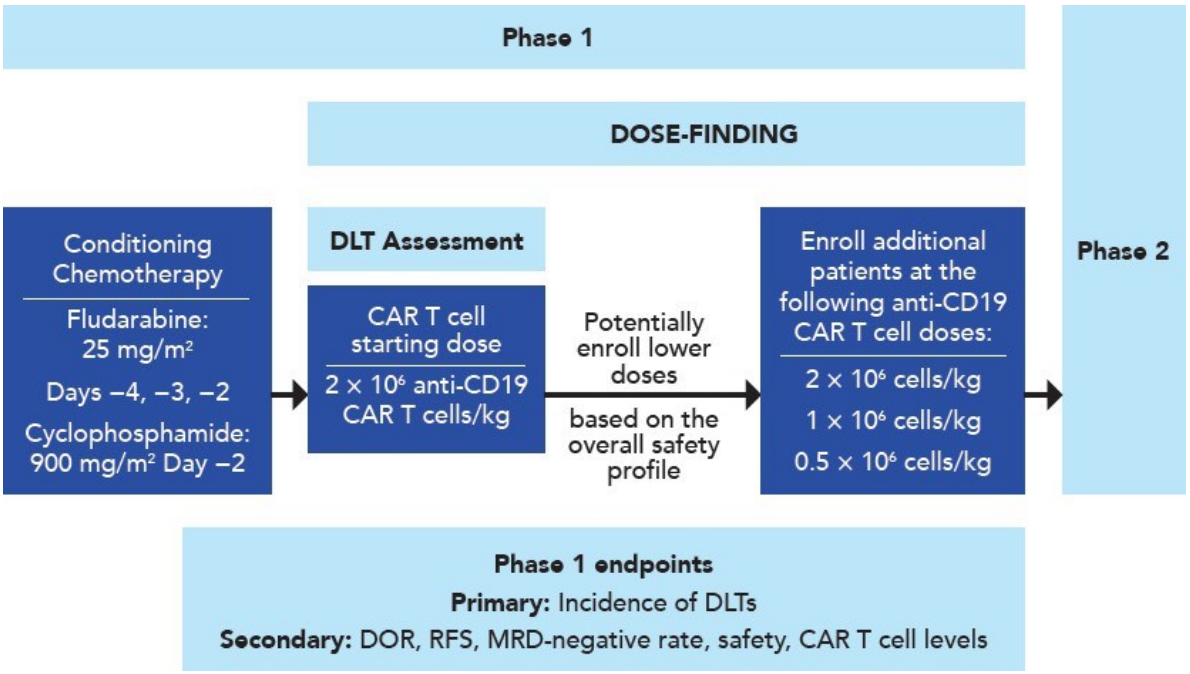
ZUMA-3 is a Phase 1/2 multicentre, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with R/R B-ALL In this study, R/R was defined as 1 of the following:

- Primary refractory

- First relapse following a remission lasting ≤12 months
- R/R after second-line or higher therapy
- R/R after allo-SCT (provided the transplant occurred ≥100 days prior to enrolment and that no immunosuppressive medications were taken ≤4 weeks prior to enrolment)

The rationale for these definitions was based on the historically poor outcomes observed in these patient populations (18,24,57,58). In particular, CR rates to salvage treatments have been shown to be lower for patients with first remission durations < 12 months compared with those who relapse after a longer first remission, and decrease with each subsequent line of treatment (24,52).

Figure 8: ZUMA-3 Phase 1 study design and dosing



Key: CAR, chimeric antigen receptor; DLT, dose-limiting toxicity; DOR, duration of remission; MRD, minimal residual disease; RFS, relapse-free survival.
Source: (41).

During Phase 1, approximately 3 to 12 subjects with high burden R/R B-ALL disease (defined as > 25% leukaemia blasts in the bone marrow [M3 marrow] or ≥ 1,000 blasts/mm^3 in the peripheral blood) who were evaluable for dose limiting toxicities (DLTs) were to be assessed to evaluate the safety of KTE-X19, with rate of DLTs within 28 days the primary endpoint (41). Additionally, around 40 subjects with high or low disease burden R/R B-cell ALL were enrolled to further assess safety and were also evaluated for secondary efficacy endpoints. A Safety Review Team (SRT), which comprised representatives of the sponsor together with at least 1 study investigator, was to review safety data and make recommendations regarding further enrolment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19 (56) (Figure 8).

The initial dose of KTE-X19 investigated in Phase 1 was 2 x 10^6 anti-CD19 CAR+ T-cells/kg based on the DLT, and maximum tolerated dose observed in first use studies of KTE-X19 at the National Cancer Institute. Other doses explored in Phase 1 were 0.5 x 10^6 anti-CD19 CAR+ T-cells/kg and 1 x 10^6 anti-CD19 CAR+ T-cells/kg.

An analysis of Phase 1 was conducted when 41 subjects treated with KTE-X19 had had the opportunity to be followed for at least 2 months. The results of this analysis were reported in the ZUMA-3 End-of-Phase 1 Summary and are presented in B.2.6 (41). On the basis of these results the SRT recommended initiating the Phase 2 portion of the study at the target dose of $1x10^6$ anti-CD19 CAR+ T-cells/kg dose.

During Phase 2, approximately 50 subjects in the modified intent-to-treat (mITT) analysis set were to be assessed to evaluate the efficacy and safety of KTE-X19 at the target dose ($1x10^6$ anti-CD19 CAR T-cells/kg). The mITT analysis set was defined as all subjects enrolled and treated with KTE-X19 in Phase 2.

In total, 125 subjects were enrolled and treated with KTE-X19 in phases 1 and 2 combined. The primary analysis was to occur when the overall study enrolment had been completed and the last treated subject in the mITT analysis set had the opportunity to complete the Month 6 disease assessment. At the time of the data cutoff date for the primary analysis (09/09/20), all subjects in the mITT analysis set had had the opportunity to be followed for at least 10 months after the KTE-X19 infusion (56).

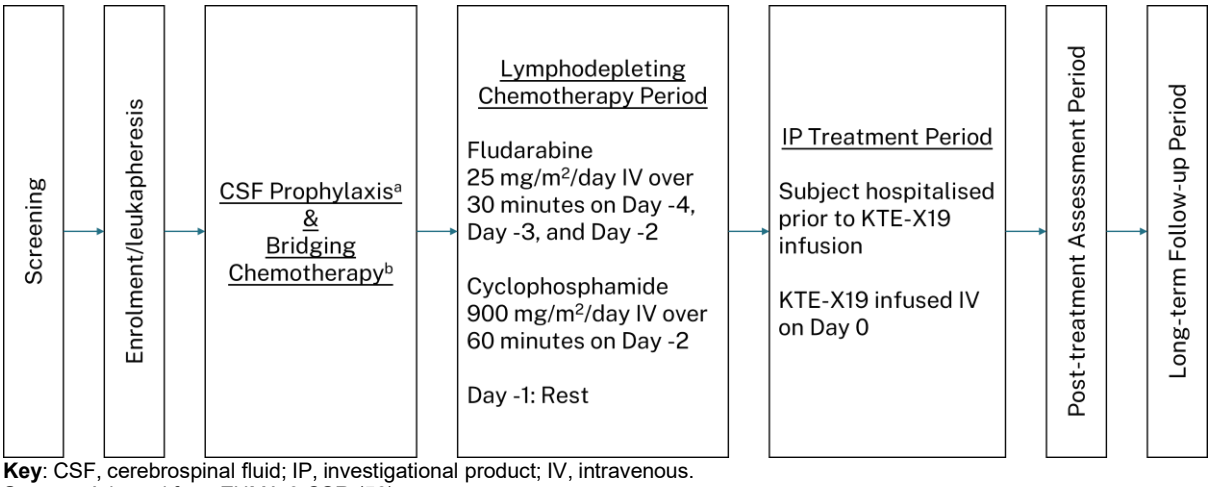
In the Phase 2 portion, adult patients with R/R cell ALL who met the criteria listed in Table 6 were enrolled and treated with KTE-X19 at a target dose of 1×10^6 anti-CD19 CAR+ T cells/kg (hereafter referred to as target dose). Phase 2 was designed to evaluate the efficacy and safety of KTE-X19 at target dose. First remission assessment was conducted at Day 28 but patients from both Phase 1 and Phase 2 will be followed up to 15 years after the last patient received KTE-X19. On this basis, the final study completion date is estimated to be September 2035 (55).

Once deemed eligible and enrolled into the study, subjects in both phases were to follow the same treatment schedule (Figure 9) and procedural requirements and proceed through the following study periods:

- Screening
- Enrolment/leukapheresis
- Bridging chemotherapy and cerebrospinal fluid (CSF) prophylaxis

- Lymphodepleting chemotherapy
- KTE-X19 treatment
- Post-treatment assessment
- Long-term follow-up

Figure 9: Subject Treatment Schema (Phase 1 and Phase 2)



Key: CSF, cerebrospinal fluid; IP, investigational product; IV, intravenous.
Source: Adapted from ZUMA-3 CSR (56).
a) CSF prophylaxis (administered any time during screening through 7 days prior to KTE-X19 infusion): All subjects were to receive CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines. CSF prophylaxis could be administered with the screening lumbar puncture.
b) Bridging chemotherapy (administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy): Bridging chemotherapy was recommended for all subjects, particularly those subjects with high disease burden at screening (M3 marrow [> 25% leukemic blasts] or ≥ 1,000 blasts/mm3 in the peripheral circulation).

B.2.3.2 Trial methodology

Table 6: Summary of trial methodology for ZUMA-3

Trial number (acronym)	NCT02614066 (ZUMA-3)
Location	This study was conducted at a total of 32 study centres across North America (US: 21; Canada: 1), and Europe (France: 4; Germany: 3; Netherlands: 3)
Trial design	ZUMA-3 is a Phase 1/2, multicentre, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with R/R B-ALL.
Eligibility criteria for participants*	**Inclusion criteria:** 1. R/R B-ALL, defined as 1 of the following: • Primary refractory disease • First relapse if first remission was ≤12 months • R/R disease after 2+ lines of systemic therapy • R/R disease after allo-SCT provided subject was at least 100 days from transplant at time of enrolment and off of

	immunosuppressive medications for at least 4 weeks prior to enrolment 2. Morphological disease in the bone marrow (>5% blasts) 3. Subjects with Ph+ disease were eligible if they were intolerant to TKI therapy or if they had R/R disease despite treatment with at least 2 different TKIs 4. Aged 18 years or older 5. ECOG performance status of 0 or 1 6. Absolute neutrophil count ≥ 500/μL unless, in the opinion of the principal investigator, cytopenia was due to underlying leukaemia and was potentially reversible with leukaemia therapy 7. Platelet count ≥ 50,000/μL unless, in the opinion of the principal investigator, cytopenia was due to underlying leukaemia and was potentially reversible with leukaemia therapy 8. Absolute lymphocyte count ≥ 100/μL 9. Adequate renal hepatic, pulmonary, and cardia function, defined as: • Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min • Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal • Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome • Left ventricular ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, no New York Heart Association class III or class IV functional classification, and no clinically significant arrhythmias • No clinically significant pleural effusion • Baseline oxygen saturation > 92% on room air 10. Females of childbearing potential must have had a negative serum or urine pregnancy test 11. In subjects previously treated with blinatumomab, CD19 tumour expression on blasts obtained from bone marrow or peripheral blood must have been documented after completion of the most recent prior line of therapy. If CD19 expression was quantified, then blasts must have been ≥ 90% $CD19^{+}$ **Exclusion criteria:** 1. Diagnosis of Burkitt's leukaemia/lymphoma according to World Health Organisation classification or chronic myelogenous leukaemia lymphoid blast crisis 2. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix bladder, breast) unless disease-free for at least 3 years 3. History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study 4. CNS abnormalities, defined as any of the following: • Presence of CNS-3 disease, defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 white

	blood cells (WBCs) per mm^3 with or without neurological changes • Presence of CNS-2 disease, defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm^3 with neurological changes • History or presence of any CNS disorder, such as a seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral oedema 5. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment 6. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment 7. Primary immunodeficiency 8. Known infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus. A history of hepatitis B or hepatitis C was permitted if the viral load was undetectable per quantitative polymerase chain reaction and/or nucleic acid testing 9. Presence of fungal, bacterial, viral or other infection that was uncontrolled or required antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment and after consultation with the Kite medical monitor
Settings and locations where the data were collected	• Subjects were to be hospitalised for treatment with KTE-X19 and remain in the hospital for a minimum of 7 days after treatment unless otherwise required by a country's regulatory agency • Subjects were to remain hospitalised until all KTE-X19-related non-haematological toxicities had returned to Grade 1 or lower or baseline. Subjects could be discharged with noncritical toxicities that were clinically stable or slowly improving even if the event was higher than Grade 1, if deemed appropriate by the investigator • Subjects were also to remain hospitalised for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurologic toxicity if the event severity was higher than Grade 1 or deemed necessary by the treating investigator
Study periods and trial drugs	• Screening • Enrolment/leukapheresis - In addition to meeting the eligibility criteria outlined above, • Bridging chemotherapy + CNS prophylaxis - Bridging therapy could be administered after leukapheresis and prior to lymphodepleting chemotherapy at the discretion of the investigator, and completed at least 7 day or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy - Recommended for all subjects, particularly those subjects with high disease burden at baseline (M3 marrow [>25%

	leukaemic blasts] or ≥ 1,000 blasts/mm^3 in the peripheral circulation) - Permitted bridging therapies and regimens included attenuated VAD, mercaptopurine, hydroxyurea, DOMP, attenuated FLAG/FLAG-IDA, and mini-hyper CVAD. A full list can be found in the supplementary materials of Shah *et al.,* (2021) (42) - All subjects were to receive CSF prophylaxis, consisting of an intrathecal regimen according to institutional or national guidelines. CSF prophylaxis was to be administered any time during screening through 7 days prior to KTE-X19 infusion - Additional CSF prophylaxis could be given after the KTE-X19 infusion at the discretion of the investigator in accordance with institutional guidelines but was to be avoided for at least 8 weeks after KTE-X19 infusion, if possible • Lymphodepleting chemotherapy - Subjects were to receive a non-myeloablative lymphodepleting regimen consisting of fludarabine 25 mg/m^2/day administered IV over 30 minutes on Day -4, -3, -2, and cyclophosphamide 900 mg/m^2/day administered IV over 60 minutes on Day -2 - Prior to the initiation of lymphodepleting chemotherapy, the subject must have shown no evidence or suspicion of an infection, and no systemic antimicrobials for a known or suspected infection within 408 hours prior to initiation of lymphodepleting chemotherapy • KTE-X19 treatment - The following medications were to be administered 1 hour prior to infusion i) Acetaminophen 650 mg orally (PO) or equivalent ii) Diphenhydramine 12.5 mg administered PO, IV, or equivalent - All patients were to receive a single IV infusion of KTE-X19 after a 2-day rest period post-completion of conditioning chemotherapy - KTE-X19 was manufactured from each subject's leukapheresis material • Post-treatment assessment: beginning at Day 14 (± 2 days) and ending at Month 3 (± 2 weeks) • Long-term follow-up: starting at Month 6
Prior and concomitant medication	• Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent dose of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion • Systemic corticosteroids were to be avoided as premedication in subjects for whom CT scans with contrast were contraindicate • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19-related toxicities. Other medications that could

	interfere with evaluation of KTE-X19, such as NSAIDs, were also to be avoided for the same time period unless medically necessary • For subjects with Ph+ ALL, all TKIs were to be stopped at least 1 week prior to KTE-X19 infusion. In subjects who achieved CR, a TKI could be resumed 2 months after KTE-X19 infusion • Investigators were allowed to prescribe concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support and routine antiemetic prophylaxis and treatment, except for the excluded medications listed above
Primary outcome	• Phase 1: incidence of adverse events defined as dose-limiting toxicities • Phase 2: OCR rate (CR + CRi) per independent review (hereafter referred to as central assessment)
Secondary outcomes used in the model /specified in the scope	• MRD^- rate, defined as the incidence of an MRD^- response, where MRD^- was defined as MRD < 10^{-4} per the standard assessment by flow cytometry performed by the central laboratory. • Duration of remission, defined as the time from the first CR or CRi to relapse or death from any cause in the absence of documented relapse • OCR rate per investigator assessment • Allo-SCT rate • Overall survival, defined as the time from KTE-X19 infusion date to the date of death from any cause - In the ITT population this was defined as time from enrolment to the date of death • Relapse-free survival, defined as time from KTE-X19 infusion date to the date of disease relapse or death from any cause - In the ITT population this was defined as time from enrolment to the date of disease relapse or death from any cause • Incidence of AEs • Changes over time in the EQ-5D and EQ-5D visual analogue scale
Pre-planned subgroups	• Subgroup analyses based on baseline disease and treatment covariates were conducted for selected efficacy and safety endpoints. These included: - Sex - Age - Baseline extramedullary disease - CNS status at screening - Philadelphia chromosome status - Prior lines of therapy - Prior allo-SCT - Prior blinatumomab - Prior inotuzumab - First relapse ≤ 12 months - Primary refractory

	- Relapsed/refractory post SCT - Relapsed/refractory after ≥2 lines of prior therapy
Key: AE, adverse event; ALL, acute lymphoblastic leukaemia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete haematological recovery; CRS, cytokine release syndrome CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events DOMP, dexamethasone, 6-mercaptopurine, methotrexate, and vincristine; ECOG, Eastern Cooperative Oncology Group; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor; GVHD, graft-versus-host disease; IL, interleukin; IV, intravenous; MRD, minimal residual disease; Ph, Philadelphia chromosome; R/R, relapsed/refractory; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor; VAD, vincristine, doxorubicin, and dexamethasone; WBC, white blood cell. **Note:** for a full list of eligibility criteria please refer to the supplementary materials of **Source:** Shah *et al.,* (2021) (42); ZUMA-3 CSR (56).	

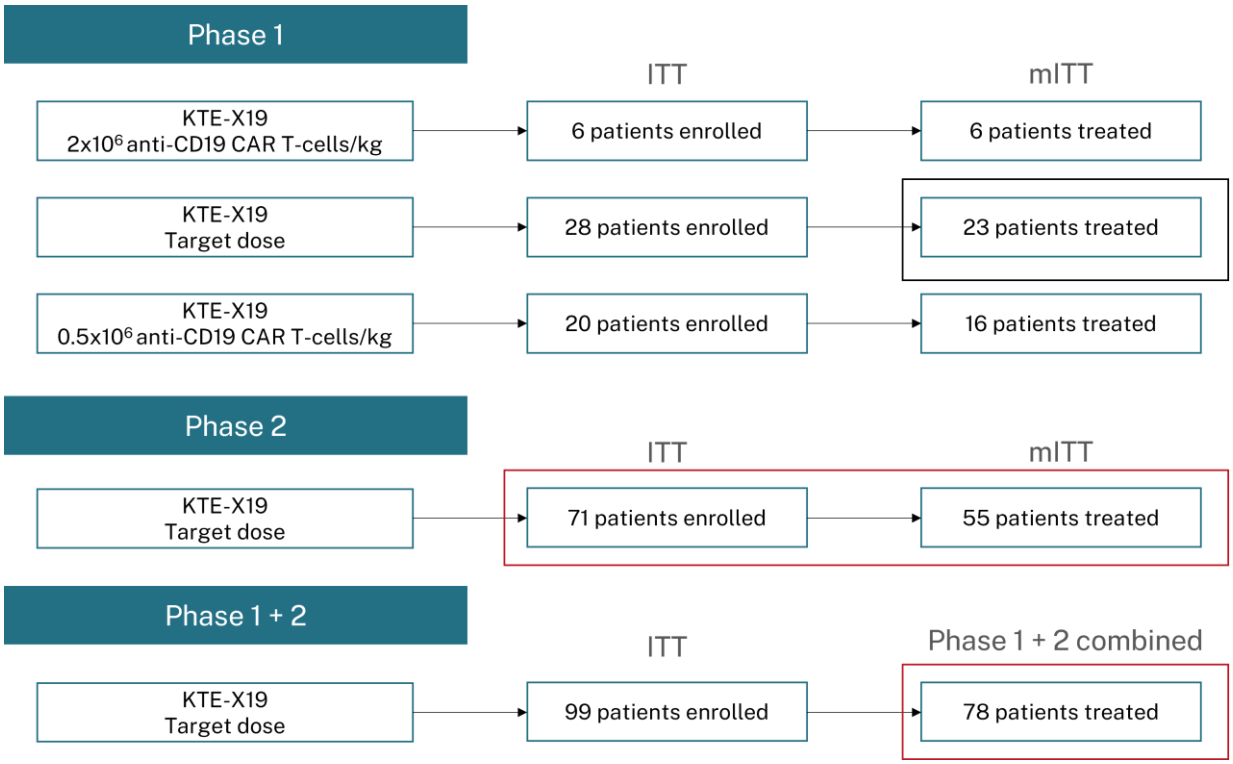
B.2.3.3 Patient datasets and baseline characteristics

Whilst there are multiple datasets within the ZUMA-3 Phase 1/2 trial (Figure 10) the clinical effectiveness section focuses on the Phase 1 + 2 combined dataset, defined as all subjects in ZUMA-3 to receive KTE-X19 at target dose (n=78) (Table 7). Treated patients align to the costing framework proposed for KTE-X19, where only treated patients are paid for by the NHS.

The Phase 2 mITT population – the results of which were published in The Lancet - is also presented to provide further support for the clinical effectiveness of KTE-X19 (42). Data from the Phase 2 intent-to-treat (ITT) population (n=71) is included for baseline characteristics in section B.2.6, with further information available in the CSR (56). Information on the Phase 1 target dose (n=23) population is provided in Appendix L.

As described in Section B.2.10, toxicity management recommendations were revised during Phase 1, with 9 of 23 subjects treated at target dose managed under the revised adverse event (AE) guidelines, which were then carried through to Phase 2.

Figure 10: Patient cohorts of ZUMA-3



Key: CAR T-cell, chimeric antigen receptor T-cell; ITT, intent-to-treat; mITT, modified intent-to-treat.
Notes: Datasets highlighted in red are presented in the main body of form B, boxes highlighted in black are presented in the appendix. Other data is available in the clinical study report. Target dose is defined as $1x10^6$ anti-CD19 CAR T-cells/kg.
Source: Adapted from ZUMA-3 publications (41,42).

Table 7: Summary of ZUMA-3 datasets

Phase	Analysis set	n	Submission location	Relevant publication
1+2	Phase 1 + 2 combined	78	Section B.2.6	Shah *et al.*, (2021) (appendix) (42)
2	mITT	55	Section B.2.6	Shah *et al.*, (2021) (42)
1	Target dose	23	Appendix L	Shah *et al.*, (2021) (41)
2	ITT	71	Section B.2.6, CSR	Shah *et al.*, (2021) (42)

Note: Phase 1 + 2 combined is defined as all patients who received KTE-X19 at the target dose of 1 x 10^6 anti-CD19 CAR+ T-cells/kg.

Table 8 presents key baseline characteristics for the Phase 1 + 2 combined dataset. Almost half ([redacted]) of subjects treated had prior treatment with blinatumomab, and [redacted] had prior treatment with inotuzumab. Outcomes in the setting of blinatumomab and inotuzumab failure have not been well studied to date, although limited reports indicate that once patients fail blinatumomab, responses to subsequent lines of therapy deteriorate, leaving patients with very limited options (59,60).

In addition, [redacted] had relapsed post-SCT. As discussed in section B.1.3.2, outcomes for patients who relapse post-SCT are especially dire. The median survival post-

relapse is 5.5 months, and the estimated post-relapse 5-year survival rate is only 8%, even with second SCT as a salvage treatment option, which is unlikely to be the case in the UK (35,43). Approximately 1 in 5 subjects ([redacted]) had Ph+ disease, a similar percentage to that reported by Fielding *et al*., (2007) in a UK adult R/R ALL population (9).

Table 9 provides a summary of key baseline characteristics for the Phase 2 mITT and ITT datasets, the populations of which are comparable to the combined population. The median age of all treated patients was 40 years (range: 19-84) and 15% were aged 65 years or over. This average age is in line with published data for adult ALL, and given the poor outcomes in this group, emphasises the stark reduction in life expectancy for adults with R/R ALL (24).

Table 8: Baseline demographics and characteristics at baseline (Phase 1 + 2 combined)

Characteristics	Phase 1 + 2 combined (n=78)
Age category, n (%)	
< 65 years	[redacted]
≥ 65 years	[redacted]
Male, n (%)	[redacted]
ECOG performance status, n (%)	
0	[redacted]
1	[redacted]
Philadelphia chromosome t(9:22) mutation, n (%)	[redacted]
MLL translocation t(4:11) of Myc translocation t(8:14), n (%)	[redacted]
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	[redacted]
Low hypodiploidy (30–39 chromosomes), n (%)	[redacted]
Near triploidy (60–78 chromosomes), n (%)	[redacted]
Number of lines of prior therapy, n (%)	
1	[redacted]
2	[redacted]
≥3	[redacted]
Prior blinatumomab, n (%)	[redacted]
Blinatumomab as the last prior therapy, n, (%)	[redacted]
Prior inotuzumab ozogamicin, n (%)	[redacted]
Prior allogenic SCT, n (%)	[redacted]

Characteristics	Phase 1 + 2 combined (n=78)
Prior autologous SCT, n (%)	[redacted]
Prior radiotherapy, n (%)	[redacted]
Refractory, n (%)*	
Primary refractory	[redacted]
R/R after ≥ 2 lines of therapy	[redacted]
R/R post-allo-SCT	[redacted]
First relapse with remission ≤ 12 months	[redacted]
BM blasts at screening, median % (range)	[redacted]
BM blasts at baseline, median % (range)	[redacted]
BM blasts after bridging chemotherapy, median % (range)	[redacted]
BM blasts >25% at baseline, n (%)	[redacted]
Extramedullary disease at screening, n (%)	[redacted]
CNS disease at baseline, n (%)	
CNS-1	[redacted]
CNS-2	[redacted]

Key: CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; LVD, longest vertical dimension; MLL, mixed lineage leukaemia; NR, no response; PD, progressive disease; PR, partial remission; SCT, stem cell
transplant; SPD, sum of the products of diameters; STDEV, standard deviation.
Notes: Excludes information collected after retreatment. Baseline is defined as the last assessment prior to the start of conditioning chemotherapy. *a number of these categories are co-incident, hence the groups combined add up to >100%.
Source: Table 14.1.4.6, ZUMA-3 CSR (56). Combined results from Phase 2 mITT and Phase 1 target dose.

Table 9: Baseline demographics and characteristics at baseline (Phase 2)

Characteristics	mITT (n = 55)	ITT (n = 71)
Age, median (range), y	40 (19, 84)	44 (19, 84)
Age category, n (%)		
< 65 years	47 (85)	60 (85)
≥ 65 years	8 (15)	11 (15)
Male, n (%)	33 (60)	41 (58)
ECOG performance status, n (%)		
0	16 (29)	18 (25)
1	39 (71)	53 (75)
Philadelphia chromosome t(9:22) mutation, n (%)	15 (27)	19 (27)
MLL translocation t(4:11) of Myc translocation t(8:14), n (%)	2 (4)	4 (6)
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	14 (25)	17 (24)
Low hypodiploidy (30–39 chromosomes), n (%)	1 (2)	1 (1)
Near triploidy (60–78 chromosomes), n (%)	1 (2)	1 (1)

Characteristics	mITT (n = 55)	ITT (n = 71)
Number of lines of prior therapy, n (%)		
1	10 (18)	11 (15)
2	19 (35)	25 (35)
≥3	26 (47)	35 (49)
Prior blinatumomab, n (%)	25 (45)	33 (46)
Prior inotuzumab ozogamicin, n (%)	12 (22)	16 (23)
Prior allogenic SCT, n (%)	23 (42)	28 (39)
Prior autologous SCT, n (%)	2 (4)	3 (4)
Prior radiotherapy, n (%)	13 (24)	16 (23)
Refractory, n (%)		
Primary refractory	18 (33)	21 (30)
R/R after ≥ 2 lines of therapy	43 (78)	54 (76)
R/R post-allo-SCT	24 (44)	29 (41)
First relapse with remission ≤ 12 months	16 (29)	20 (28)
BM blasts at screening, median % (range)	65 (5.01–100)	70 (5–100)
BM blasts at baseline, median % (range)	60 (0–98)	66.5 (0–98)
BM blasts after bridging chemotherapy, median % (range)	59 (0–98)	62.5 (0–98)
BM blasts >25% at baseline, n (%)	40 (73)	54 (76)
Extramedullary disease at screening, n (%)	6 (11)	8 (11)
CNS disease at baseline, n (%)		
CNS-1	55 (100)	69 (97)
CNS-2	0 (0)	2 (3)

Key: ALL, acute lymphoblastic leukaemia; allo-SCT, allogenic stem cell transplantation; BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; mITT, modified intention to treat; MLL, mixed lineage leukaemia; NR, not reported; Ph+, Philadelphia chromosome-positive; R/R, relapse/refractory; SCT, stem cell transplant.
Note: Baseline is defined as the last assessment prior to the start of the lymphodepleting chemotherapy.
Source: (42).

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Analysis population

The Phase 2 mITT analysis set was considered to include all patients who received a dose of KTE-X19; this analysis set was used for the hypothesis testing of the primary endpoint and other efficacy analyses, as well as safety analyses.

The Phase 2 ITT dataset comprised all enrolled patients. The Phase 1 + 2 combined dataset consisted of all patients treated in Phase 1 and Phase 2 at the recommended Phase 2 dose of KTE-X19 (Table 7) (42).

During Phase 1, the SRT was chartered to review safety data and make recommendations on further study conduct and progression of the study from Phase 1 to Phase 2 based on the incidence of DLTs and serious adverse events (SAEs). The DLT-evaluable cohort included the first 3 patients treated at the 2 x 10^6 anti-CD19 CAR T cells/kg dose level (41).

B.2.4.2 Sample size

ZUMA-3 used a single-arm design to test for an improvement in overall complete remission (OCR) (defined as achieving CR/CRi) rate. A sample size of 50 subjects in Phase 2 was to provide approximately 93% power to distinguish between an active therapy with a 65% true OCR rate from a therapy with a response rate of ≤ 40%, with a 1-sided alpha level of 0.025.

The rationale for a prespecified 40% OCR historical control rate was informed by rates observed in published studies of second-line or later chemotherapy and SCT regimens and in pivotal studies of blinatumomab. The blinatumomab studies, which included subject populations similar to those who were to be enrolled in ZUMA-3, resulted in CR/complete response with incomplete haematologic recovery (CRh) rates of approximately 42%; the CR rates were 32.4% in the Phase 2 trial (Study MT103-211) and 33.6% in the Phase 3 TOWER study (25,61).

A step-down test of the secondary endpoint of MRD^- rate was to be performed against an MRD^- rate of 30% only if the testing of the OCR rate reached statistical significance, so that the family-wise type I error would be controlled at a 1-sided 2.5% level under the hierarchical testing scheme (42).

B.2.4.3 Statistical analysis

A summary of the statistical analyses for ZUMA-3 is available in Table 10.

Table 10: Summary of statistical analyses: ZUMA-3

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ZUMA-3 (Ph 2)	The primary hypothesis tested in this study was that the OCR rate with KTE-X19 is significantly greater than the historical control rate of 40%	An exact binomial test was used to compare the observed rate of CR/CRi to the historical control rate. Two-sided 95% Cis were calculated using the Clopper-Pearson method	A sample size of 50 subjects was to provide approximately 93% power to distinguish between an active therapy with a 65% true CR/CRi rate from a therapy with response rate ≤ 40% with a 1-sided α-level of 0.025	The method for handling missing data varies by endpoint. Time-to-event endpoints for subjects who had not met criteria for the event at the data cut-off were censored at the last evaluable disease assessment date. Patients who had a new anticancer therapy (including SCT) while in response were censored at the last evaluable disease assessment date prior to the initiation of the new therapy

Key: CR/CRi, complete response/complete response with incomplete haematological recovery; SCT, stem cell transplant.
Source: (56).

Primary efficacy endpoint

Per protocol, the primary efficacy analysis was carried out when all KTE-X19-treated patients had completed at least the 6-month disease assessment. An exact binomial test was used to compare the observed rate of CR/CRi to the historical control rate. Two sided 95% CIs were calculated using the Clopper-Pearson method. This test assumed the independence of the individual subject responses. CIs were provided about the CR/CRi rate, as well as the CR rate and CRi rate separately (42).

Secondary efficacy endpoints

Hypothesis testing of the secondary endpoint of MRD^- rate was to be performed against an MRD^- rate of 30% if the testing of the OCR rate was significant. The control rate was selected based on the MRD^- rates of approximately 30% that were observed among all subjects treated with blinatumomab in the pivotal studies (25,62)

- **MRD$^-$ remission**: rate and 95% CIs estimated for treated subjects, subjects with a CR, subjects with a CRi, and subjects with either a CR or CRi combined

- **Duration of remission (DOR)**: the primary analysis of DOR used the Kaplan-Meier (KM) method, considering all relapses and deaths as events for DOR. The reverse Kaplan-Meier approach was to be used to estimate the follow-up time for DOR (63)

- **Allo-SCT rate**: subject incidence rate of on-study allo-SCT was to be summarised overall, and by subjects achieving CR, CRi, or CR/CRi

- **Relapse-free survival**: KM plots, estimate of the median RFS, and 2-sided 95% CIs were generated

- **Overall survival**: KM plots, estimates of median OS, and 2-sided 95% CIs were generated.

Subgroup analyses

The CR/CRi rate with 95% CIs was generated for subgroups of the mITT analysis set defined by the selected covariates listed in Table 6.

Safety analyses

Safety analyses were conducted on the safety analysis set. The primary analysis of safety data summarised all AEs and laboratory values with an onset on or after KTE-X19 infusion.

B.2.4.4 Participant flow

Details of participant flow in Phase 1 and Phase 2 of ZUMA-3 in the form of a CONSORT diagram are provided in Appendix D1.2.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of ZUMA-3 was conducted using the Downs and Black checklist, full details of which are provided in Appendix D1.3.

Within the context of a single-arm study design, the overall risk of bias is considered to be low. The primary endpoint of OCR was determined independently by central assessment and provides an objective assessment of treatment effect that is directly relevant to clinical practice, where response to treatment is the primary measure of effect.

The single-arm nature of ZUMA-3 does however necessitate a need for an indirect treatment comparison (ITC) to provide relative effect estimates required for decision making. Use of ITCs is associated with higher uncertainty compared to a controlled trial, with this discussed in more detail in section B.2.9. In terms of intervention, all patients in the combined Phase 1 + 2 dataset (N = 78) treated with KTE-X19 reflect the administration and dosing of KTE-X19 expected in clinical practice, and that of the anticipated marketing authorisation.

With regard to generalisability to clinical practice in England, ZUMA-3 included subjects who had received a number of prior therapies considered as standard of care (SoC) in the R/R adult ALL treatment pathway. These include [redacted] of subjects receiving prior blinatumomab, and [redacted] receiving prior inotuzumab. In addition, the percentage of Ph+ patients were comparable between ZUMA-3 ([redacted]) and UK R/R clinical practice (22%) (section B.2.13).

B.2.6 Clinical effectiveness results of the relevant trials

Summary of clinical effectiveness results

- The efficacy and safety of KTE-X19 in the treatment of adults with R/R ALL has been demonstrated in the open-label, multi-centre, ZUMA-3 trial.
- Patients with R/R disease were defined as primary refractory, in first relapse following a remission lasting ≤ 12 months, R/R after second-line or higher therapy, or R/R after allo-SCT.
- At the most recent data cut-off (23/07/21), with median follow-up of [redacted] months, KTE-X19 demonstrated an unprecedented median OS of [redacted] months in the Phase 1 + 2 combined dataset.
- KM estimates of OS at 6 and 12 months were [redacted] and [redacted], respectively, with [redacted] estimated to be alive at 24 months
- The OCR rate per investigator assessment was 74.4%, with 58 of 78 subjects treated with KTE-X19 at target dose achieving OCR. The CR rate was 62.8% (50 of 78 subjects).
- 79.5% (62 of 78 subjects) treated with KTE-X19 achieved MRD negativity, including all but one patient – for whom data was not available - to achieve CR/CRi.
- KTE-X19 induced durable remission in patients achieving OCR, with a median duration of remission of [redacted] months.
- A sensitivity analysis of median OS stratified by censoring at allo-SCT demonstrate that survival appeared to be independent of subsequent SCT

Table 11: Summary of clinical effectiveness: ZUMA-3

			Primary efficacy endpoint	Secondary efficacy endpoints				Submission location	Relevant publication
Phase	**Analysis set**	**n**	**OCR**	**MRD**	**KM median DOR**	**KM median OS**	**KM median RFS**		
1*	Target dose	23	82.6% (19 of 23 subjects)	87.0% (20 of 23 subjects)	17.6 months	22.4 months	[redacted]	Appendix L	Shah *et al*., (2021) (41)
2*	mITT	55	70.9% (39 of 55 subjects)	76.0% (42 of 55 patients)	12.8 months	18.2 months	11.6 months	Section B.2.6	Shah *et al*., (2021) (42)
1+2**	Combined	78	74.4% (58 of 78 subjects)	79.5% (62 of 78 subjects)	[redacted]	[redacted]	[redacted]	Section B.2.6	Shah *et al*., (2021) (appendix) (42) Data on file (64)

Key: DOR, duration of remission, ITT, intent-to-treat; mITT, modified intent-to-treat, MRD, minimal residual disease, OCR, overall complete remission; RFS, relapse-free survival.
Notes: ITT includes all patients enrolled to the relevant phase of the study. mITT refers to subjects who received treatment with KTE-X19, or with regard to the Phase 1 portion the subjects who received KTE-X19 at the target dose of 1 x 10^6 CAR T-cells/kg. *, based on data cutoff 09/09/20. **, based on data cutoff 23/07/21.

KTE-X19 cohorts and analysis sets are summarised in Table 7, including the location within the submission that data is presented.

The primary analysis was planned when the overall study enrolment was complete and the last treated patient in the mITT population had had the opportunity to complete the Month 6 disease assessment. This occurred on 9th September 2020, with a median actual follow-up from KTE-X19 infusion of [redacted] months in Phase 1 and [redacted] months in Phase 2 (56).

Preliminary results from the most recent interim analysis with data cutoff 23/07/21 provide longer-term data on the durability of all patients treated with KTE-X19 at target dose. Whilst more detail will be made available through the evaluation process, key results are provided.

B.2.6.1 ZUMA-3: (Phase 1 + 2 combined)

B.2.6.1.1 Data cut off 23/07/21:

Initial data from the 23/07/21 data cutoff is presented to provide evidence on the long-term efficacy of KTE-X19 where available. Median actual follow-up for all treated subjects in Phase 1 + 2 at this data cutoff was [redacted] months (95% CI: [redacted]). Further data (including a CSR) will become available during technical engagement.

Overall survival:

Data from the most recent data cutoff of ZUMA-3 demonstrates the durable effect of KTE-X19 on OS (Figure 11). At a median actual follow-up of [redacted] months (95% CI: [redacted]) in all treated subjects, the KM median OS was [redacted] months (95% CI: [redacted]) (Figure 11). Notably, in a sensitivity analysis of median OS stratified by censoring at allo-SCT, survival in responders appeared to be independent of subsequent SCT at the most recent data analysis (Figure 12). KM estimates of OS at 6 months and 12 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively (Table 12).

Table 12: Overall survival (Phase 1 + 2 combined, data cut 23/07/21)

Overall survival	Phase 1 + 2 combined (N = 78)
Number of subjects, n	78
Death, n (%)	[redacted]
Censored, n (%)	[redacted]
Death after DCO, n (%)	[redacted]
Alive on or after DCO, n (%)	[redacted]
Full withdrawal of consent, n (%)	[redacted]
Lost to follow-up, n (%)	[redacted]
KM median (95% CI) OS (months)	[redacted]
Min, Max OS (months)	[redacted]
Survival free rates (%) (95% CI) by KM estimation at	
3 months	[redacted]
6 months	[redacted]
9 months	[redacted]
12 months	[redacted]
15 months	[redacted]
18 months	[redacted]
24 months	[redacted]
30 months	[redacted]
36 months	[redacted]

42 months	[redacted]
48 months	[redacted]
54 months	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 23/07/2021.
Key: CI, confidence interval; DCO, data cutoff date; KM, Kaplan-Meier; NE, not estimable; OS, overall survival.
Notes: Overall survival for subjects treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. '+' indicates censoring.
Source: (64).

Figure 11: Kaplan-Meier plot of OS (Phase 1 + 2 combined: data cut 23/07/21)

Key: CI, confidence interval; NE, not estimable.
Source: (64).

Figure 12: Kaplan-Meier plot of OS for OCR subjects using investigator review by subsequent allogeneic SCT group (Combined Phase 1 + 2: data cut 23/07/21)

Data cutoff date = 23/07/21.
Key: CI, confidence interval; NE, not evaluable; NR, not reached; OCR, overall complete remission; SCT, stem cell transplant.
Source: (64).

Duration of remission

At the most recent data cutoff (23/07/21), among the 58 subjects who achieved a CR or CRi, the KM median duration of remission (DOR) was [redacted] months (95% CI: [redacted]), with a reverse KM median follow-up time for DOR of [redacted] months (95% CI: [redacted]). Overall, [redacted] subjects were censored: [redacted] subjects were in ongoing remission as of the data cut off date, 14 subjects had an allo-SCT, [redacted] subjects started new anticancer therapy, and [redacted] subject was lost to follow-up. [redacted] subjects relapsed, and [redacted] died. The KM estimates of the proportion of responders who remained in remission at 6 and 12 months from first response were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively (Figure 13) (Table 13).

Figure 13: Kaplan-Meier plot of DOR (Phase 1 + 2 combined: data cut 23/07/21)

Data cutoff date: 23/07/21
Key: CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete haematologic recovery; NE, note evaluable.
Source: (64).

Table 13: DOR using investigator review (Phase 1 + 2 combined: data cut 23/07/21)

Duration of Response (DOR)	Phase 1 + 2 combined (N = 78)
Number of subjects with OCR, n	58
Events, n (%)	
Censored, n (%)	
KM median (95% CI) DOR (months)	
Min, Max DOR (months)	
Events	
Relapse, n (%)	
Death, n (%)	
Censoring reason	
Ongoing remission, n (%)	
Allogeneic SCT, n (%)	
Started new anti-cancer therapy, n (%)	
Lost to follow-up, n (%)	
Withdrawal of consent, n (%)	
Event-free rates % (95% CI) by KM estimation at	
3 months	
6 months	
9 months	
12 months	

15 months	[redacted]
18 months	[redacted]
24 months	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 23/07/21.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of response; KM, Kaplan-Meier; mITT, modified intent-to-treat; NE, not estimable; OCR, overall complete remission; SCT, stem cell transplant.
Notes: Investigator review is presented in this table. Percentages are based on number of all dosed subjects in Phase 1 two 1e6 cohorts and Phase 2 with overall complete remission (CR + CRi). DOR is defined as the time from the first complete remission (CR or CRi) to relapse or death from any cause in the absence of documented relapse. '+' indicates censoring.
Source: (64).

Relapse-free survival:

KM estimates of relapse-free survival (RFS) rates at 6 and 12 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The KM median RFS was [redacted] months (95% CI: [redacted]), with a reverse KM median follow-up time for RFS of [redacted] months (95% CI: [redacted]) (Figure 14).

It is important to note that the rate of censoring is high due primarily to patients either being in remission at time of data cut-off or receiving a SCT.

Figure 14: Kaplan-Meier plot of RFS (Phase 1 + 2 combined; data cut 23/07/21)

Data cutoff date: 23/07/21.
Key: CI, confidence interval; NE, not estimable.
Source: (64).

Table 14: RFS using investigator review (Phase 1 + 2 combined; data cut 23/07/21)

RFS	Phase 1 + 2 combined (N = 78)
Number of subjects, n	78
Events, n (%)	[redacted]
Censored, n (%)	[redacted]
KM median (95% CI) RFS (months)	[redacted]
Min, Max RFS (months)	[redacted]
Events	
Relapse, n (%)	[redacted]
Death, n (%)	[redacted]
Subject's best overall response not CR or CRi, n (%)	[redacted]
Censoring reason	
Ongoing remission, n (%)	[redacted]
Allogeneic SCT, n (%)	[redacted]
Started new anti-cancer therapy, n (%)	[redacted]
Lost to follow-up, n (%)	[redacted]
Withdrawal of consent, n (%)	[redacted]
Event-free rates % (95% CI) by KM estimation at	
3 months	[redacted]
6 months	[redacted]
9 months	[redacted]
12 months	[redacted]
15 months	[redacted]
18 months	[redacted]
24 months	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 23/07/21.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; RFS, relapse-free survival; SCT, stem cell transplant.
Notes: Percentages are based on the number of subjects in safety analysis set.
Relapse-free survival for subjects who received KTE-X19 is defined as the time from the KTE-X19 infusion date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response are counted as events on KTE-X19 infusion date.
Source: (64).

B.2.6.1.2 Data cut off 09/09/20:

Key efficacy endpoint data for the Phase 1 + Phase 2 combined dataset is presented in Table 15, with results then described in greater detail.

Table 15: Summary of efficacy endpoints (Phase 1 + 2 combined)

	Phase 1 + 2 combined (N = 78)
Number of OCR (CR + CRi) N (%)	58 (74.4)
CR	49 (62.8)
CRi	9 (11.5)
CRh	0 (0)
BFBM	4 (5.1)
Unknown or not evaluable	3 (3.8)
Median DOR (95% CI), months	13.4 (9.4, NE)
Median RFS (95% CI), months	10.3 (5.6, 14.4)
Median OS (95% CI), months	22.4 (15.9, NE)

Data cutoff date = 09/09/2020.
Key: BFBM, blast-free hypoplastic or aplastic bone marrow; CI, confidence interval; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; DOR, duration of remission; OCR, overall complete remission; OS, overall survival; RFS, relapse-free survival.
Source: Table S12 (42).

OCR rate by investigator assessment:

Among the 78 subjects who were treated with the target dose across Phase 1 + 2, the OCR rate per investigator assessment was 74.4% (58 of 78 subjects; 95% CI: [redacted]), with a CR rate of 62.8% (49 of 78 subjects, 95% CI: [redacted]) (56).

DOR by investigator assessment:

Among the 58 subjects who achieved a CR or CRi, the KM median DOR was 13.4 months (95% CI: [redacted]), with a reverse KM median follow-up time for DOR of [redacted] months (95% CI: [redacted]). Overall, [redacted] subjects were censored: 19 subjects were in ongoing remission as of data cutoff ([redacted] of those patients with CR/CRi), 13 had an allo-SCT, [redacted] started a new anti-cancer therapy, and [redacted] was lost to follow-up. [redacted] subjects relapsed, and [redacted] died. The KM estimates of the proportion of responders who remained in remission at 6 and 12 months from first response were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively (56).

The KM median DOR was [redacted] months (95% CI: [redacted]) for subjects with CR, and [redacted] months (95% CI: [redacted]) for subjects with CRi (56).

Figure 15: Kaplan-Meier plot of DOR per investigator assessment (Phase 1 + 2 combined)

Data cutoff date = 09/09/2020.
Key: CI, confidence interval; CR, complete remission; Cri, complete remission with incomplete haematological recovery; NE, not estimable.
Source: ZUMA-3 clinical study report Figure 14.2.8.7 (56).

OS:

KM estimates of OS at 12 and 18 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The KM median OS was 22.4 months (95% CI: 15.9 months, NE), with a reverse KM median follow-up time for OS at [redacted] months (95% CI: [redacted]) (Table 16).

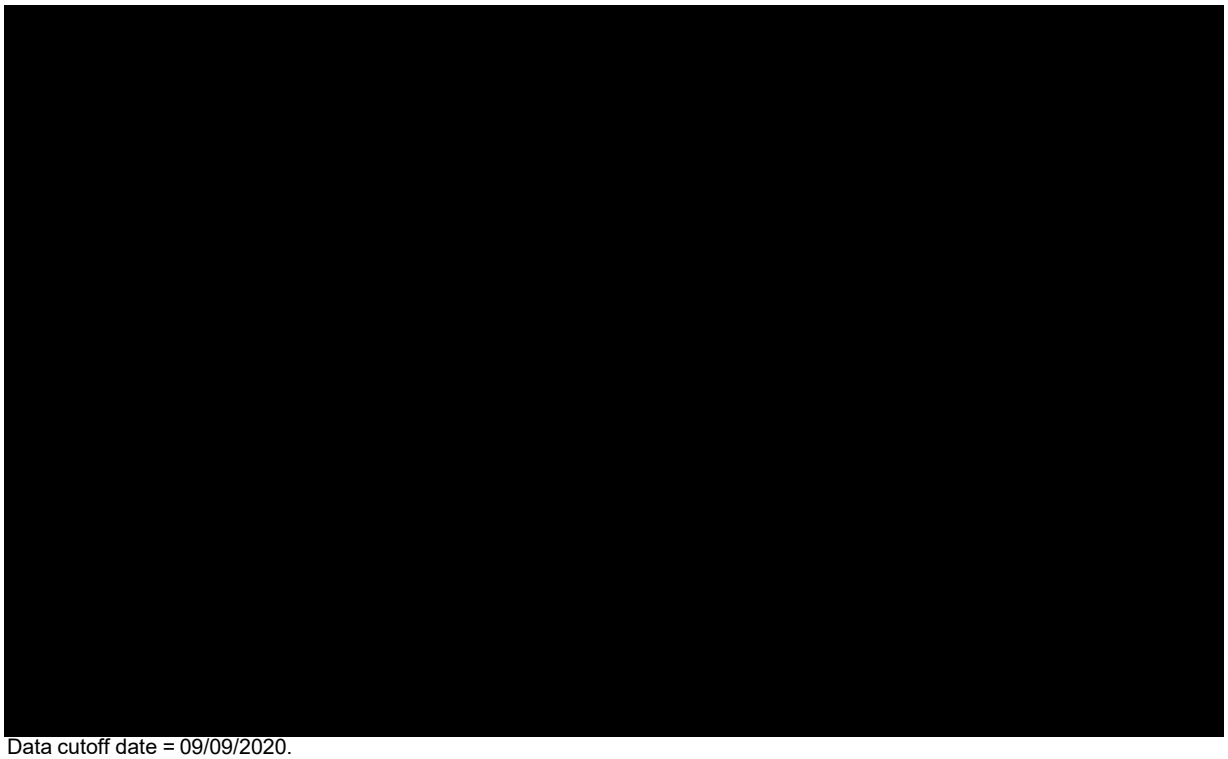
Table 16: Overall survival (Phase 1 + 2 combined)

Overall survival	Phase 1 + 2 combined (N = 78)
Number of subjects, n	78
Events (death), n (%)	[redacted]
Censored, n (%)	[redacted]
Alive on or after data cut-off	[redacted]
Withdrawal of consent	[redacted]
Lost to follow-up	[redacted]
KM median OS, months (95% CI)	22.4 (15.9, NE)
Min, Max OS (months)	[redacted]

Survival free rates (%) (95% CI) by KM estimation at	
3 months	[redacted]
6 months	[redacted]
9 months	[redacted]
12 months	[redacted]
15 months	[redacted]
18 months	[redacted]
24 months	[redacted]
Reverse KM median follow-up time for OS, months (95% CI)	[redacted]

Data cutoff date = 09/09/2020.
Key: CI, confidence interval; DCO, data cutoff date; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; OS, overall survival.
Notes: 1e6 = 1 x 10^6 anti-CD19 CAR T cells/kg. OS for subjects treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date, with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date. '+' indicates censoring.
Source: ZUMA-3 clinical study report Table 14.2.7.5 (56).

Figure 16: Kaplan-Meier plot of OS (Phase 1 + 2 combined)



Data cutoff date = 09/09/2020.
Key: CI, confidence interval; NE, not estimable; OS, overall survival.
Source: ZUMA-3 clinical study report Figure 15 (56).

MRD:

79.5% (62 of 78 subjects) treated with KTE-X19 achieved MRD negativity, including all but one patient – for whom data was not available - to achieve CR/CRi.

RFS by investigator assessment:

KM estimates of RFS rates at 6 and 12 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The KM median RFS was 10.3 months (95% CI: 5.6, 14.4 months), with a reverse KM median follow-up time for RFS of [redacted] months (95% CI: [redacted]) (56).

It is important to note that the rate of censoring is high due primarily to patients either being in remission at time of data cut-off or receiving a SCT.

Table 17: RFS per investigator assessment (Phase 1 + 2 combined)

RFS	Phase 1 + 2 combined (n=78)
Number of subjects, n	78
Events, n (%)	[redacted]
Censored, n (%)	[redacted]
KM median (95% CI) RFS (months)	10.3 (5.6, 14.4)
Min, Max RFS (months)	[redacted]
Events	
Relapse, n (%)	[redacted]
Death, n (%)	[redacted]
Subject's best overall response not CR or CRi, n (%)	[redacted]
Censoring reason	
Ongoing remission, n (%)	[redacted]
Allogeneic SCT, n (%)	[redacted]
Started new anti-cancer therapy, n (%)	[redacted]
Lost to follow up, n (%)	[redacted]
Withdrawal of consent, n (%)	[redacted]
Event-free rates % (95% CI) by KM estimation at	
3 months	[redacted]
6 months	[redacted]
9 months	[redacted]
12 months	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 09/09/2020.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery;KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; RFS, relapse-free survival; SCT, stem cell transplant.
Notes: 1e6 = Percentages are based on the number of subjects in safety analysis set. RFS for subjects who received KTE-X19 is defined as the time from the KTE-X19 infusion date to the date of relapse or death from anycause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response are counted as events on theKTE-X19 infusion date. '+' indicates censoring.
Source: Table 32 (56)

Figure 17: Kaplan-Meier plot of RFS per investigator assessment (Phase 1 + 2 combined)

Data cutoff date = 09/09/2020.
Source: ZUMA-3 clinical study report Figure 16 (56).

Rate of allo-SCT

In total, 17.9% (14 of 78 subjects) of the Phase 1 + 2 combined dataset went on to receive an allo-SCT during ZUMA-3 at the investigators discretion. This included 18.1% (10 of 55 subjects) treated with KTE-X19 at Phase 2, and 17.4% (4 of 23 subjects) treated with KTE-X19 at target dose at Phase 1.

Of those to receive a subsequent allo-SCT; 9 subjects had achieved CR, and 3 subjects had achieved a CRi with KTE-X19 treatment. One subject treated at Phase 2 had inconsistent assessment between investigator and central assessment (CRi by investigator assessment vs. blast-free hypoplastic/aplastic bone marrow by central assessment) (56). A further subject treated at Phase 1 (who had extramedullary disease at baseline) had achieved a best overall response of PR to KTE-X19 treatment based on the investigator assessment of disease response.

B.2.6.2 ZUMA-3 Phase 2 mITT

Primary efficacy endpoint: OCR

The primary efficacy endpoint was met, with an OCR rate of 70.9% (39 of 55 subjects) in the phase 2 mITT population; significantly greater than the prespecified historical control rate of 40% (p < 0.0001) (95% CI: 57%, 82%). Among the 70.9% who achieved a CR or CRi, the median time to response was 1.1 months (range: [redacted] months). A summary of OCR and best overall response per central assessment for the mITT population is provided in Table 18.

Table 18: Summary of overall complete response rates (Phase 2, mITT)

Response category, n (%)	Phase 2 (N = 55)
OCR (CR + CRi)	39 (70.9)
95% CI	57,82
P-value of exact test for OCR rate ≤ 40%	< 0.0001
CR	31 (56.4)
95% CI	42,70
CRi	8 (14.5)
95% CI	6, 27
CRh	0 (0)
BFBM	4 (7.3)
PR	0 (0)
NR	9 (16.4)
Unknown or not evaluable	3 (5.5)

Key: BFBM, blast-free hypoplastic or aplastic bone marrow; CI, confidence interval; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; mITT, modified intent-to-treat; NR, no response; OCR, overall complete remission; PR, partial remission.
Notes: 95% confidence interval is based on Clopper-Pearson method. Data cutoff date = 09/09/20.
Source: ZUMA-3 clinical study report Table 14.2.1.1 and Table 14.2.2.1 (56). Shah et al (2021) (42).

Secondary efficacy endpoints

Minimal residual disease:

A summary of MRD negative status as determined by the central laboratory for the mITT population is provided in Table 19.

The overall MRD negative rate for patients treated in Phase 2 (mITT) was 76% (42 of 55 patients; 95% CI: [redacted]), significantly higher than the prespecified control rate of 30%, therefore the secondary efficacy endpoint was met (p < 0.0001). MRD^- rate increased to 97% in patents achieving CR or CRi (38 of 39 patients; 95% CI: [redacted]), with 1 subject who achieved CR not having samples available for MRD

assessment (42). In total, 30 subjects with CR, 8 subjects with CRi, and 4 subjects with blast-free hypoplastic or aplastic bone marrow (BFBM), hence the higher MRD negative rate compared to OCR rate.

The survival advantage of achieving MRD negativity in both adults and children has been demonstrated by Berry *et al*., (2017) in a meta-analysis of 39 studies (albeit following induction therapy), and was further re-enforced by recent long-term blinatumomab data (65,66). This supports the clinical value of every evaluable subject to achieve CR/CRi achieving MRD$^-$ remission in the ZUMA-3 mITT population.

Of the 13 subjects who were not considered MRD$^-$ overall, 9 subjects were nonresponders, 3 subjects were not evaluable for disease response, and as mentioned above 1 subject with a CR did not have MRD assessments performed (56).

Table 19: Summary of MRD status (Phase 2, mITT)

	Phase 2 (N = 55)
MRD negativity status [a], n (%)	
MRD negative at Day 28, n (%)	[redacted]
MRD negative at Week 8, n (%)	[redacted]
MRD negative at Month 3, n (%)	[redacted]
MRD negative rate overall [a], n (%)	42 (76)[b]
95% CI	[redacted]
p-value of exact test for MRD negativity rate ≤ 30%	< 0.0001
MRD negative rate among OCR (CR or CRi) patients c, n (%)	38 (97)
95% CI	[redacted]
p-value of exact test for MRD negativity rate ≤ 30%	< 0.0001
MRD negative rate among CR patients [d], n (%)	30 (97)
95% CI	[redacted]
MRD negative rate among CRi patients [d], n (%)	8 (100)
95% CI	[redacted]
MRD negative rate among CRh patients [d], n (%)	0 (0)
MRD negative rate among BFBM patients [d], n (%)	4 (100)
95% CI	[redacted]

Key: BFBM, blast-free hypoplastic or aplastic bone marrow; CI, confidence interval; CR, complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete haematological recovery; mITT, modified intent to treat; MRD, minimal residual disease; OCR, overall complete remission.
Notes: MRD status is determined by the central laboratory. 95% confidence interval is based on Clopper-Pearson method. [a], The numerator for MRD negative rate overall is based on an MRD-negative finding at any post infusion visit. Percentage for MRD negative rate overall is based on the number of patients in the mITT population; [b], 30 patients with CR, eight patients with CRi, and four patients with BFBM achieved MRD negativity at any post infusion visit; [c], The numerator for MRD negative rate is based on an MRD-negative finding at any post infusion visit. Percentage is based on the number of patients with OCR (CR or CRi). Disease response is based on central assessment; [d], The numerator for MRD negative rate is based on an MRD-negative finding at any post infusion visit. Percentage is based on the number of patients with the corresponding best overall response. Disease response is based on central assessment.
Source: ZUMA-3 clinical study report Table 14.2.8.1 (56).

DOR by central assessment:

Among the 39 subjects who achieved OCR (CR or CRi), the median time to response was 1.1 months (range: [redacted]).

The KM median DOR for all patients treated in Phase 2 was 12.8 months (95% CI: 8.7, NE), with a reverse KM median follow-up time for DOR of [redacted] months (95% CI: [redacted]). Overall, 26 patients were censored including 12 patients in ongoing remission at data cut-off and nine patients who had subsequent allo-SCT. Only one patient who achieved remission with KTE-X19 had subsequently died at the time of data cut-off. The longest DOR to date is [redacted] months (censored at data cut-off). The proportion of patients still in remission with KTE-X19 at 6 and 12 months from first remission was 76% and 56%, respectively (42,56).

At data cut-off, 31% (12 of 39) with CR/CRi were in ongoing remission, 23% (9 of 39) had proceeded to subsequent allo-SCT, 13% (5 of 39) proceeded to other anticancer therapies, 31% (12 of 39) had relapsed, and 3% (1 of 39) had died (Table 20).

A sensitivity analysis was conducted in which disease assessments obtained after allo-SCT were included in the derivation of DOR. Notably, in this analysis the median DOR was also 12.8 months (95% CI: 9.4 months, NE), consistent with the main analysis, with a reverse KM median follow-up time for DOR of [redacted] months (95% CI: [redacted]), suggesting that KTE-X19 has the potential to be used as a standalone therapy (42,56).

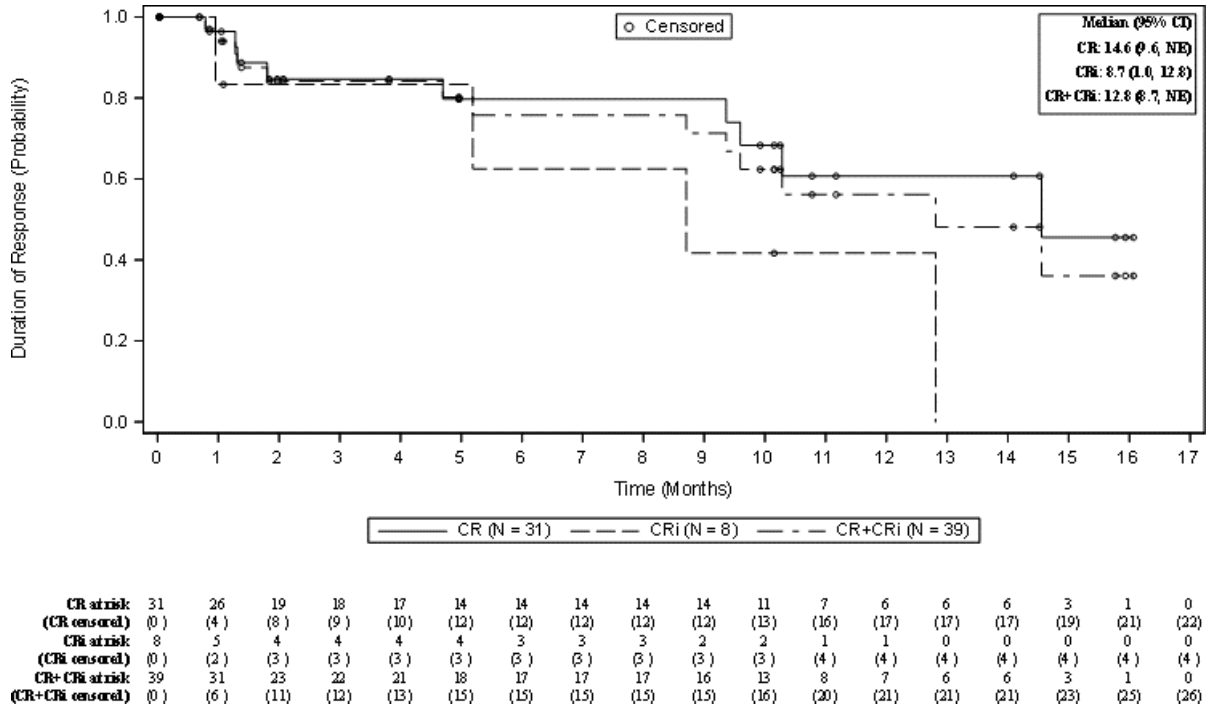
Table 20: Duration of remission per central assessment (Phase 2, mITT)

	Phase 2 (N = 55)
Number of patients with OCR, n	39
Events, n (%)	13 (33)
Censored, n (%)	26 (67)
KM median DOR, months (95% CI)	12.8 (8.7, NE)
Min, max DOR (months)	[redacted]
Events	
Relapse, n (%)	12 (31)
Death, n (%)	1 (3)
Censoring reason	
Ongoing remission, n (%)	12 (31)
Allogeneic SCT, n (%)	9 (23)
Started new anti-cancer therapy, n (%)	5 (13)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
KM estimates of DOR rates, % (95% CI)[a]	
3 months	84.2 [redacted]
6 months	75.7 [redacted]
9 months	71.3 [redacted]
12 months	56.1 [redacted]
Reverse KM median follow-up time for DOR, months (95% CI)	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DOR, duration of remission; KM, Kaplan–Meier; mITT, modified intent-to-treat; NE, not estimable; OCR, overall complete remission; SCT, stem cell transplant.
Notes: Percentages are based on the number of patients in the mITT population with OCR (CR or CRi). DOR is defined as the time from the first complete remission (CR or CRi) to relapse or death from any cause in the absence of documented relapse. Patients not meeting the criteria by the analysis data cut-off date were censored at their last evaluable disease assessment date prior to the data cut-off date, new anticancer therapy (excluding resumption of a TKI) start date, or SCT date, whichever was earlier. [a], KM estimates represent the proportion of responders remaining in remission by time from first response.
Source: ZUMA-3 clinical study report Table 14.2.5.1.1 (56).

The KM median DOR was 14.6 months (95% CI: 9.6, NE) for patients with CR and 8.7 months (95% CI 1.0, 12.8) for patients with CRi (Figure 18).

Figure 18: Kaplan-Meier plot of DOR per central assessment (Phase 2, mITT)



Data cutoff date: 09/09/2020.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DOR, duration of remission; KM, Kaplan–Meier; mITT, modified intent to treat; NE, not estimable; NR, not reached.
Source: Adapted from Figure 3a (42).

Overall survival

At the time of data cut-off, 32 patients (58%) in the mITT population were alive; the proportion of patients estimated to be alive at 12 and 18 months was 71% and 59%, respectively (42,56).The KM median OS was 18.2 months (95% CI: 15.9, NE), with a reverse KM median follow-up time for OS of [redacted] months (95% CI: [redacted]) (Table 21).

Table 21: Overall survival (Phase 2, mITT)

	Phase 2 (N = 55)
Events (death), n (%)	20 (36.4)
Censored, n (%)	35 (63.6)
Alive on or after DCO, n (%)	32 (58.2)
Full withdrawal of consent, n (%)	3 (5.5)
KM median OS, months (95% CI)	18.2 (15.9, NE)
Min, Max OS (months)	[redacted]
KM estimates of OS rates, % (95% CI)	

3 months	83.3 [redacted]
6 months	81.4 [redacted]
9 months	73.4 [redacted]
12 months	71.4 [redacted]
15 months	65.9 [redacted]
18 months	58.6 [redacted]
Reverse KM median follow-up time for OS, months (95% CI)	[redacted]
KM estimates of OS rates in patients with OCR, % (95% CI)	
12 months	86.8 [redacted]
18 months	70.3 [redacted]
KM estimates of OS rates in patients with CR, % (95% CI)	
12 months	96.8 [redacted]
18 months	85.4 [redacted]
KM estimates of OS rates in patients with CRi, % (95% CI)	
12 months	[redacted]
18 months	[redacted]
KM estimates of OS rates in MRD negative patients, % (95% CI)	
12 months	[redacted]
18 months	[redacted]
KM estimates of OS rates in MRD positive patients, % (95% CI)	
12 months	[redacted]
18 months	[redacted]

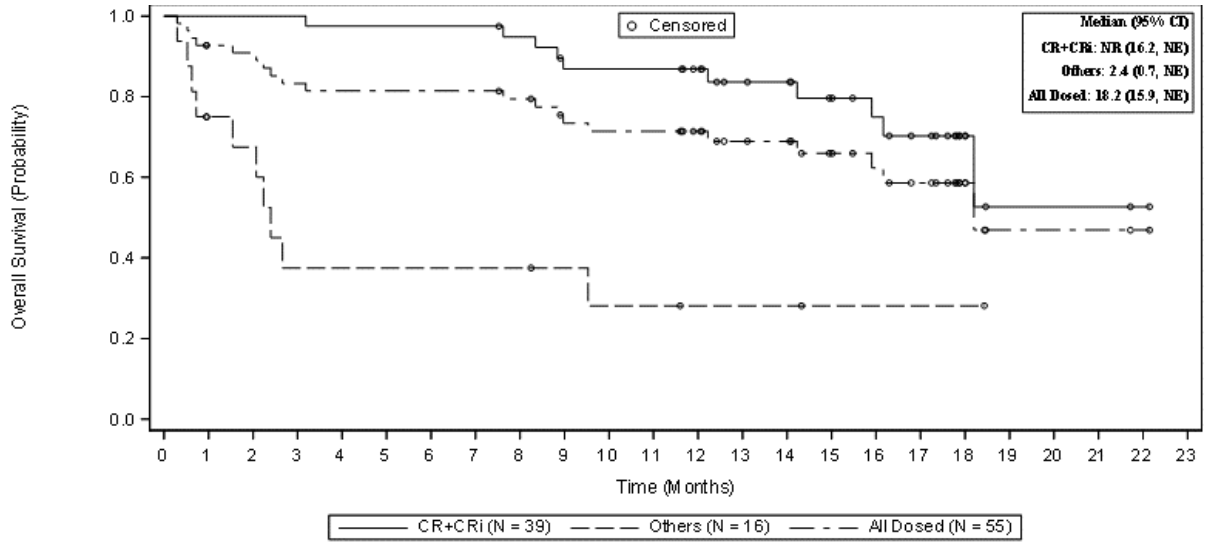
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DCO, data cut-off date; KM, Kaplan–Meier; mITT, modified intent-to-treat; MRD, minimal residual disease; NE, not estimable; OS, overall survival.
Notes: Overall survival for patients treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. Patients who had not died by the analysis data cut-off date were censored at their last contact date prior to the data cut-off date, with the exception that patients known to be alive or determined to have died after the data cut-off date were censored at the data cut-off date. '+' indicates censoring.
Source: ZUMA-3 clinical study report Table 14.2.7.1 (56).

As detailed in Table 21, KM estimates of OS at 12 and 18 months were 71.4% (95% CI: [redacted]) and 58.6% (95% CI: [redacted]), respectively (Figure 19). The KM median OS was not reached (95% CI: [redacted]) for subjects with CR or CRi and was 2.4 months (95% CI: [redacted]) for all other subjects in the mITT analysis set (Figure 20). The KM median OS was not reached (95% CI: [redacted]) for subjects with CR and was [redacted] months (95% CI: [redacted]) for subjects with CRi. Almost all patients who achieved CR with KTE-X19 were estimated to be alive at 12 months ([redacted]). At the time of primary data cut-off,

providing a median actual follow-up of [redacted] months, [redacted] OCR patients ([redacted]) including [redacted] CR patients ([redacted]) were known to be alive (56).

The KM median OS was [redacted] (95% CI: [redacted]) for subjects who were MRD- and was [redacted] (95% CI: [redacted]) for subjects who were MRD+ and [redacted] (95% CI: [redacted]) for subjects with missing MRD assessments (Figure 21). The proportion of patients who achieved MRD- estimated to be alive at 12 and 18 months was [redacted] and [redacted] respectively (56).

Figure 19: Kaplan-Meier plot of overall survival (Phase 2, mITT Analysis Set)



CR+CRi at risk:	39	39	39	39	38	38	38	38	36	32	32	32	29	24	23	19	16	13	6	2	2	2	1	0
(CR+CRi censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(2)	(2)	(2)	(5)	(9)	(10)	(13)	(15)	(17)	(24)	(27)	(27)	(27)	(28)	(29)
Others at risk:	16	10	9	5	5	5	5	5	5	4	3	3	2	2	2	1	1	1	1	0	0	0	0	0
(Others censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(3)	(3)	(4)	(4)	(4)	(5)	(5)	(5)	(5)	(6)	(6)	(6)	(6)	(6)
All Dosed at risk:	55	49	48	44	43	43	43	43	41	36	35	35	31	26	25	20	17	14	7	2	2	2	1	0
(All Dosed censored)	(0)	(2)	(2)	(2)	(2)	(2)	(2)	(2)	(3)	(5)	(5)	(5)	(9)	(13)	(14)	(18)	(20)	(22)	(29)	(33)	(33)	(33)	(34)	(35)

Data cutoff date: 09/09/2020.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; KM, Kaplan–Meier; mITT, modified intent to treat; NE, not evaluable; NR, not reached; OS, overall survival.
Source: Adapted from Figure 3d (42)

Figure 20: Kaplan-Meier plot of overall survival: CR versus CRi (Phase 2, mITT: patients with a CR or CRi)

Data cutoff date: 09/09/2020.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; KM, Kaplan–Meier; mITT, modified intent to treat; NE, not evaluable; NR, not reached; OS, overall survival.
Source: ZUMA-3 clinical study report Figure 14.2.10.1.1 (56).

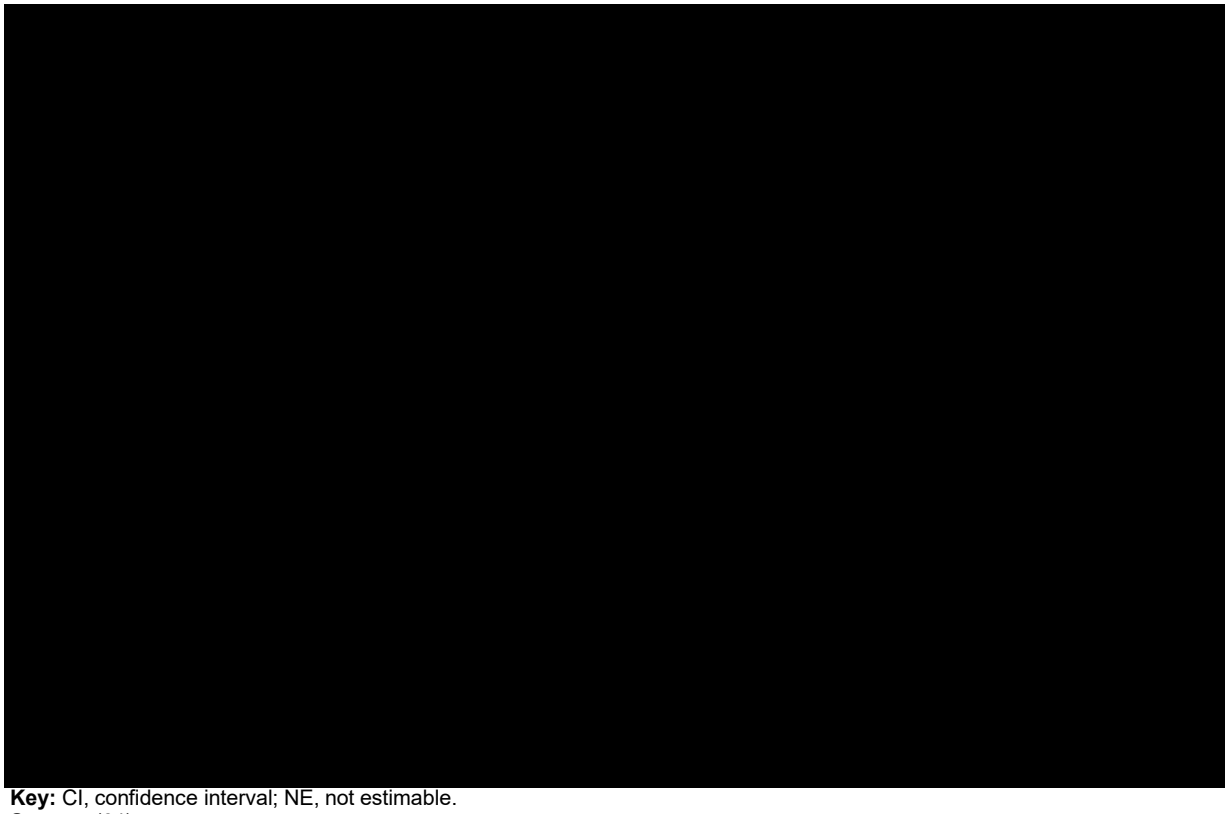
Figure 21: Kaplan–Meier plot of overall survival: MRD negative versus MRD positive (Phase 2, mITT population)

Data cutoff date: 09/09/2020.

Key: CI, confidence interval; KM, Kaplan–Meier; mITT, modified intent to treat; MRD, minimal residual disease; NE, not evaluable; NR, not reached; OS, overall survival.
Source: ZUMA-3 clinical study report Figure 14.2.10. (56).

Data from the most recent data cutoff (23/07/21) provides longer-term evidence on the effect of allo-SCT consolidation of KTE-X19 (Figure 22). Of note is that sensitivity analysis of median OS stratified by censoring at allo-SCT demonstrate that survival appeared to be independent of subsequent SCT based on the Phase 2 mITT population (56). This supports the curative, standalone potential of KTE-X19.

Figure 22: Kaplan-Meier plot of OS stratified by subsequent SCT and OCR (Phase 2 mITT CR/CRi; data cut 23/07/21)



Key: CI, confidence interval; NE, not estimable.
Source: (64).

Relapse-free survival:

KM estimates of RFS rates at 6 and 12 months were 57.6% (95% CI: [redacted]) and 44.3% (95% CI: [redacted]), respectively. The KM median RFS was 11.6 months (95% CI: 2.7, 15.5 months), with a reverse KM median follow-up time for RFS of [redacted] months (95% CI: [redacted]) (Figure 23).

Among subjects with CR or CRi, the KM median RFS was 14.2 months (95% CI: 11.6 months, NE). The proportion of patients achieving CR/CRi estimated to be

relapse-free and alive at 6 and 12 months was 81% and 63%, respectively. The KM median RFS was [redacted] months (95% CI: [redacted]) for subjects with CR and [redacted] months (95% CI: [redacted]) for subjects with CRi (56).

In patients achieving MRD negativity with KTE-X19, the KM median RFS was [redacted] (95% CI: [redacted]), and the proportion estimated to be relapse-free and alive at 6 and 12 months was [redacted] and [redacted], respectively (Table 22).

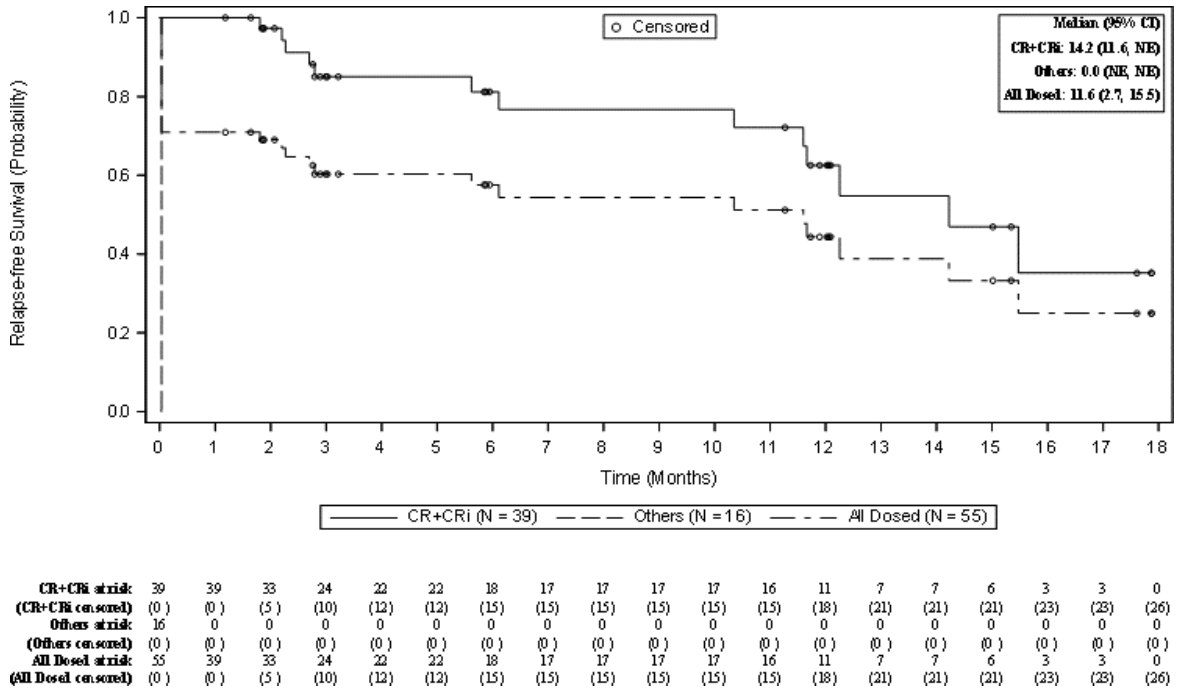
Table 22: RFS per central assessment (Phase 2, mITT)

RFS	Phase 2 (N = 55)
Number of patients, n	55
Events, n (%)	29 (52.7)
Censored, n (%)	26 (47.3)
KM median RFS, months (95% CI)	11.6 (2.7, 15.5)
Min, max RFS (months)	[redacted]
Events	
Relapse, n (%)	12 (21.8)
Death, n (%)	1 (1.8)
Patient's best overall response not CR or CRi, n (%)	16 (29.1)
Censoring reason	
Ongoing remission, n (%)	12 (21.8)
Allogeneic SCT, n (%)	9 (16.4)
Started new anti-cancer therapy, n (%)	5 (9.1)
Lost to follow up, n (%)	0 (0)
Withdrawal of consent, n (%)	0 (0)
KM estimates of RFS rates, % (95% CI)	
3 months	60.3 [redacted]
6 months	57.6 [redacted]
9 months	54.4 [redacted]
12 months	44.3 [redacted]
Reverse KM median follow-up time for RFS, months (95% CI)	[redacted]
KM estimates of RFS rates in patients with OCR, % (95% CI)	
6 months	81.2 [redacted]
12 months	62.5 [redacted]
KM estimates of RFS rates in patients with CR, % (95% CI)	
6 months	[redacted]

12 months	[redacted]
KM estimates of RFS rates in patients with CRi, % (95% CI)	
6 months	[redacted]
12 months	[redacted]
KM estimates of RFS rates in MRD negative patients, % (95% CI)	
6 months	[redacted]
12 months	[redacted]

Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; KM, Kaplan–Meier; mITT, modified intent-to-treat; NE, not estimable; RFS, relapse-free survival; SCT, stem cell transplant.
Notes: Percentages are based on the number of patients in the mITT population. RFS for patients who received KTE-X19 is defined as the time from the KTE-X19 infusion date to the date of relapse or death from any cause. Patients who received KTE-X19 but did not achieve CR or CRi as the best overall response are counted as events on the KTE-X19 infusion date. '+' indicates censoring.
Source: ZUMA-3 clinical study report Table 14.2.6.1 (56).

Figure 23: Kaplan-Meier plot of RFS by central assessment (Phase 2, mITT)



CR+CRi at risk:	39	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(CR+CRi censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)
Others at risk:	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(Others censored)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
All Dosed at risk:	55	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
(All Dosed censored)	(0)	(0)	(5)	(10)	(12)	(12)	(15)	(15)	(15)	(15)	(15)	(15)	(18)	(21)	(21)	(21)	(23)	(23)	(26)

Data cutoff date: 09/09/2020.
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; KM, Kaplan–Meier; mITT, modified intent to treat; NE, not evaluable; NR, not reached; RFS, relapse free survival.
Source: Adapted from Figure 3c (42).

Rate of allo-SCT

The incidence of allo-SCT after KTE-X19 infusion in the mITT analysis set is summarised in Table 23. 18% (10 of 55 subjects) in the mITT analysis set received allo-SCT while in remission after the initial KTE-X19 infusion; of these, 7 subjects had achieved a CR and 2 subjects had achieved a CRi to KTE-X19 based on central assessment of disease response. One subject received an allo-SCT after achieving

a CRi per investigator assessment but was considered to have a best response of BFBM per central assessment. Overall, the median time from KTE-X19 infusion to allo-SCT was 98 days (range: [redacted] days).

Data from the most recent data cutoff (23/07/21) provides longer-term evidence on the effect of allo-SCT consolidation of KTE-X19. Of note is that sensitivity analysis of median OS stratified by censoring at allo-SCT demonstrate that survival appears to be independent of subsequent SCT (Figure 22). This supports the curative, standalone potential of KTE-X19.

Of the 10 subjects who received allo-SCT after KTE-X19 infusion, [redacted] ([redacted] subjects) died within 100 days after allo-SCT. The remaining [redacted] ([redacted] subjects) were in ongoing remission 100 days after the transplant.

Table 23: Patient incidence of allo-SCT after treatment (Phase 2, mITT)

Incidence of SCT	**Phase 2 (N = 55)**
Patient incidence of allo-SCT post treatment, n (%)	10 (18)[a]
Patient incidence of allo-SCT for complete remission (CR or CRi) patients, % (95% CI)	[redacted]
Patient incidence of allo-SCT for CR patients, % (95% CI)	[redacted]
Patient incidence of allo-SCT for CRi patients, % (95% CI)	[redacted]
Time from KTE-X19 infusion to allo-SCT (in days)	
Median	98.0
Min, max	[redacted]
Mortality rate 100 days after allo-SCT[b], n (%)	[redacted]
Ongoing response 100 days after allo-SCT[b], n (%)	[redacted]

Key: allo-SCT, allogeneic stem cell transplant; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete haematological recovery; mITT, modified intent to treat; SCT, stem cell transplant.
Notes: Only transplants received while in remission after KTE-X19 infusion and before retreatment are included. Transplants that were received after subsequent anticancer therapy are not included. Response of CR or CRi is based on central assessment. a, the overall patient incidence includes one patient who had CRi per investigator assessment but was assessed as BFBM (blast free hypoplastic or aplastic bone marrow) as per central assessment; b, mortality rate and ongoing response 100 days after allo-SCT were calculated using the number of patients who received an allo-SCT as the denominator.
Source: ZUMA-3 clinical study report Table 14.2.9.1 (56).

When comparing the 9 of 39 subjects to achieve OCR who were consolidated with allo-SCT with the 30 of 39 subjects who were not, those receiving consolidation with allo-SCT were less heavily pre-treated (median [redacted] vs [redacted] prior lines of therapy), none of them were Ph+, none had prior allo-SCT (vs [redacted] in the OCR without consolidation),

and subjects consolidated with allo-SCT had a lower % blasts in the bone marrow after bridging chemotherapy ([redacted] vs [redacted]) (56).

Notably, all treated subjects at Phase 2 who went on to receive an allo-SCT after KTE-X19 had not received a previous allo-SCT. Based on discussion with clinical experts, Kite understand that a second allo-SCT is not seen as a viable treatment option in the UK (35). Additionally, in the UK allo-SCT would not be considered as an option to consolidate remission, as was the case for all subjects to receive allo-SCT post-KTE-X19 in the ZUMA-3 Phase 2 mITT population. Given the anticipated positioning of KTE-X19 in adults with R/R ALL who have relapsed post-allo-SCT, are ineligible for allo-SCT, or are unlikely to achieve allo-SCT due to poor prognostic factors, it is highly unlikely that KTE-X19 would be used as a bridge to allo-SCT, instead being considered as a standalone treatment option in UK clinical practice.

Other outcome measures: EQ-5D-5L

Across all 5 dimensions of the EQ-5D-5L, the proportion of evaluable subjects who reported no health problems at screening (baseline) ranged from [redacted] (pain/discomfort) to [redacted] (self-care). Shortly after KTE-X19 treatment, the proportion of subjects reporting no problems ranged from [redacted] (usual activities) to [redacted] (self-care) at Day 28. By month 3, the proportion of subjects reporting no problems rebounded (mobility and pain/discomfort) or reached higher levels (self-care, usual activities, and anxiety/depression) as compared to proportions at baseline. By month 12, the proportions of subjects reporting no problems were higher than those proportions at screening across all 5 domains, ranging from [redacted] (pain/discomfort) to [redacted] (self-care), suggesting a trend of recovery or improvement over time. Additionally, the proportion of subjects reporting severe or extreme problems on each domain was consistently low ([redacted]) at each time point after KTE-X19 treatment (56).

The median VAS score was 70.0 (range: 5 to 100) at screening and increased over time, with higher median scores of 80.0 (range: 20 to 100) at Day 28, 80.0 (range: 50 to 100) at Month 3, 85.0 (range: 40 to 100) at Month 6, and 87.5 (range: 70 to 100) at Month 12. The vast majority of subjects maintained stable VAS scores (absolute change of <7 points) or demonstrated clinically meaningful improvement (increase of

≥7 points) relative to their scores at screening over time: [redacted] at Day 28, [redacted] at Month 3, [redacted] at Month 6, and [redacted] at Month 12 (56,67).

In summary, patient-reported outcomes as measured by the EQ-5D-5L VAS remained stable or improved relative to values at baseline for the majority of subjects following treatment with KTE-X19 (≥70% of evaluable subjects considered stable or improved across time points from Day 28 through Month 12).

B.2.6.3 Summary of KTE-X19 clinical effectiveness

The efficacy and safety of KTE-X19 for the treatment of adult R/R ALL has been demonstrated in the single-arm Phase 1/2 ZUMA-3 trial (55). Patients with R/R disease were defined as primary refractory, in first relapse following a remission lasting ≤ 12 months, R/R after second-line or higher therapy or R/R after allo-SCT, representing the heterogenous adult R/R ALL population presenting in clinical practice. Definitions were based on the historically poor outcomes observed in these patient populations (18,24,57,58).

The ZUMA-3 Phase 1 + 2 combined population represents an adult R/R ALL group with an especially poor prognosis, including almost half ([redacted]) with prior blinatumomab treatment, and a similar proportion receiving ≥3 prior treatments at baseline ([redacted]) (Table 8). In addition, [redacted] had relapsed post-SCT, a group with an especially dire prognosis, where median OS is 5.5 months (43).

Despite having received multiple prior therapies to which they had experienced suboptimal response, 74.4% of adult R/R ALL patients treated with KTE-X19 achieved OCR, and 62.8% achieved CR.

Furthermore, 79.5% had no detectable cancer cells remaining as demonstrated by MRD negativity, including all but one patient – for whom data was not available – to achieve CR/CRi. The survival advantage of achieving MRD negativity in both adults and children has been demonstrated by Berry *et al*., (2017) in a meta-analysis of 39 studies (albeit following induction therapy), and was further re-enforced by recent long-term blinatumomab data (65,66). This supports the clinical value of every KTE-X19-treated evaluable subject to achieve CR/CRi also achieving MRD^- remission.

At the most recent data cutoff with actual median follow-up of [redacted] months, [redacted] and [redacted], were estimated to be alive at 12 and 18 months, respectively. Survival measurements from time of KTE-X19 treatment report an unprecedented median OS estimate of KM median OS was [redacted] months (95% CI: [redacted]). Notably, survival in responders appeared to be independent of subsequent SCT.

B.2.7 Subgroup analysis

Subgroup analyses based on baseline disease and treatment covariates were prespecified and conducted for selected efficacy and safety endpoints. These subgroups were explored to better characterise patient populations for whom KTE-X19 may provide the most benefit.

The OCR rate with 95% CIs was generated for subgroups of the mITT analysis set defined by selected treatment covariates. A forest plot of proportions (and 95% CI) of subjects achieving an OCR for each subgroup was generated. Full results are presented in Appendix E .

The OCR rate was largely consistent across most pre-planned subgroups, including those defined by baseline demographics, clinical characteristics and treatment history. Whilst OCR in the Phase 1 + 2 combined dataset was highest in those with 1 prior line of therapy ([redacted]) ([redacted]), the OCR rate in the [redacted] subjects with ≥4 prior lines of therapy was [redacted], supporting the effectiveness of KTE-X19 in heavily pre-treated subjects. Of note is that OCR rate was actually higher in those with a prior SCT ([redacted]) than it was in those without prior SCT ([redacted]) ([redacted] vs [redacted] respectively). This [redacted] OCR rate for subjects with prior SCT supports one of the proposed positionings of KTE-X19, as a treatment option for those who have relapsed post-allo-SCT.

While subgroup analyses must be interpreted with caution given the small sample sizes involved, clinical benefit was observed compared to historical controls irrespective of patient demographics, disease characteristics or treatment history. It should also be noted that while relatively small on face value, the sample size in ZUMA-3 is representative of the rarity of adult R/R ALL.

B.2.8 Meta-analysis

Meta-analysis is not required for KTE-X19 as a single study provides data for this intervention.

B.2.9 Indirect and mixed treatment comparisons

Table 24: Summary of comparators

Population		Intervention	Comparators			
Overall	Ph-	KTE-X19	Inotuzumab	FLAG-IDA	Blinatumomab	-
	Ph+				-	Ponatinib

Key: FLAG-IDA, Fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin; Ph+, Philadelphia chromosome-positive; Ph-, Philadelphia chromosome-negative.

In the absence of head-to-head clinical trial evidence of KTE-X19 versus either inotuzumab, blinatumomab, ponatinib, or salvage chemotherapy (FLAG-IDA), an SLR was conducted to identify relevant evidence on the comparator treatments for the purposes of conducting a possible indirect treatment comparison.

A total of 68 publications were included, of which 17 were RCT publications related to the TOWER and INO-VATE trials and the remaining 51 publications reported on non-randomised studies (i.e., single-arm trials and observational studies). The SLR was conducted on June 12, 2019, and subsequently updated in November 2020 to ensure all relevant literature was captured. For methods and results of the SLR please refer to Appendix D1.1.

Details of the 12 studies included in the SLR that were further evaluated for eligibility to be included in an ITC are listed in Table 97.

In the context of the evidence base available (single-arm trial data), it was not feasible to perform an anchored indirect treatment comparison to evaluate the comparative effectiveness of KTE-X19 versus relevant comparators. As such, both naïve ITCs and matching-adjusted indirect comparisons (MAICs) were conducted in line with the NICE decision support unit (DSU) technical support document (TSD) 18 (68). MAICs use individual patient-level data (IPD) from trials of one treatment to match baseline summary statistics reported from trials of another treatment (69,70). Matching baseline characteristics in this way enables the comparison of treatment outcomes across balanced trial populations. Full details of the ITC methodology and results are available in the separate ALL MAIC report (71).

In addition, a retrospective cohort study (SCHOLAR-3) was conducted, utilising a matched cohort derived from IPD sampled from historical clinical trials to further contextualise the results of ZUMA-3. A *post-hoc* analysis was conducted which

matched patients from ZUMA-3, irrespective of whether they had prior treatment with blinatumomab and inotuzumab to patients from historical trials who had not previously received blinatumomab therapy (SCHOLAR-3 synthetic control arm [SCA]-3). As the treatment assignments in SCA-3 were either blinatumomab ([redacted]) or SoC chemotherapy ([redacted]), the study population was further restricted within the analyses to include only patients who had received blinatumomab in the SCA-3 arm (i.e., excluding SoC chemotherapy patients) matched to patients from ZUMA-3.

The SCHOLAR-3 analysis meant that two data sources were available for the comparison with blinatumomab: the matched SCHOLAR-3 SCA-3 cohort and the pseudo-IPD recreated from TOWER. The key difference between these two analyses can be summarised as follows:

- When using the SCHOLAR-3 SCA-3 cohort, the ZUMA-3 patient characteristics remain unadjusted while the IPD of patients who received blinatumomab was matched to that of patients in the ZUMA-3 phase 2 mITT cohort based on their individual propensity score. In addition, use of SCA-3 ensures the comparison retains almost all of the ZUMA-3 mITT dataset ([redacted]) compared to 37-39 of 55 subjects for the MAIC comparison vs blinatumomab

- Conversely, when using the MAIC analyses, the ZUMA-3 IPD was weighted to match the reported average characteristics reported in TOWER for the intervention arm, and adjusted event-free survival (EFS) and OS KM for KTE-X19 were provided based on the weighted data. As TOWER enrolled Ph- patients only, the MAIC excluded ZUMA-3 patients that were Ph+

For our base case economic analyses, SCHOLAR-3 SCA-3 was considered a more appropriate source for comparison with blinatumomab than the MAIC or naïve comparison because the target population to which characteristics were matched was that of ZUMA-3. As explained in B.2.6.2, 100% of patients recruited to ZUMA-3 matched the anticipated positioning of KTE-X19 in UK clinical practice, that is, patients who have either failed or are unlikely to achieve SCT. Conversely, blinatumomab requires consolidation with SCT to be curative, therefore the patients recruited to TOWER are unlikely to be generalisable to the population treated with

KTE-X19 in UK clinical practice. Furthermore, the point estimates for relative efficacy of KTE-X19 versus blinatumomab from SCHOLAR-3 and the naïve comparison were aligned, whereas that from the MAIC diverged, although are unlikely to be statistically different (Table 26).

On the same principle, the naïve comparisons against inotuzumab and salvage chemotherapy (FLAG-IDA) underpin our base case economic analyses for these comparators, as the MAICs involve re-weighting of the ZUMA-3 patient characteristics to match those of INO-VATE and/or TOWER. INO-VATE notably excluded patients who had failed two or more prior therapies.

While ponatinib is considered a relevant comparator for adults with Ph+ R/R B-cell ALL disease, performing a MAIC was not deemed feasible. This is due to the small number of patients with Ph+ ALL in ZUMA-3 phase 1/2. Therefore, a naive comparison was conducted using data from the mITT ZUMA-3 Phase 1/2 and overall PACE population (note that in the economic model, the overall mITT ZUMA-3 phase 1/2 survival analysis is used for the ponatinib analysis, rather than the Ph+ subgroup). Although there are limitations of a naïve approach, clinical advisors felt that Ph expression is not expected to have an impact on the efficacy of CAR T-cells, including KTE-X19, and that Ph status was a low-rank prognostic factor (35). Unadjusted analyses for EFS were not conducted given different progression-related time-to-event outcomes were reported in the TKI studies (i.e. progression-free survival [PFS] in PACE), and RFS in ZUMA-3).

In summary, three categories of ITC were carried out against the various comparators that are of particular relevance to the economic analysis:

i. MAIC (vs inotuzumab, blinatumomab, FLAG-IDA)
ii. SCHOLAR-3 SCA-3: a matched cohort derived from IPD data from historical clinical trials (vs blinatumomab)
iii. Naïve (unadjusted) comparison (vs ponatinib, inotuzumab, blinatumomab, FLAG-IDA)

A summary of the key ITCs of particular relevance to the economic analysis is presented in Table 25. The outcomes of focus (EFS and OS) are those needed for

the economic analysis (see Section B.3). Results of the ITC for OS are summarised in Table 26, with EFS summarised in Table 27.

Table 25: Summary of key ITCs used in the economic model

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
ZUMA-3 vs. INO-VATE (inotuzumab)					

• IPD from ZUMA-3 for KTE-X19
• Published AD from INO-VATE for inotuzumab
	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup	mITT phase 1+2 (N=78)	ITT (N=164)	• OS (KM curves)
				• EFS (KM curves)
				• Response rate
					• **Naïve analysis (base case)**
					  • Observed absolute effects by treatment (CR rate, KM curves)
					• **MAIC analysis**
					  • Propensity score weighted absolute effects for KTE-X19 matched to the population in INO-VATE (CR rate, KM curves)

ZUMA-3 vs. pooled INO-VATE/TOWER (proxy for FLAG-IDA)					

• IPD from ZUMA-3 for KTE-X19
• Published AD from pooled INO-VATE and TOWER for FLAG-IDA
	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup	mITT phase 1+2 (N=78)	INO-VATE (N=162)
			
			TOWER (N=134)
				• OS (KM curves)
				• EFS (KM curves)
				• Response rate
					• **Naïve analysis (base case)**
					  • Observed absolute effects by treatment (CR rate, KM curves)
					• **MAIC analysis**
					  • Propensity score weighted absolute effects for KTE-X19 matched to the population in pooled INO-VATE/TOWER (CR rate, KM curves)

ZUMA-3 vs. SCHOLAR-3 (blinatumomab)					

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
• IPD from ZUMA-3 phase 2 for KTE-X19 • IPD from SCHOLAR-3 synthetic control arm (SCA) 3 for blinatumomab	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup; SCA-3 cohort represents patients from historical clinical trials who had not previously been treated with blinatumomab or inotuzumab	mITT phase 2 (N=[redacted]) *Note: the economic model utilizes the ZUMA-3 mITT phase 1+2 Ph- overall population for the comparison*	SCHOLAR-3 SCA-3 (N=[redacted])	• OS (KM curves) • EFS (KM curves) • Response rate	• **SCHOLAR-3 analysis (base case)** • (SCHOLAR-3 IPD constructed matching to ZUMA-3 IPD) observed absolute effects by treatment (CR rate, KM curves)
ZUMA-3 vs. TOWER (blinatumomab)					
• IPD from ZUMA-3 for KTE-X19 • Published AD from TOWER for blinatumomab	Adult patients with R/R ALL, irrespective of relapsed/refractory subgroup, Philadelphia chromosome negative	mITT phase 1+2 Ph- (N=61)	ITT (N=271)	• OS (KM curves) • EFS (KM curves) • Response rate	• **Naïve analysis** • Observed absolute effects by treatment (CR rate, KM curves) • **MAIC analysis** • Propensity score weighted absolute effects for KTE-X19 matched to the population in TOWER (CR rate, KM curves)
ZUMA-3 vs. PACE (ponatinib)					
• IPD from ZUMA-3 for KTE-X19	Adult patients with R/R ALL, irrespective of	mITT phase 1+2 Ph+ (N=17)	PACE (N=32)	• OS (KM curves)	• **Naïve analysis (base case)** • Observed absolute effects by treatment (KM curves)

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
• Published AD from PACE for ponatinib	relapsed/refractory subgroup, Philadelphia chromosome positive	*Note: the economic model utilizes the ZUMA-3 mITT phase 1+2 overall population for the comparison*			

Key: AD, aggregate data; ALL, acute lymphoblastic leukaemia; CR, complete remission; EFS, event-free survival; HR, hazard ratio; IPD, individual patient data; ITT, intention to treat; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; mITT, modified intention to treat; OS, overall survival; R/R, relapsed or refractory
The mITT phase 1+2 dataset comprises 55 phase 2 patients and the 23 phase 1 patients treated with the target dose of 1 x 10^6 cells/kg.

Table 26: Summary of ITC results (OS)

Comparison	ZUMA-3 analytical set	ESS*	ZUMA-3 Median OS naïve	Naïve HR (CI)	ZUMA-3 MAIC median OS (months) (CI) 3 salvage status*	MAIC HR (CI) 3 salvage status*	MAIC median OS (months) (CI) 2 salvage status*	MAIC HR (CI)2 salvage status*	SCHOLAR-3 median OS (months) (CI)	SCHOLAR-3 HR (CI)
X19 vs Blinatumomab (TOWER)	Phase 1 + 2 combined	37-39	22.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
X19 vs Blinatumomab (SCHOLAR-3)	Phase 2 mITT	[redacted]	18.2 (15.9, NE)	-	-	-	-	-	[redacted]	[redacted]
X19 vs Inotuzumab (INO-VATE)	Phase 1 + 2 combined	23-24	22.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
KTE-X19 vs pooled chemo	Phase 1 + 2 combined	30-32	22.44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
KTE-X19 vs ponatinib	Phase 1 + 2 combined		[redacted]	[redacted]	-	-	-	-	-	-

Key: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; mITT, modified intention-to-treat; NE, not estimable
Note: 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest. SCHOLAR-3 is a retrospective cohort study utilizing data from the Phase 2 ZUMA-3 investigational trial (mITT) and IPD sampled from historical clinical trials in relapsed or refractory adult ALL contained within the Medidata Enterprise Data Store (MEDS) database to create a matched synthetic control arm.

Table 27: Summary of ITC results (EFS)

Comparison	ZUMA-3 analytical set	ESS*	ZUMA-3 Median EFS	Naïve HR (CI)	MAIC median EFS (months) (CI) 3 salvage status*	MAIC HR (CI) 3 salvage status*	MAIC median EFS (months) (CI) 2 salvage status*	MAIC HR (CI) 2 salvage status*
X19 vs Blinatumomab (TOWER)	Phase 1 + 2 combined	37-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X19 vs Inotuzumab (INO-VATE)	Phase 1 + 2 combined	23-24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
X19 vs Pooled Chemo (TOWER +INO-VATE)	Phase 1 + 2 combined	30-32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; MAIC, Matching-adjusted indirect comparison.
Note: 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest. SCHOLAR-3 is a retrospective cohort study utilizing data from the Phase 2 ZUMA-3 investigational trial (mITT) and IPD sampled from historical clinical trials in relapsed or refractory adult ALL contained within the Medidata Enterprise Data Store (MEDS) database to create a matched synthetic control arm. For the naïve comparison with ponatinib and SCHOLAR-3 comparison versus blinatumomab, no data on EFS is available. *range based on salvage status (2-level, 3-level).

B.2.9.1 MAIC:

For the MAIC, of the 12 studies identified in the SLR to be evaluated for eligibility, two studies were included in the final comparisons: INO-VATE and TOWER Table 98. Rationale behind the exclusion of the remaining 10 studies is provided in Table 99.

The MAIC was conducted in several steps. The first step was to conduct a feasibility assessment to determine the degree of overlap in study designs and populations and the extent that it is possible to generate unbiased comparisons. In the next step, we redefined outcomes in the IPD for ZUMA-3 to match the outcomes definitions of the aggregate data from comparator trials. A logistic propensity score model was used to estimate weights for the IPD such that the weighted mean baseline characteristics of interest for the population in ZUMA-3 matched those reported in the comparator trials. The choice of covariates for the propensity score models was based on clinician interviews regarding prognostic factors of significance in R/R ALL, as well as potential effect modifiers (71).

These above steps resulted in a ZUMA-3 IPD dataset with a weighted trial population that matched those of the comparator trial(s) of interest for the included covariates. Using these weights, outcomes for KTE-X19 were predicted for the population in the comparator trial by reweighting the observed outcomes from ZUMA-3. Treatment comparisons were then conducted across the balanced trial populations. Full details of the methodology and results for OS and RFS/PFS/EFS of KTE-X19 versus interventions considered to represent SoC are presented in the MAIC report (71).

After exploring different models and examining the effective sample size (ESS) for the four analysis populations, the most inclusive model that achieved convergence was selected for the MAIC comparisons. The MAIC with INO-VATE matched on duration of first remission <12 months, prior SCT, age, Eastern Cooperative Oncology Group (ECOG) (0 vs. rest), salvage status, bone marrow blast at screening, complex karyotype and Philadelphia chromosome status. For TOWER, the MAIC matched on primary refractory, duration of first remission < 12 months,

prior SCT, age, ECOG (0 vs. rest), salvage status, and Philadelphia chromosome status. Covariates reported by both trials (INO-VATE and TOWER) were matched for the comparison with chemotherapy. Given INO-VATE only enrolled patients who were due to receive their first or second salvage treatment, additional scenario analyses were conducted for salvage status: a) 3-level salvage (i.e., first salvage, second salvage vs. rest), and b) 2-level salvage (first salvage vs. rest).

Results

Comparisons were performed for each of the four analysis population sets of ZUMA-3 (mITT Phase 2, mITT Phase 1+2, ITT Phase 2, ITT Phase 1+2) with INO-VATE, TOWER and the pooled chemotherapy arms in INO-VATE and TOWER for OS and EFS. Results for the Phase 1 + 2 combined dataset are presented here. For the results of other populations please refer to the MAIC report (71).

Overall survival

Note that for the ZUMA-3 Phase 1 + 2 combined population, OS was calculated from date of KTE-X19 infusion.

Inotuzumab:

The estimated HRs for the Phase 1 + 2 combined population including the two salvage status scenario analyses were all in favour of KTE-X19; after adjustment, these differences were significant. Given the overall small sample size in Phase 2 ZUMA-3 populations, and the matching to INO-VATE resulting in very small ESS, the results of the comparisons with INO-VATE should be interpreted with caution (Figure 24).

Figure 24: Overall survival for ZUMA-3 Phase 1+2 combined versus INO-VATE inotuzumab

Key: ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; m, median; OS, overall survival. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

Blinatumomab:

Following adjustment, the KM curves shifted downwards; however, the estimated HRs were all in favour of KTE-X19 (range: [redacted]). Similar to the comparisons with INO-VATE, differences were statistically significant for the Phase 1+2 combined population after adjustment (Figure 25).

Figure 25: Overall survival for ZUMA-3 Phase 1+2 combined versus TOWER

Key: ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; m, median; OS, overall survival. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

FLAG-IDA:

In the MAICs with chemotherapy, reconstructed IPD for INO-VATE and TOWER were combined to create a single chemotherapy arm. Results suggested that KTE-X19 was superior to the combined chemotherapy arm in terms of OS, including for both salvage status scenarios (Figure 26).

Figure 26: Overall survival for ZUMA-3 Phase 1+2 combined versus stacked IPD in INO-VATE and TOWER chemotherapy

Key: ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; m, median; OS, overall survival. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

Event-free survival

Note that for ZUMA-3 mITT populations, EFS was calculated from date of infusion.

Inotuzumab:

Unlike the results from the OS analysis, although the estimated HRs for the Phase 1 + 2 combined dataset and for the two salvage status scenarios were all in favour of KTE-X19 after adjustment, these differences were not statistically significant (Figure 27).

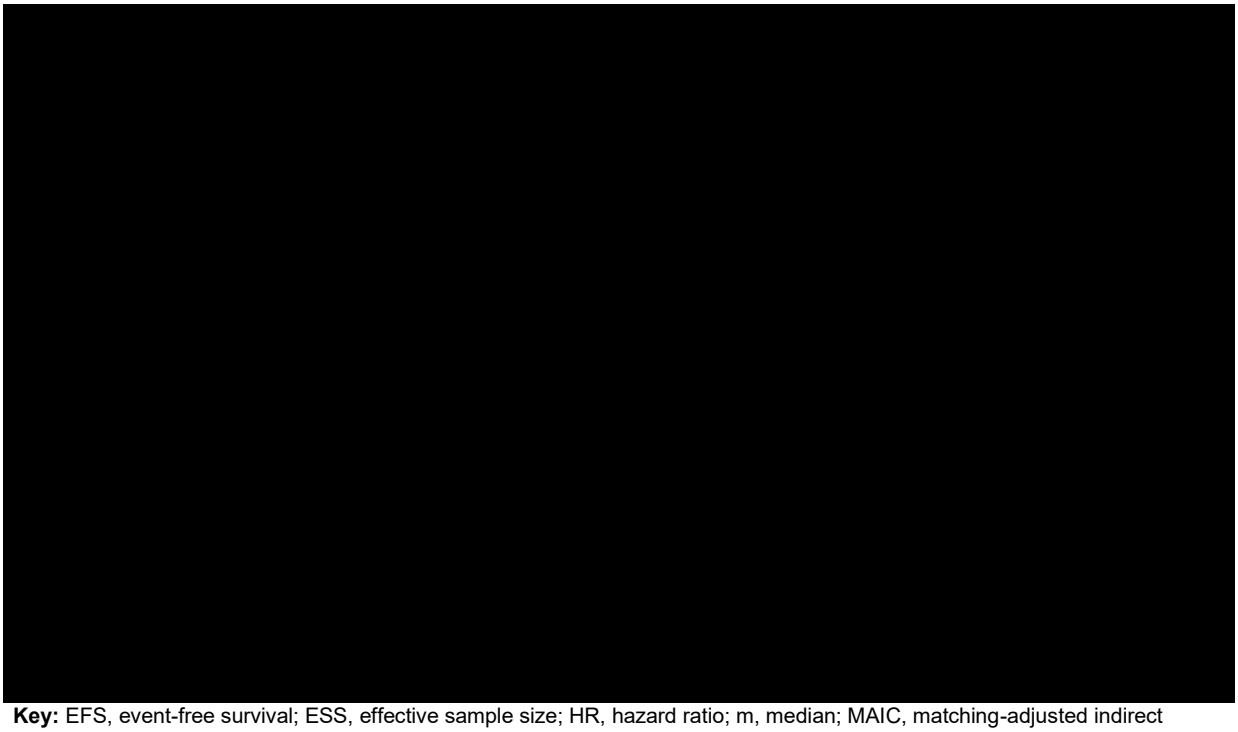
Figure 27: Event-free survival for ZUMA-3 Phase 1+2 combined versus INO-VATE

Key: EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; m, median; MAIC, matching-adjusted indirect comparison. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

Blinatumomab:

Following adjustments, the EFS KM curves shifted minimally, and the HRs for the unadjusted and adjusted comparisons were very similar. Although the 95% CIs became wider after applying weights, the results showed a statistically significant difference in EFS with KTE-X19 compared to blinatumomab for all four populations, both before and after adjustment. It should be noted that the proportional hazards assumption was violated for the mITT Phase 1+2 population when the 3-level salvage was matched, and therefore these results should be interpreted with caution (Figure 28).

Figure 28: Event-free survival for ZUMA-3 Phase 1+2 combined versus TOWER



Key: EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; m, median; MAIC, matching-adjusted indirect comparison. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

FLAG-IDA:

Overall, the EFS KM curves shifted minimally after adjustment, but the number of patients at risk dropped significantly from 0 to 6 months. It should be noted that the proportional hazards assumption was violated for the mITT Phase 1+2 population (Figure 29).

Figure 29: Event-free survival for ZUMA-3 Phase 1+2 combined versus stacked IPD in INO-VATE and TOWER

Key: EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; m, median; MAIC, matching-adjusted indirect comparison. 3-level salvage: first salvage, second salvage vs. rest, 2-level salvage: first salvage vs. rest.
Source: (71).

Conclusions of the MAIC

Findings from the MAICs suggested KTE-X19 had a favourable effect on OS and EFS compared to inotuzumab, blinatumomab, and chemotherapy regimens in R/R ALL patients. The methods used for the MAIC in this analysis aligned with recommendations from the NICE guidance for population-adjusted indirect comparisons (68). Limitations of the MAIC are discussed in section B.2.9.4.

Given the anticipated positioning of KTE-X19 in patients who have relapsed post-SCT, or are unlikely to achieve/ineligible for SCT, it was concluded that the population of ZUMA-3 was most reflective of anticipated use in clinical practice. Therefore, rather than adjusting ZUMA-3 for comparisons to the populations from the TOWER and INO-VATE trials, it was considered that the most appropriate comparison for the cost-effectiveness analysis were the unadjusted ones.

B.2.9.2 Naïve comparison

For each outcome of interest in each patient population, a model without individual weights provides a ‘naïve’ estimate of the treatment effect of KTE-X19 versus each

comparator where the relative treatment effect was estimated based on the observed outcomes of interest from each trial without adjusting for any between-study differences.

HRs for OS and EFS were estimated by means of a Cox proportional hazards model based on the (unadjusted) IPD from ZUMA-3 and the reconstructed IPD from the published KM curves from each external study. Treatment effects of interest were expressed with point estimates and 95% CIs.

Results from the naïve comparisons with inotuzumab and FLAG-IDA are presented in Figure 24 and Figure 26, respectively for OS, and Figure 27 and Figure 29, respectively, for EFS.

Results from the naïve comparison between Ph+ population in ZUMA-3 and PACE (ponatinib 45mg) for OS are presented in Figure 30 (36,42). As a result of the small sample size in ZUMA-3, there were minimal changes in the number of patients at risk across the different time points, resulting in relatively flat KM curves for ZUMA-3. Across the comparisons, all naïve analyses suggested KTX-19 was favourable to ponatinib.

Figure 30: Overall survival for ZUMA-3 Phase 1+2 combined versus ponatinib (45mg)

Key: HR, hazard ratio; m, median; N, number; OS, overall survival.

Source: (71).

B.2.9.3 SCHOLAR-3:

SCHOLAR-3 is a retrospective cohort study that selected patients from the Medidata Enterprise Data Store (MEDS) database of historical clinical trials that matched the inclusion/exclusion criteria of ZUMA-3. From the resulting pool a matched cohort of patients with similar baseline characteristics to ZUMA-3 was analysed for clinical outcome to quantify the relative effectiveness of KTE-X19.

The primary objective of SCHOLAR-3 was to describe the OCR rate in patients sampled from historic clinical trials that were previously naïve to blinatumomab or inotuzumab therapy. Baseline characteristics for matched populations are available in the SCHOLAR-3 CSR (72).

There were three subsets for SCHOLAR-3, SCA-1 (blinatumomab/inotuzumab naïve) and SCA-2 (blinatumomab/inotuzumab experienced) were pre-specified, with SCA-3 added post-hoc. As clinical outcomes beyond OS were not available for patients exposed to blinatumomab or inotuzumab in the MEDS database, SCA-3 only included blinatumomab and inotuzumab naïve patients for whom all clinical outcomes were available and matching to ZUMA-3 was done on the other baselines characteristics. This might have led to bias against KTE-X19 given that prior treatment with blinatumomab has been shown to impact effectiveness of subsequent CD19 CAR-T treatment in ALL (60). SCA-3 was considered worthwhile to obtain two relatively large, matched cohorts to quantify the clinical effectiveness of KTE-X19 compared to blinatumomab.

A brief summary of the SCHOLAR-3 study is provided in Table 28.

Table 28: Overview of design for SCHOLAR-3

Study description	A retrospective cohort study of adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia sampled from historical clinical trials
Patient population	Patients must have been diagnosed with r/r B-ALL defined as one of the following: • Primary refractory disease • First relapse if first remission ≤ 12 months

	• Relapsed or refractory disease after two or more lines of systemic therapy • Relapsed or refractory disease after allogeneic transplant provided patient is at least 100 days from stem cell transplant at the time of enrolment and off of immunosuppressive medications for at least 4 weeks prior to enrolment
Study size	SCA-1: n = [redacted] ([redacted] ZUMA-3, [redacted] blinatumomab/inotuzumab naïve) SCA-2: n = [redacted] ([redacted] ZUMA-3, [redacted] blinatumomab/inotuzumab experienced) Post-hoc analysis: SCA-3: n = [redacted] ([redacted] ZUMA-3, [redacted] blinatumomab/inotuzumab naïve)
Primary objective	OCR rate in the historical control arm for those naïve to blinatumomab or inotuzumab

Key: OCR, overall complete remission; r/r, relapsed/refractory; SCA, synthetic control arm.
Source: (72).

Full details of the methodology and results for SCHOLAR-3 are available in the SCOLAR-3 CSR (72).

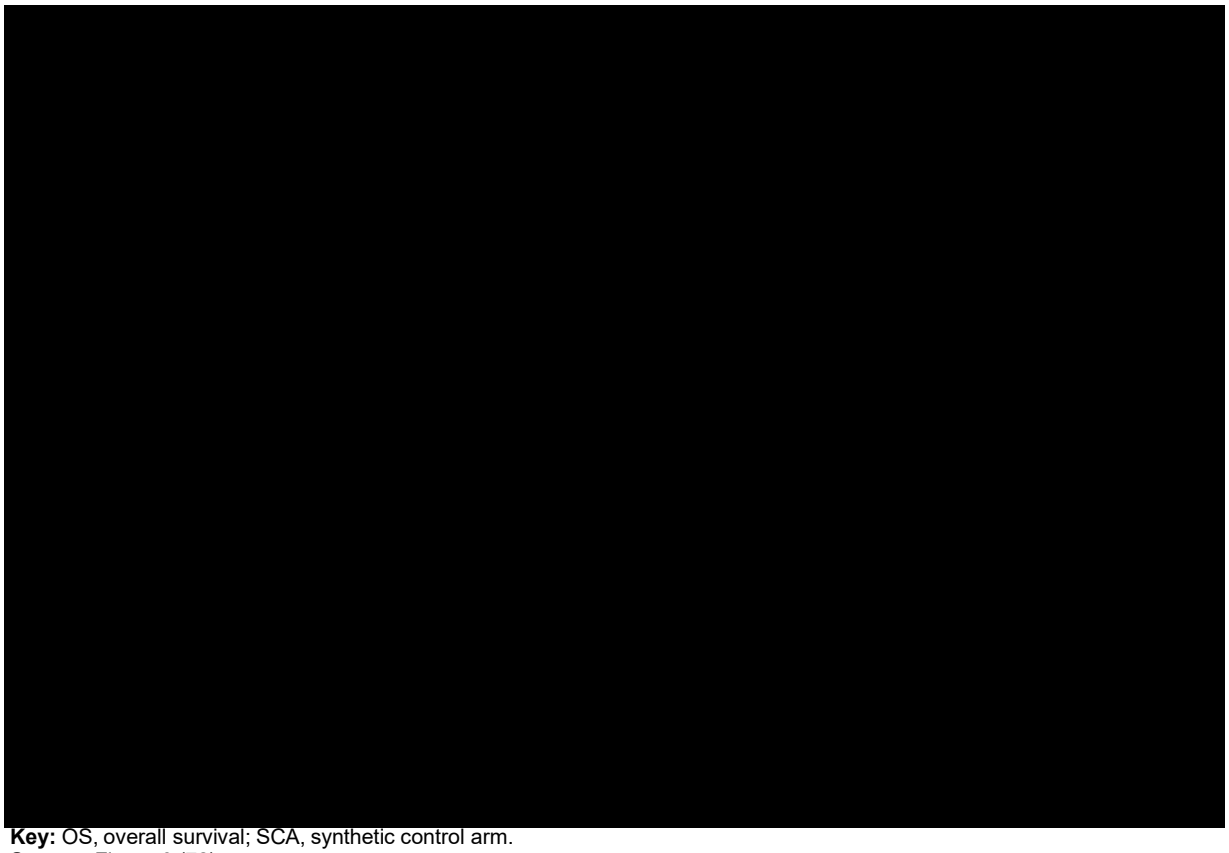
Results

SCA-1

For the primary objective, it was estimated that [redacted] (95% CI [redacted]) of patients in SCA-1 (blinatumomab/ inotuzumab naïve) achieved OCR at week 24. For the first secondary objective, the comparison of OCR rate between matched ZUMA-3 and SCA-1 arms, matched patients from ZUMA-3 had an OCR rate of [redacted] (95% CI: [redacted]). When compared to SCA-1 patients, matched ZUMA-3 patients had a significantly higher odds of achieving OCR [redacted] (95% CI: [redacted]) (p=[redacted]).

The comparison of OS between matched ZUMA-3 and SCA-1 patients showed that ZUMA-3 patients had a higher median OS in comparison to SCA-1 patients, [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]) respectively. A hazard ratio (HR) derived through a univariate Cox regression showed that ZUMA-3 patients were [redacted] likely to die than patients in the SCA-1 group, HR [redacted] (95% CI: [redacted]) (p = [redacted]).

Figure 31: Kaplan-Meier median OS (ZUMA-3 vs SCA-1)



Key: OS, overall survival; SCA, synthetic control arm.
Source: Figure 6 (72)

SCA-2

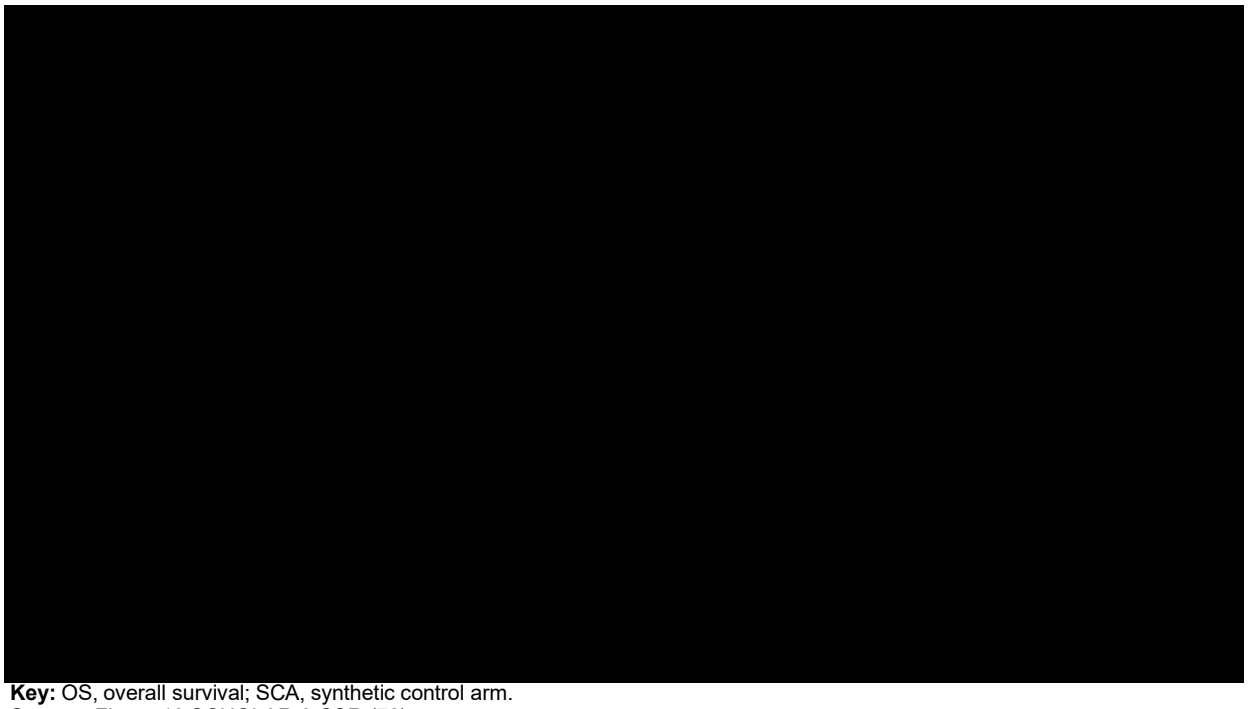
The comparison of OS between matched ZUMA-3 and SCA-2 patients showed that ZUMA-3 patients had a higher median OS in comparison to SCA-2 patients, [redacted] months (95% CI: [redacted]) versus [redacted] months (95% CI: [redacted]), respectively. A HR derived through a multivariate Cox regression adjusted for percentage bone marrow blasts and prior lines of therapy did not indicate a statistically significant difference, HR [redacted] (95% CI [redacted]).

SCA-3

In the non-prespecified post hoc analysis, [redacted] (95% CI: [redacted]) of patients in the ZUMA-3 arm achieved OCR at Week 24 while [redacted] (95% CI: [redacted]) from SCA-3 achieved OCR at the same timepoint. ZUMA-3 patients had [redacted] times higher odds of achieving OCR in comparison to SCA-3 patients (95% CI: [redacted]) (p-value [redacted]).

A further post-hoc analysis comparing OS between matched ZUMA-3 and SCA-3 patients showed ZUMA-3 patients to have a median OS of [redacted] months (95% CI: [redacted]) and SCA-3 patients to have a median OS of [redacted] months (95% CI: [redacted]). A univariate Cox regression showed that ZUMA-3 patients were [redacted] likely to die in comparison to SCA-3 patients; HR (95% [redacted]) (p = [redacted]).

Figure 32: Kaplan-Meier median OS (ZUMA-3 vs SCA-3)



Key: OS, overall survival; SCA, synthetic control arm.
Source: Figure 13 SCHOLAR-3 CSR (72).

B.2.9.4 Uncertainties in the indirect and mixed treatment comparisons

MAIC:

The methods used for the MAIC in this analysis aligned with recommendations from the NICE guidance for population-adjusted indirect comparisons (70). However, it is important to highlight the limitations of this type of cross-study comparison. Specifically, the analysis is limited to study-level aggregate data from the publications of the comparator studies. In the absence of IPD from the comparator studies, it is challenging to evaluate the extent of bias in the treatment effect estimates and it is likely that some confounding variables remained unbalanced. For example, unlike ZUMA-3, which only enrolled patients with an ECOG score of 0 or 1,

both INO-VATE and TOWER also enrolled patients with an ECOG score of 2. While the proportion of patients with ECOG 0 was matched, outcomes had to be assumed to be comparable for those with ECOG 1 or 2.

In contrast, some of the patients in ZUMA-3 would not have been eligible for the comparator studied. INO-VATE required patients to have received no more than one prior salvage therapy, while there was no limit on the number of salvage therapies received in ZUMA-3. TOWER only enrolled patients with Ph- ALL, whereas [redacted] of patients had Ph+ ALL in the ZUMA-3 combined Phase 1+2 population. Differences in the proportions of other key clinical characteristics were found to be influential on the associated weighting of ZUMA-3. For instance, in ZUMA-3 the proportion of patients with prior SCT ranged from [redacted] to [redacted] in the four analysis populations, whereas in INO-VATE only 18% of patients received prior SCT. Therefore, patients with prior SCT were down-weighted whereas patients without prior SCT were up weighted in ZUMA-3. A closer examination of some of the patients with extreme weights showed that in general patients who were in first salvage status, with a duration of remission less than < 12 months, with no prior SCT, or with bone marrow blast >50% at screening tend to be up-weighted in the model.

Despite these limitations, the HRs for EFS and OS versus blinatumomab, inotuzumab and FLAG-IDA from the Phase 1+2 MAICs used in the economic model largely remained stable when compared with the naïve comparisons. The largest difference was observed with OS versus blinatumomab (naïve [redacted]; MAICs [redacted] [3-salvage status] and [redacted] [2-salvage status]), indicating that these treatment effects are likely robust despite the statistical uncertainty associated with individual MAICs.

Of note, the point estimate of the naïve OS HR for blinatumomab ([redacted]) was identical to that from the SCHOLAR-3 analysis, whereas that from the MAIC ([redacted]) diverged. Thus, the naïve ITC appears to have produced more valid results than the MAIC, given the SCHOLAR-3 analysis involved matching individual patients to the correct target population. This also supports, by inference, use of a naïve comparison for inotuzumab in the economic analysis.

SCHOLAR-3:

Despite the study using IPD from historical clinical trials that have been captured using electronic case report forms (eCRFs) and verified through originating sponsors' verification processes, the risk of misclassification bias can't be completely ruled out. To mitigate this, plausibility checks for the data from historical clinical trials were carried out if the historical trials had published results. To limit further misclassification bias during the derivation of the cohorts all statistical procedures were double programmed.

Variation in the definition of various endpoints across historical clinical trials could lead to information bias in this study. To mitigate against this, baseline variables and all endpoints were defined based on their constituent variables as per definitions in the ZUMA-3 study.

In order to minimise selection bias, ZUMA-3 inclusion criteria were used for this study, with Kite blinded to patient selection, treatment and outcomes until analysis was complete. In addition, propensity matching was used to minimise heterogeneity.

In order to account for confounding a robust strategy was developed for this study and while double robust multivariate models were considered for comparative analysis, limitations due to the final sample sizes led to issues of convergence.

This study seeks to emulate a "physicians' choice" arm from a randomised experiment. Furthermore, as this study is building matched cohorts from historic clinical trials treatment effects may be over-estimated in comparison to real world practice. This may affect the external validity of the study design.

The consistently superior efficacy of KTE-X19 was demonstrated in all three cohorts. The SCA-3 cohort analysis represented a comparison potentially biased against KTE-X19, given that the ZUMA-3 cohort included a large number of patients who had previously failed targeted therapies, whereas the SCA-3 cohort included only those naïve to inotuzumab and blinatumomab. Given that failure of targeted therapies is generally considered a poor prognostic factor, it is notable that a significant OS benefit HR [redacted] ([redacted]) was observed, demonstrating the value of KTE-X19 in its proposed position in the pathway.

B.2.10 Adverse reactions

The safety and tolerability of KTE-X19 for the treatment of adult patients with R/R B-cell ALL was evaluated as a secondary outcome in ZUMA-3. The Phase 2 safety analysis set was defined as all subjects treated with KTE-X19 (N = 55).

Of note is that, based on the safety and efficacy observations at Phase 1, the SRT decision was to explore the safety profile of the 1 x 10^6 anti-CD19 CAR T cells/kg dose level with the implementation of modified toxicity management recommendations. Under the revised AE management guidelines, patients were not administered tocilizumab for neurological events unless in the context of CRS, and steroid use was initiated for Grade 2 neurological events in comparison to Grade 3 neurological events in the previous guidelines.

Data on AEs for the Phase 1 target dose population (N = 23) is not reported separately from the safety analysis set (N = 45), except for on a few instances, such as exposure to KTE-X19. Given almost half (22 of 45 subjects) of those in the safety analysis set did not receive KTE-X19 at target dose, and 36 of 45 subjects received KTE-X19 prior to the revised toxicity management guidelines, data from the Phase 1 safety analysis set is not presented here.

AEs were coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0.

B.2.10.1 Exposure to KTE-X19:

In Phase 2, the median weight-adjusted dose of KTE-X19 was [redacted] x 10^6 anti-CD19 CAR T-cells/kg (range: [redacted] x 10^6 anti-CD19 CAR T-cells/kg. the median total number of anti-CD19 CAR T-cells in the KTE-X19 infusion was [redacted] x 10^6 cells (range: [redacted] x 10^6 cells [redacted] x 10^6 cells), and the median total number of T cells infused was [redacted] x 10^6 cells (range: [redacted] x 10^6 cells – [redacted] x 10^6 cells). Of the 55 subjects treated, [redacted] ([redacted]) received KTE-X19 within 10% of the planned target dose (56).

Among all subjects treated at target dose at Phase 1, the median weight-adjusted dose of KTE-X19 was [redacted] x 10^6 anti-CD19 CAR T-cells/kg (range: [redacted] x 10^6 cells/kg). The median total number of anti-CD19 CAR T cells in the KTE-X19 infusion

was [redacted] x 10^6 cells (range: [redacted] x 10^6 to [redacted] x 10^6 cells), and the median total number of T cells infused was [redacted] x 10^6 cells (range: [redacted] x 10^6 to [redacted] x 10^6). Of the 23 subjects, [redacted] ([redacted]) received within 10% of the planned total dose (56).

B.2.10.2 Duration of hospitalisation for KTE-X19 infusion

For subjects in Phase 2, the median duration of hospitalisation during the KTE-X19 infusion and until discharge following the infusion was [redacted] days (range: [redacted] days). For subjects treated at target dose in Phase 1, the median duration of hospitalisation during the KTE-X19 infusion until discharge following the infusion was [redacted] days (range: [redacted] days) (56).

B.2.10.3 Safety summary

The safety profile of KTE-X19 in ZUMA-3 was generally similar to that observed in other indications, although a higher incidence of Grade 3 or higher cytokine release storm (CRS) was observed. This was also the case for tisagenlecleucel, where CRS was more commonly observed in ALL compared to other indications (73).

All treated patients had at least one AE, and [redacted] of 55 patients ([redacted]) had KTE-X19 related AEs, with [redacted] patients ([redacted]) experiencing KTE-X19 related AEs that were worst Grade 3 or higher (Table 29). The most common worst Grade 3 or higher KTE-X19 related AEs were [redacted], [redacted] and [redacted].

Forty-one of 55 patients (75%) experienced an SAE, while [redacted] of 55 patients ([redacted]) had at least one SAE related to KTE-X19, the most frequently reported of which were [redacted], [redacted], and [redacted]. There were two deaths observed due to AEs that were considered related to KTE-X19 (brain herniation [day 8] and septic shock [day 18]) (42).

An overview of AEs experienced by subjects in the Phase 2 safety analysis set, as well as the Phase 1 + 2 combined dataset are presented in Table 29, demonstrating the consistency of KTE-X19's safety profile, with slightly more favourable results in the Phase 2 safety analysis set potentially as a result of the revised AE management plan described earlier on in this section.

Table 29: Overall summary of AEs

	KTE-X19 (Phase 2 safety analysis set; n=55)	KTE-X19 (Phase 1 + 2 combined; n=78)
Any adverse event, n (%)	55 (100)	[redacted]
Worst Grade 3	8 (15)	[redacted]
Worst Grade 4	34 (62)	[redacted]
Worst Grade 5	10 (18)	[redacted]
Any serious adverse event, n (%)	41 (75)	[redacted]
Worst Grade 3	[redacted]	[redacted]
Worst Grade 4	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Any KTE-X19-related adverse event, n (%)	[redacted]	[redacted]
Worst Grade 3	[redacted]	[redacted]
Worst Grade 4	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]
Any KTE-X19-related serious adverse event, n (%)	[redacted]	[redacted]
Worst Grade 3	[redacted]	[redacted]
Worst Grade 4	[redacted]	[redacted]
Worst Grade 5	[redacted]	[redacted]

Data cutoff date = 09Sep2020.
Key: mITT, modified intent-to-treat.
Notes: TEAEs include all AEs with an onset on or after initiation of the KTE-X19 infusion. For subjects who underwent retreatment with KTE-X19, the AEs occurring during the retreatment period are not included. Subjects were summarized at their highest grade per the Common Terminology Criteria for Adverse Events version 4.03.
Source: ZUMA-3 clinical study report Table 47; Table 14.3.1.1.4 (56).

B.2.10.4 Common adverse events

AEs that occurred in ≥ 10% of patients in the Phase 2 mITT population are summarised in Table 30.

Table 30: Subject incidence of AEs occurring in >10% of subjects by preferred term and worst grade (Phase 2, safety analysis set)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any TEAE	55 (100)	0 (0)	3 (5)	8 (15)	34 (62)	10 (18)[a]
Pyrexia	52 (95)	8 (15)	24 (44)	17 (31)	3 (5)	0 (0)
Hypotension	37 (67)	2 (4)	19 (35)	13 (24)	3 (5)	0 (0)
Anaemia	29 (53)	0 (0)	2 (4)	25 (45)	2 (4)	0 (0)
Nausea	21 (38)	12 (22)	9 (16)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	21 (38)	9 (16)	9 (16)	3 (5)	0 (0)	0 (0)
Headache	20 (36)	12 (22)	8 (15)	0 (0)	0 (0)	0 (0)
Chills	18 (33)	13 (24)	5 (9)	0 (0)	0 (0)	0 (0)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Platelet count decreased	18 (33)	1 (2)	0 (0)	3 (5)	14 (25)	0 (0)
Hypoxia	16 (29)	1 (2)	4 (7)	7 (13)	4 (7)	0 (0)
Fatigue	15 (27)	12 (22)	3 (5)	0 (0)	0 (0)	0 (0)
Hypokalaemia	15 (27)	5 (9)	6 (11)	3 (5)	1 (2)	0 (0)
Hypophosphataemia	15 (27)	2 (4)	2 (4)	11 (20)	0 (0)	0 (0)
Neutrophil count decreased	15 (27)	0 (0)	0 (0)	1 (2)	14 (25)	0 (0)
Tremor	15 (27)	14 (25)	0 (0)	1 (2)	0 (0)	0 (0)
Confusional state	14 (25)	5 (9)	7 (13)	2 (4)	0 (0)	0 (0)
Tachycardia	14 (25)	3 (5)	11 (20)	0 (0)	0 (0)	0 (0)
White blood cell count decreased	14 (25)	0 (0)	1 (2)	4 (7)	9 (16)	0 (0)
Alanine aminotransferase increased	12 (22)	4 (7)	1 (2)	6 (11)	1 (2)	0 (0)
Diarrhoea	12 (22)	7 (13)	3 (5)	2 (4)	0 (0)	0 (0)
Encephalopathy	12 (22)	1 (2)	7 (13)	3 (5)	1 (2)	0 (0)
Hypomagnesaemia	12 (22)	12 (22)	0 (0)	0 (0)	0 (0)	0 (0)
Abdominal pain	10 (18)	4 (7)	6 (11)	0 (0)	0 (0)	0 (0)
Aspartate aminotransferase increased	10 (18)	3 (5)	2 (4)	4 (7)	1 (2)	0 (0)
Oedema peripheral	10 (18)	7 (13)	3 (5)	0 (0)	0 (0)	0 (0)
Aphasia	9 (16)	2 (4)	2 (4)	5 (9)	0 (0)	0 (0)
Hypocalcaemia	9 (16)	1 (2)	4 (7)	4 (7)	0 (0)	0 (0)
Thrombocytopenia	9 (16)	0 (0)	2 (4)	0 (0)	7 (13)	0 (0)
Vomiting	9 (16)	9 (16)	0 (0)	0 (0)	0 (0)	0 (0)
Constipation	8 (15)	6 (11)	2 (4)	0 (0)	0 (0)	0 (0)
Decreased appetite	8 (15)	6 (11)	2 (4)	0 (0)	0 (0)	0 (0)
Dizziness	8 (15)	7 (13)	1 (2)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	8 (15)	0 (0)	2 (4)	6 (11)	0 (0)	0 (0)
Neutropenia	8 (15)	0 (0)	0 (0)	2 (4)	6 (11)	0 (0)
Agitation	7 (13)	1 (2)	4 (7)	2 (4)	0 (0)	0 (0)
Cough	7 (13)	6 (11)	1 (2)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	7 (13)	0 (0)	0 (0)	7 (13)	0 (0)	0 (0)
Hypertension	7 (13)	0 (0)	4 (7)	3 (5)	0 (0)	0 (0)
Insomnia	7 (13)	3 (5)	4 (7)	0 (0)	0 (0)	0 (0)
Pain	7 (13)	2 (4)	4 (7)	1 (2)	0 (0)	0 (0)
Dyspnoea	6 (11)	3 (5)	2 (4)	1 (2)	0 (0)	0 (0)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Muscular weakness	6 (11)	4 (7)	1 (2)	1 (2)	0 (0)	0 (0)
Myalgia	6 (11)	5 (9)	1 (2)	0 (0)	0 (0)	0 (0)
Rash	6 (11)	4 (7)	2 (4)	0 (0)	0 (0)	0 (0)

Data cutoff date = 09/09/2020.
Key: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment emergent adverse event.
Notes: Preferred terms are sorted in descending order of total frequency in the 'Any' column. Adverse events are coded using MedDRA version 23.0 and graded using CTCAE 4.03. Multiple incidences of the same AE in one patient are counted once at the highest grade for that patient. TEAEs include all AEs with an onset on or after initiation of the KTE-X19 infusion. For patients who underwent retreatment with KTE-X19, the AEs occurring during the retreatment period are not included.
a, four patients had Grade 5 acute lymphocytic leukaemia, and six patients had other Grade 5 AEs.
Source: Shah et al., 2021; ZUMA-3 clinical study report Table 14.3.3.1.1. (42,56).

A summary of AEs related to KTE-X19 that occurred in ≥ 10% of subjects in Phase 2 is provided in Table 31. The most common KTE-X19-related AEs of any grade were [redacted], [redacted], and [redacted]. The most common KTE-X19-related AEs that were worst Grade 3 or higher were [redacted], [redacted], and [redacted].

Table 31: Subject incidence of KTE-X19-related AEs occurring in ≥ 10% of subjects by preferred term and worst grade (Phase 2, safety analysis set)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Data cutoff date = 09/09/2020.
Key: AE, adverse event; Medical Dictionary for Regulatory Activities.
Notes: AEs that occurred during retreatment period are not included. Preferred terms are sorted in descending order of total frequency in the 'Any' column. AEs are coded using MedDRA version 23.0 and graded using the Common Terminology Criteriafor Adverse Events version 4.03. Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.
Source: ZUMA-3 clinical study report Table 50 (56).

The most common SAEs at Phase 2 were hypotension ([redacted]), pyrexia ([redacted]) and hypoxia ([redacted]). The most common worst Grade 3 or higher SAEs were hypotension ([redacted]), hypoxia ([redacted]) and pyrexia ([redacted]) (Table 32).

Table 32: Subject incidence of SAEs occurring in ≥ 2 patients by preferred term and worst grade (Phase 2, safety analysis set)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any serious TEAE	41 (75)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted])
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acute lymphocytic leukaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seizure	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemophagocytic lymphohistiocytosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Paraparesis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TEAE, treatment emergent adverse event.
Notes: Preferred terms are sorted in descending order of total frequency in the 'Any' column. Adverse events are coded using MedDRA version 23.0 and graded using CTCAE 4.03. Multiple incidences of the same AE in one patient are counted once at the highest grade for that patient. TEAEs include all AEs with an onset on or after initiation of the KTE-X19 infusion. For patients who underwent retreatment with KTE-X19, the AEs occurring during the retreatment period are not included. The safety analysis set compromises 55 patients.
Source: ZUMA-3 clinical study report Table 14.3.4.1.1. (56).

At Phase 2, [redacted] patients ([redacted]) had at least 1 SAE related to KTE-X19, the most frequently reported of which were [redacted], [redacted] and [redacted]. The most common worst Grade 3 or higher SAEs related to KTE-X19 were [redacted], [redacted] and [redacted] (Table 33)

Table 33: Subject incidence of KTE-X19-related SAEs occurring in ≥ 2 patients by preferred term and worst grade (Phase 2, safety analysis set)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Subjects with any KTE-X19-related serious AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cutoff date = 09/09/2020.
Key: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event.
Notes: AEs that occurred during retreatment period are not included. Preferred terms are sorted in descending order of total frequency in the 'Any' column. Adverse events are coded using MedDRA version 23.0 and graded using CTCAE 4.03. Multiple incidences of the same AE in one patient are counted once at the highest grade for that patient.
Source: ZUMA-3 clinical study report Table 14.3.13.1.1. (56).

B.2.10.5 Adverse events of special interest

Cytokine release syndrome

In the Phase 2 safety analysis set, 89% (49 of 55 subjects) had CRS, and 24% (13 of 55 subjects) had CRS that was worst Grade 3 or higher. No subject had Grade 5 CRS.

Of the 49 subjects with CRS, the most common CRS symptoms of any grade were pyrexia (46 subjects, 94%), hypotension (33 subjects, 67%), and sinus tachycardia (18 subjects, 37%). The most common worst Grade 3 or higher CRS symptoms were pyrexia (19 subjects, 39%), hypotension (16 subjects, 33%) and hypoxia (11 subjects, 22%) (42).

Among subjects who had CRS, the median time to onset was 5.0 days (range: [redacted]) after KTE-X19 infusion. As of the data cut off, CRS had resolved in 46 of 49 subjects. For the remaining 3 subjects, CRS was ongoing at the time of death due to progressed disease (PD) on Day 21 in 1 subject, brain herniation on Day 8 in 1 subject, and pneumonia on Day 15 in 1 subject.

For subjects whose CRS had resolved, the median duration of CRS was [redacted] days (range: [redacted]). Two subjects had CRS with a total duration [redacted]: 1 subject had CRS for [redacted] days with a prolonged CRS symptom of Grade 2 nonserious nausea for [redacted] days, and 1 subject had CRS for [redacted] days with a prolonged CRS symptom of Grade 1 nonserious increased C-reactive protein (CRP) for [redacted] days.

Neurological events

In Phase 2, 60% (33 of 55 subjects) had at least 1 neurologic AE of any grade, including 25% (14 of 55 subjects) with worst Grade 3 or higher neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation (42).

The most common neurologic AEs of any grade were tremor (15 subjects, 27%), confusional state (14 subjects, 25%), and encephalopathy (12 subjects, 22%) (42). The most common worst Grade 3 or higher neurologic AEs were [redacted], encephalopathy (4 subjects, 7%), and [redacted].

Among subjects who had neurologic AEs, the median time to onset was 9.0 days (range: [redacted] days) after KTE-X19 infusion. As of the data cutoff date, neurologic AEs had resolved in 29 of 33 subjects. Among the 29 subjects whose neurologic AEs had resolved, the median duration of neurologic AEs was [redacted] days (range: [redacted]).

The four subjects with unresolved neurologic AEs either at data cutoff date or time of death are described below:

- One subject had Grade 4 serious encephalopathy, Grade 3 nonserious agitation, and Grade 1 nonserious confusion, which all started on Day 5; Grade 4 cerebral oedema, which started on Day 6; and a fatal event of Grade 5 serious cerebral herniation on Day 8. All events were ongoing at the time of death and were deemed related to KTE-X19.
- One subject had Grade 3 serious paralysis of the lower extremity, which started on Day 10 and was ongoing at the time of death due to PD on Day 553. The event was deemed related to KTE-X19.
- One subject had Grade 3 serious paraparesis, which started on Day 9 and was ongoing at the time of death due to PD on Day 483. The event was deemed unrelated to KTE-X19.
- One subject had Grade 1 nonserious finger numbness, which started on Day 29 and was ongoing as of the data cutoff date. The event was deemed unrelated to KTE-X19.

Other AEs of interest:

- **Cytopenias:** 49% (27 of 55 subjects) had thrombocytopenia in Phase 2, including 44% (24 of 55 subjects) with worst Grade 3 or higher thrombocytopenia, 49% (27 of 55 subjects) had neutropenia, all of which were worst Grade 3 or higher, and 53% (29 of 55 subjects had anaemia at Phase 2, including 49% (27 of 55 subjects) with worst Grade 3 or higher anaemias.
- **Infections:** 40% (22 of 55 subjects) had infections in Phase 2, including 25% (14 of 55 subjects) with worst Grade 3 or higher infections.
- **Hypogammaglobulinaemia:** 7% (4 of 55 subjects) had hypogammaglobulinaemia in Phase 2, none of which was Grade 3 or higher

Tocilizumab was given to 80% (44 of 55 subjects), steroids were given to 75% (41 of 55 subjects) and vasopressors were given to 40% (22 of 55 subjects) (42).

B.2.10.6 Safety overview

The safety profile observed in ZUMA-3 is similar to that observed with other CAR T-cell therapies, and the risk management protocol for KTE-X19 is well established, typified by CRS and neurological events that are the most prominent toxicities of cellular immunotherapy. The safety profile of KTE-X19 in ZUMA-3 was generally similar to that observed in other indications, although a higher incidence of Grade 3 or higher CRS was observed. This was also the case for tisagenlecleucel, where CRS was more commonly observed in ALL compared to other indications (73).

ALL is clinically associated with cytopenias of 1 or more lineage, with cytopenias and infections among the most common AEs observed with SoC therapies. Across TOWER and INO-VATE, grade ≥ 3 neutropenia occurred in 38%-58% of subjects, with Grade 3 or higher infections occurring in 34% of subjects treated with blinatumomab and 52% treated with chemotherapy in TOWER (25,74). The rate of these identified risks in ZUMA-3 was therefore similar to those observed across different studies and treatment modalities, consistent with the underlying disease.

Notably, health-related quality of life (HRQoL) data presented in Section B.2.6.2 suggest no long-term impact on QoL, with results either stabilising or improving versus baseline from Day 28 to Month 12.

In addition, in a long-term analysis of patients treated at the pivotal dose level in Phase 1, no new safety signals were observed after the median follow-up time of 39.9 months, indicating favourable long-term safety in R/R B-precursor ALL (42).

Of the 55 subjects treated with KTE-X19 at Phase 2 in ZUMA-3, there were 2 deaths considered related to treatment. This compares favourably with SCT, where treatment-related mortality rates of 20-40% are typically observed, even with reduced-intensity conditioning (75,76).

Since the approval of tisagenlecleucel, axicabtagene ciloleucel, and KTE-X19 (in mantle cell lymphoma) through the Cancer Drugs Fund (CDF) in NHS England,

clinicians are increasingly experienced and familiar with toxicity management for CAR T-cell therapy in UK clinical practice. Real-world data of CD19 CAR T-cell therapy - albeit in high-grade lymphoma – in England showed lower rates of Grade ≥ 3 CRS or neurological events, with increased use of tocilizumab and steroids compared to pivotal trials (77). When taken in the context of the growing familiarity and knowledge of the CAR T-cell safety profile, as well as better patient selection and overall management, we may therefore expect a similar translation of ZUMA-3 safety data into clinical practice.

As recommended in the draft SmPC for KTE-X19, patients should be monitored daily for the first 10 days following infusion of KTE-X19 for signs and symptoms of potential CRS, neurological events, and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurological events; after the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Patient should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

B.2.11 Ongoing studies

ZUMA-3 is ongoing and will provide additional evidence of KTE-X19 for the treatment of adults with r/r ALL. Patients will be followed up to 15 years after the last patient received KTE-X19. On this basis, the final study completion date is estimated to be September 2035.

Preliminary results from the most recent analysis with data cut-off 23/07/21 provides longer-term data on the durability of all patients treated with KTE-X19 at target dose. Whilst more detail will be made available through the evaluation process, key results are presented in Section B.2.6. The CSR for this data cutoff is expected to be available in January 2022.

B.2.12 Innovation

KTE-X19 is a personalised medicine in which the patient's own T cells are collected and engineered *ex-vivo* to express a chimeric antigen receptor which programmes them to target and kill the cancer cells when they are returned to the patient in a

single infusion. The production of KTE-X19 includes a specific step designed to remove tumour cells from the leukapheresis harvest and enrich for mature T-cells. This is unique to the production of KTE-X19, distinguishing it from axicabtagene ciloleucel.

KTE-X19 represents a breakthrough treatment in the R/R adult ALL setting. Whilst SCT offers a potentially curative treatment option with 5-year OS rates of 23% in R/R ALL, a significant portion of R/R adult ALL patients relapse post-SCT, are ineligible for SCT, or are unlikely to achieve a CR required for SCT (9). As discussed in Section B.1.3.4.3, in the absence of consolidation with SCT, current treatment options are life-extending but not curative and are associated with OS of 4-8 months. Demonstrating an unprecedented median OS estimate of [redacted] months at latest data cutoff, with [redacted] and [redacted] of subjects estimated to be alive at 12 and 18 months respectively, and OS appearing independent of subsequent SCT, KTE-X19 represents a significant advancement for this patient population. The hope KTE-X19 could offer to patients, carers and healthcare professionals should not be undervalued.

Collectively, the outcomes achieved with current treatments (see section B.1.3.5) highlight the need for additional therapies such as KTE-X19 that can induce deeper and more durable responses and potentially achieve long-term survival in adult patients with R/R B-ALL, particularly in patients who have relapsed post-SCT or are ineligible for SCT, or those with particularly poor prognostic indicators that mean they are unlikely to achieve SCT, such as primary refractory disease or first relapse within 12 months. In these patient populations, KTE-X19 represents a paradigm shift as a potentially curative treatment option.

While the main health-related benefits will have been captured in the QALYs for KTE-X19, it is difficult to capture true innovation in such a calculation, and the significant difference this treatment choice could make to patients, carers and healthcare services is such that KTE-X19 access would represent a step change in management of R/R adult ALL.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Principal findings from the clinical evidence

The efficacy and safety of KTE-X19 in the treatment of adults with B-precursor R/R ALL has been demonstrated in the open-label, multi-centre, ZUMA-3 trial.

The ZUMA-3 Phase 1 + 2 combined population represents an adult R/R ALL group with an especially poor prognosis, including almost half ([redacted]) with prior blinatumomab treatment, and a similar proportion receiving ≥3 prior treatments at baseline ([redacted]) (Table 8). In addition, [redacted] had relapsed post-SCT, a group with a particularly dire outlook, where median OS is 5.5 months (see Section B.1.3.5) (43).

Among all patients to receive KTE-X19 at target dose, almost three-quarters of subjects (74.4%) achieved an OCR, including 62.8% who achieved CR.

Additionally, 79.5% (62 of 78 subjects) had no detectable cancer cells remaining as demonstrated by MRD negativity, including all but one patient – for whom data was not available – to achieve CR/CRi. The survival advantage of achieving MRD negativity in both adults and children has been demonstrated in a previous 39-study meta-analysis (albeit following induction therapy), and was further re-enforced by long term blinatumomab data (65,66). The KM median DOR for the 58 subjects who achieved CR or CRi was [redacted] months.

At the time of primary data cut-off, providing a median actual follow-up of [redacted] months for all treated subjects, [redacted] of subjects were known to be alive. KM estimates of OS at 12 and 18 months were [redacted] and [redacted], respectively. This OS is unprecedented in the adult R/R ALL population, particularly in the context of the heavily pre-treated population recruited to ZUMA-3, with currently approved treatments demonstrating median OS of 4-8 months in pivotal trials (25,26).

B.2.13.2 Strengths and limitations of the evidence base

The autologous cellular therapy nature of KTE-X19 necessitates open-label treatment.

The response rates achieved in ZUMA-3 compare favourably to those observed with currently available treatment options for adults with R/R ALL. In a meta-analysis of OCR rate using the ZUMA-3 Phase 2 mITT dataset, only the Phase 3 TOWER study, which compared blinatumomab to SoC chemotherapy, used the same stringent haematologic recovery criteria for OCR as used in ZUMA-3 (78). The pooled estimates of OCR rate in the TOWER study was 32%. By contrast, ZUMA-3 demonstrated an OCR rate of 70.9% in the mITT analysis set. Furthermore, a further meta-analysis of 12 studies focusing on CR yielded a pooled CR rate of 30%, compared to the 56.4% rate observed in ZUMA-3. Additionally median OS in ZUMA-3 Phase 2 mITT (18.2 months) compared favourably to the pooled estimate for SoC (6.9 months) (78).

It should also be noted that almost all of the studies included in the 12-study meta-analysis enrolled subjects who were naïve to blinatumomab and inotuzumab. Outcomes in the setting of blinatumomab or inotuzumab failure have not been well studied to date, although limited reports indicate that once patients fail blinatumomab, responses to subsequent lines of therapy deteriorate, leaving patients with very limited options (59,60). In the ZUMA-3 study, the OCR rate in subjects even after prior blinatumomab treatment (accounting for nearly half of those in the Phase 1 + 2 combined dataset [[redacted] of 78 subjects]) remained high at [redacted]. For the [redacted] of 78 subjects with prior inotuzumab, the OCR rate was [redacted] (Figure 63).

In addition to the observed survival benefits, results of the EQ-5D-5L and VAS suggest that long-term HRQoL is not negatively impacted by KTE-X19 therapy.

Given the high CR rate and magnitude of improvements in DOR, OS, and RFS observed with KTE-X19 when compared with currently available treatments, as well as the high unmet need in this patient population, including elderly patients, KTE-X19 represents an important new therapeutic option for patients with R/R B-ALL. Overall, the results of ZUMA-3 demonstrate a clinically meaningful benefit over currently available therapies and a positive benefit-risk profile of KTE-X19 for the treatment of R/R B-ALL.

To address the evidence gap regarding long-term benefit, a series of survival scenarios have been modelled within the cost-effectiveness analyses presented in

section B.3. Kite, a Gilead Company, are also open to KTE-X19 being a CDF candidate to facilitate timely patient access alongside longer-term data collection.

B.2.13.3 Applicability of clinical evidence to practice

B.2.13.3.1 Patient characteristics

The combined Phase 1 + 2 population of ZUMA-3 represents a heavily pre-treated patient group, with [redacted] having received ≥3 prior treatments at baseline. Subjects had failed a range of standard treatment options, including allo-SCT ([redacted]), blinatumomab ([redacted]), and inotuzumab ([redacted]). NICE guidelines recommend the latter two targeted therapies for the treatment of Ph- R/R adult ALL, and R/R adult ALL, respectively. Blinatumomab is also recommended for Ph- R/R adult ALL patients who achieve remission with MRD+ (>0.1%) if the disease is in first remission. These recommendations combined with clinical feedback inform us that these two therapies are SoC for R/R adult ALL, and therefore prior use in ZUMA-3 can be considered representative of UK clinical practice (35). In addition, [redacted] of subjects enrolled in ZUMA-3 Phase 2 were Ph+, consistent with the 22% Ph+ in UK R/R clinical practice (9).

Whilst the population enrolled to ZUMA-3 was heterogeneous, this is representative of the R/R adult ALL population, which is heterogeneous in nature. Although ZUMA-3 did not include any UK sites, there were study sites in France, Germany, and the Netherlands, where treatment and management of R/R adult ALL is likely to be influenced by ESMO guidelines (see Section B.1.3.4.1).

Based on feedback received from clinical experts, we understand that KTE-X19 would be positioned for patients who have relapsed post-SCT, are ineligible for SCT, or unlikely to be able to achieve an SCT via current SoC (35). It is noteworthy that 100% of those treated in ZUMA-3 meet this positioning criteria. The patient characteristics at baseline can therefore be considered generalisable to those who are likely to receive KTE-X19 in clinical practice.

It should also be acknowledged that 14 of 78 subjects (17.9%) with a KTE-X19 induced-remission received a subsequent allo-SCT; 9 subjects had achieved CR, 3 subjects had achieved a CRi. In addition, 1 subject had achieved CRi by investigator

assessment but BFBM per central assessment, while a further subject with extramedullary disease had achieved partial remission (PR). We understand that consolidating CAR T-cell induced remission with an allo-SCT is not considered an appropriate option in the UK (35). If a patient suffers a relapse following KTE-X19 treatment, a subsequent allo-SCT may theoretically be an option, but clinical expert opinion suggests that the number of people who would be candidates for a subsequent allo-SCT at this stage would be negligible (35,79).

Of note is that 13 of the 14 of the subjects that received an allo-SCT in ZUMA-3 had not received a prior allo-SCT at baseline. In the anticipated positioning of KTE-X19 in the high unmet need population who have relapsed post-SCT or are ineligible/unlikely to achieve SCT, all patients will have either had prior SCT, or be ineligible. Based on clinical feedback, we understand that a second allo-SCT is not considered a viable treatment approach in the UK, even though it is permitted in certain cases (35). KTE-X19 can therefore be considered a standalone treatment option.

Notably, the median OS at the most recent data cutoff for the Phase 1+2 combined dataset was comparable when subjects were censored (main analysis) or were not censored (sensitivity analysis) at the time of allo-SCT, further supporting use of KTE-X19 as a standalone therapy (Figure 12) (Figure 22).

B.2.13.3.2 Analysis sets

In consideration of the most appropriate analysis set for decision making, the KTE-X19 Phase 1 + 2 combined dataset (N = 78) is presented and used in the subsequent cost-effectiveness analysis. This analysis set provides data on all subjects treated with KTE-X19 at the anticipated dose of the EU marketing authorisation and provides the longest follow-up on treated subjects. This analysis set provides data for all treated patients, irrespective of follow-up.

B.2.13.3.3 Service provision

The manufacturing process of KTE-X19 has a unique step whereby tumour cells are removed from the leukapheresis harvest prior to *ex-vivo* expansion of patient T-cells. This should help KTE-X19 manufacturing attempts to be successful first-time and

facilitate prompt delivery of KTE-X19 to the patient. This is particularly important with a rapidly progressing disease where being able to manufacture the CAR T product successfully during the first attempt is important for ensuring the patient receives therapy as promptly as possible. In June 2020, a European CAR T-cell manufacturing facility was approved for use by the EMA, with the objective of substantially reducing time from apheresis to Qualified Person release, while avoiding transatlantic transport, thus enabling a faster product manufacturing period for European patients. In ZUMA-3, KTE-X19 was successfully manufactured for 53 of 54 subjects at Phase 1, and 65 of 71 subjects at Phase 2. The median time between leukapheresis and KTE-X19 infusion was [redacted] days (range: [redacted] days) for patients in the US, and [redacted] days (range: [redacted] days) for patients in the EU. All KTE-X19 product administered within the ZUMA-3 trial was manufactured in the US; the manufacturing times are expected to reduce in the EU when the manufacturing facility in the Netherlands is able to manufacture KTE-X19, currently anticipated to be [redacted].

Importantly, KTE-X19 does not have additional or different infrastructure and personnel needs compared with other CAR T-cell therapies and therefore would fit into current service provisions for such treatment, already set up within NHS England.

B.2.13.3.4 End-of-life

KTE-X19 satisfies the criteria to be considered an effective end-of-life therapy. Previous pivotal trials in R/R adult ALL demonstrate a median OS with current SoC of 4-8 months (25,26). Taken in the context of a median OS of [redacted] months demonstrated for treated patients in ZUMA-3, KTE-X19 is expected to extend this life expectancy by far more than the requisite 3 months.

It should also be noted that blinatumomab, inotuzumab, and ponatinib were all considered to meet the criteria for end-of-life (80–82). KTE-X19 eligibility for end-of-life is presented in Table 34.

Table 34: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	*Clinical data* Current 'standard of care' median OS: 4-8 months Median OS inotuzumab: 5.3 months (INO-VATE) Median OS FLAG-IDA: 5.3 months (INO-VATE/TOWER) Median OS blinatumomab: 6.9 months (SCHOLAR-3) Median OS ponatinib: 7.3 months (PACE)	Section B.1.3.2, Page 21 Appendix J Table 110
	Economic model output Median OS inotuzumab: 5.3 months Median OS FLAG-IDA: 5.3 months Median OS blinatumomab: 7.6 months Median OS ponatinib: 7.4 months	Appendix J Table 110
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 (July 2021 data cut, ZUMA-3 mITT Phase 1 and Phase 2 combined)	Appendix J Table 110
	Economic model output Median OS KTE-X19: 18.4 months	Appendix J Table 110

Key: ITT, intention-to-treat; OS, overall survival
Note that the clinical data refers to patients that receive KTE-X19 infusion in ZUMA-3 only, while the model output accounts for the survival of patients that did not receive KTE-X19 infusion

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify economic evidence within the relapsed/refractory B-precursor ALL indication (adult population patients of ≥18 years) to inform a health-economic model. A detailed description of the methods underpinning the SLR is provided in Appendix G. Following full text screening, 14 economic evaluation studies were identified from the SLR.

Two of the studies presented economic evaluations based on TOWER, a randomized, open-label, phase III clinical trial which compared blinatumomab with standard of care chemotherapy in adult patients with relapsed/refractory ALL. Four studies were economic evaluations based on INO-VATE, a randomized, open-label, phase III clinical trial in which inotuzumab ozogamicin was compared to investigator's choice of chemotherapy regimen in adult patients with relapsed/refractory CD22-positive ALL. Furthermore, 3 studies based their economic evaluations on both the TOWER and the INO-VATE trials. One study was based on the ALCANTARA study, which was a Phase 2 study of blinatumomab in adult subjects with relapsed/refractory Ph+ B-precursor ALL (83). The remaining publications did not provide information regarding whether the evaluations utilised outcomes from clinical trials. A summary of the identified studies is provided in Table 35.

Table 35: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
TOWER (NCT02013167)						
Delea (84)	2017	A partitioned survival model was used to estimate the cost-effectiveness of blinatumomab vs SoC. Compared with SoC, blinatumomab is a cost-effective treatment option for adults with R/R Ph- B-precursor ALL from the US healthcare perspective at an ICER threshold of $150,000 per QALY gained.	Adults with R/R Ph-B-precursor ALL. Mean age of 40.9 years.	BLN: 3.82 SC: 2.18	BLN: US$ 395,094 SC: US$ 214,452	US$ 110,108/ QALY
Severin (85)	2018	Abstract presenting a cost-effectiveness model comparing blina vs. salvage SoC chemotherapy for the treatment of adult patients with Ph- R/R B-precursor ALL. A partitioned-survival model was used to compare long-term survival outcomes.	Adult patients with Ph- R/R B-precursor ALL. Mean age not reported.	QALYs early treatment (first salvage therapy) BLN: 6.48 SoC: 3.12 QALYs late treatment (subsequent salvage therapy) BLN: 4.43 SC: 2.55	N/R	N/R

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
INO-VATE (NCT01564784)						
Batteson (84)	2017	Abstract presenting a UK-based Markov model estimating the mean life year (LY) and QALY gains associated with ino compared to investigators choice (IC) of therapy. InO was shown to increase survival and QALYs compared to IC demonstrating it to be an effective treatment for r/r B-ALL.	Patients with r/r B-ALL. Mean age not reported.	QALYs InO vs. IC: 2.23 QALYs	N/R	N/R
Chen (84)	2018	Abstract presenting a Markov model comparing InO vs. SoC for the treatment of R/R ALL from a U.S. Medicare perspective. The base-case analysis accounted for drug wastage.	Patients with R/R ALL. Mean age not reported.	N/R	N/R	US$ 190,829 per QALY
Silva-Miguel (86)	2020	Abstract presenting a Markov model comparing InO vs. SoC for the treatment of relapsed or refractory CD22-positive B cell precursor ALL in Portugal. InO allows relevant health gains when compared to SoC, in the Portuguese setting. Most gains are due to patients undergoing HSCT after achieving complete response with InO.	Patients with relapsed or refractory CD22-positive B cell precursor ALL with no previous allogeneic hematopoietic stem cell transplantation (HSCT). Mean age not reported.	QALY gain of 2.89 QALYs with Ino compared to SoC. Total QALYs per arm NR.	NR	NR
van Oostrum (87)	2017	Abstract presenting a Markov model comparing InO vs. SoC chemotherapy for the treatment of R/R ALL. InO offers considerable QoL gains compared to SoC, mainly driven by long-term gains of SCT.	Patients with R/R ALL. Mean age not reported.	QALYs: InO: 2.48 SC: 0.67	N/R	N/R
TOWER & INO-VATE						

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Delea (84)	2018	Abstract presenting a cost-effectiveness model of blinatumomab vs. inotuzumab from the US payer perspective. The analysis comprised a partitioned survival model with outcomes based on published summary data from INO-VATE and patient-level data from TOWER adjusted to match patient characteristics in INO-VATE using MAIC. Blinatumomab was cost-effective vs. inotuzumab.	Adult patients with R/R ALL with zero or one prior salvage therapy. Mean age not reported.	N/R	N/R	1) US$ 14,341/ QALY* 2) US$ 49,131/ QALY* 3) US$ 24,952/ QALY*
Delea (84)	2018	Abstract presenting a cost-effectiveness model of blinatumomab vs. inotuzumab from the US payer perspective. The analysis comprised a partitioned survival model with outcomes based on published summary data from INO-VATE and patient-level data from TOWER adjusted to match patient characteristics in INO-VATE using MAIC. In all analyses, BLIN was more costly and more effective than INO.	Adult patients with R/R ALL with no more than one prior salvage therapy	N/R	N/R	1) US$ 16,814** 2) US$ 57,310** 3) US$ 17,095**

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Delea (88)	2019	Study comparing the cost effectiveness of Blina versus InO in R/R B-cell precursor ALL patients with one or no prior salvage therapy from a United States (US) payer perspective using a partitioned survival model. Blinatumomab was estimated to be cost effective versus InO in R/R B-cell precursor ALL adults who have received one or no prior salvage therapy.	Adults with R/R B-cell precursor ALL. Mean age of 45.9 years	InO: 2.86 Blina: 4.61	InO: 409,128 (US$) Blina: 445,372 US$	20,737 per QALY (US$)
ALCANTARA (NCT02000427)						
Delea (89)	2020	Abstract presenting the cost-effectiveness of blinatumomab vs. chemotherapy in patients with minimal residual disease (MRD) from a US payer perspective. Analysis comprised a combined decision-tree and Markov cohort model.	Patients with MRD. Mean age not reported.	Incremental QALYs for Blina vs. chemotherapy: 2.05	Incremental costs for Blina vs. chemotherapy: $242,940	$118,507 per QALY
Source of clinical outcomes unknown						

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Djambazov (90)	2018	Abstract presenting a Markov model to evaluate the cost-effectiveness of inotuzumab ozogamicin vs. blinatumomab in the treatment of adult patients with relapsed or refractory B-cell precursor ALL. From the Bulgarian payer perspective, InO is a cost-effective option in the treatment of ALL as it dominates blinatumomab.	Adult patients with relapsed or refractory B-cell precursor ALL. Mean age not reported.	N/R	InO: BGN 221,107 Blina: BGN 223,566	N/R as inotuzumab dominates blinatumomab
Lee (91)	2019	Abstract presenting a cost-utility analysis of inotuzumab ozogamicin versus standard chemotherapy for adults with relapsed or refractory B-cell ALL from the payer perspective in Taiwan. The presented Markov model estimated that treatment with inotuzumab is more costly but also more effective compared to standard chemotherapy.	312 relapsed or refractory B-cell ALL patients. Mean age of 52 years	QALYs: InO: 2.25 SC: 0.84	InO: US$ 176,79 SC: US$ 69,496	US$ 76,004 per QALY

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Kolbin (92)	2019	Abstract presenting a cost minimisation and budget impact analysis comparing InO, Blina and HDC for the treatment of patients with refractory or relapsed forms of B-cell ALL. Compared with Blina, the use of InO in case of relapsed or refractory ALL is economically viable in the context of CMA and a preferred medical technology from the BIA perspective.	NR	NR	In the CMA, costs per patient for therapy with InO compared to Blina with a modeling horizon of 18 months amounted to €69,499, indicating a 38.4% reduction in direct costs.	NR
van Oostrum (93)	2020	Abstract presenting a budget impact analysis (BIA) of inotozumab ozogamicin (InO) for the treatment of adults with relapsed or refractoru B-cell precursor ALL in the Netherlands. Comparators in the BIA were blinatumomab (Blina) and standard of care chemotherapy with FLAG-IDA. Blina was associated with the highest annual costs.	NR	NR	Assuming equal market shares for all 3 comparators, annual costs are: Blina: €1.83 million InO: €1.77 million FLAG-IDA: €1.03 million	NR

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

*Three separate analyses were conducted: (1) InO OS obtained by applying the anchored MAIC-adjusted hazard ratio (HR) for InO vs. blinatumomab (1.40, 95%CI 0.87-2.24) to blinatumomab MAIC-adjusted TOWER OS (Gompertz distribution); (2) InO and SoC OS based on Weibull mixture cure distribution fit to INO-VATE-ALL OS; blinatumomab OS obtained by applying MAIC-adjusted HR for blinatumomab vs. SoC (0.55, 95%CI 0.38-0.80) to INO-VATE-ALL SoC OS; and (3) unanchored comparison of MAIC-adjusted Weibull mixture cure fit to blinatumomab OS from TOWER and InO OS from INO-VATE-ALL.

** Three analyses were conducted based on alternative approach for the MAIC (anchored through standard of care [SoC] vs unanchored), proportional hazards (PH) assumptions, and reference overall survival (OS) distributions. Complete remission rates, utilities, duration of therapy, and use of subsequent therapies also were MAIC-adjusted.

B.3.2 Economic analysis

None of the identified cost-effectiveness studies addressed the decision problem. A *de novo* cost-effectiveness model was thus developed for the economic analysis. The model structure was informed by the previous NICE appraisals of CAR T-cell therapies in diffuse large B-cell lymphoma (DLBCL) (94) and in R/R mantle cell lymphoma (MCL) (95) (TA559 and TA677).

B.3.2.1 Patient population

The patient population considered in the analysis is adults (≥18 years old) with relapsed or refractory (R/R) B-precursor ALL for whom SCT is not indicated. This is in line with the anticipated market authorisation for KTE-X19 in R/R B-cell ALL and the pivotal trial evaluating KTE-X19 in R/R B-cell ALL: ZUMA-3 (41,42). This population is considered generalisable to the anticipated positioning of KTE-X19 in the UK according to clinical expert opinion (see section B.1.3.4.4):

- Relapsed post SCT
- Ineligible for SCT (on the basis of age, frailty or other exclusion criteria)
- Unlikely to achieve SCT via existing bridging therapies (primary refractory, relapsed within 12 months, failed ≥2 lines of prior therapy)

The economic analysis was performed for three different patient populations:

- overall population (mITT population of ZUMA-3)
- Ph- population
- Ph+ population

All three populations are considered to be of clinical relevance to decision makers in the R/R ALL treatment landscape since the comparator regimens differ based on Ph expression. The ZUMA-3 trial was not powered to detect outcome differences by Ph status. However, unlike with some targeted therapies (TKIs), clinical experts did not expect the effectiveness of KTE-X19 to differ based on the Ph status of the patients.

B.3.2.2 Model structure

The cost-effectiveness model was built as a three-state partitioned survival model (Figure 33). The partitioned survival model comprises three mutually exclusive health states: EFS, PD, and death.

All patients enter the model in the EFS state. Patients who achieve CR or CRi remain in the EFS state, while those who do not achieve CR or who relapse or progress transition to the PD state. From the EFS health state, patients can transition to either the PD or death health state. Following progression, patients can only transition to the death state, an absorbing health state. The model uses a weekly cycle length. As is common in partitioned survival models, transitions across health states were not explicitly modelled. The health state occupancy at each model cycle was determined from the cumulative survival probabilities derived from independently modelled EFS and OS curves, for both the intervention and comparators:

- The EFS curve enabled the modelling of patients in the EFS health state at each cycle (patients' event-free and alive)
- The proportion of patients occupying the PD health state at each cycle was estimated by subtracting the proportion of patients that were event-free and alive (EFS curve) from the proportion of patients alive (OS curve)
- Patients occupying the death state at each cycle were estimated by subtracting the proportion of patients alive (OS curve) from the total cohort.

The partitioned survival model structure reflects the clinical pathway of the disease; once patients progress, they cannot return to the EFS health state.

In the partitioned survival model, patients alive at 3 years are assumed to be 'cured' and are thus considered to be long-term survivors. This assumption is applied for both KTE-X19 and the comparators.

The possibility of achieving cure is an accepted outcome in ALL, usually following allo-SCT (96) and has been accepted as an outcome following CAR T-cell therapy in other indications appraised by NICE (94), (97), (95). The factors contributing to defining it are mainly centered on deep and durable eradication of cancer cells linked with prolonged survival. Although there were various discussions on the time of cure and the estimated cure fraction in the technology appraisals for blinatumomab (NICE TA450) and tisagenlecleucel (NICE TA554) (79,80), the committees were in favour of the assumption that patients who survive beyond 2 to 5 years are effectively cured. Figure 16 (2020 September data cut, see section B.2.6.1.2) shows that KTE-X19 was associated with a survival plateau where no death events were reported for a period of 25 months among patients remaining in the study (mITT, Phase 1 and Phase 2 combined). The latest ZUMA-3 data cut (2021 July, too recent to be incorporated into the model) demonstrates that around 40% of the ZUMA-3 mITT Phase 1 and Phase 2 combined population is alive from 3 years (see section B.2.6.1.1, Figure 11). This indicates that among patients achieving a response, a proportion of R/R B-cell ALL patients may achieve long-term remission following treatment with KTE-X19. Furthermore, clinical experts were supportive that KTE-X19 could be positioned as a potentially curative, standalone therapy in R/R ALL (35).

In previous NICE appraisals of CAR T-cell therapies in diffuse large B-cell lymphoma (DLBCL) and in R/R mantle cell lymphoma (MCL) (TA559, TA567, and TA677) (94), (97), (95), it was assumed that cured patients, albeit having heightened risk of death versus the age-equivalent general population, incur lower resource use and have improved HRQoL compared to non-cured patients. Similarly in the current analysis, patients assumed to be cured (those alive beyond the 3-year time-point) incur an increased risk of death (excess mortality) compared to the general population. A standardised mortality ratio (SMR) of 1.09 was applied to the background mortality (section B.3.3.3). The SMR of 1.09 has been sourced from a study in DLBCL, Maurer et al., 2014 (98), which was used by the company in the most recent NICE appraisal for KTE-X19 in mantle cell lymphoma (TA677) and was the ERG's preferred SMR in TA567 (Tisagenlecleucel in R/R DLBCL). Although no long-term data are available that compare outcomes post allo-SCT in R/R DLBCL vs. those in R/R ALL, short-term outcomes (up to 2 years) on current SoC for DLBCL are very

similar to those observed in the blinatumomab and inotuzumab R/R ALL clinical studies (99) (Table 110). Furthermore, a recent study from Australia and New Zealand (Kliman et al. 2020) showed that recipients of allo-SCT who survived to at least 2 years and were disease-free continued to experience long-term outcomes close to the general population (100). Survival ratios ranged from 96% to 99% of the age matched population per year (lowest CI above 94%) (100). 25% of the cohort included in the Kilman et al., 2020 study had a diagnosis of ALL (100).

Patients alive at the 3-year time-point in the partitioned survival model then incur general population utility. With the current ZUMA-3 data cut, RFS (used as a proxy for EFS, see section B.3.3.2.1) modelled curves appear to plateau at 20-25% whereas the OS curves suggest a plateau around 40%. This would result in a proportion of patients in the PD health state being alive for a long time which is not compatible with the pathology. This is because the way RFS KM are derived does not allow for robustly informative extrapolation:

- The curves start from lower probability of survival (excluding the non-responders, looking at RFS curves for only CR/CRi patients the RFS at 2-3 year is more aligned to the plateau seen for OS (~35-40%)
- There is also a high level of censoring 40% consisting mainly of patients in ongoing remission (15%) and patients who received a subsequent allo-SCT (18%), representing a proportion without progression of 33% again much more aligned with the OS plateau ~40%.

This assumption is applied for both intervention and comparators as it is not a ZUMA-3 specific issue but is seen also in other studies:

- The INO-VATE modelled OS curve plateau around 16% at 3 years, while the EFS modelled curve plateau around 8% at 3 years
- The SCHOLAR-3 SCA-3 modelled OS curve plateau at 11% at 3 years, while the EFS modelled curve plateau at 0% at 3 years.

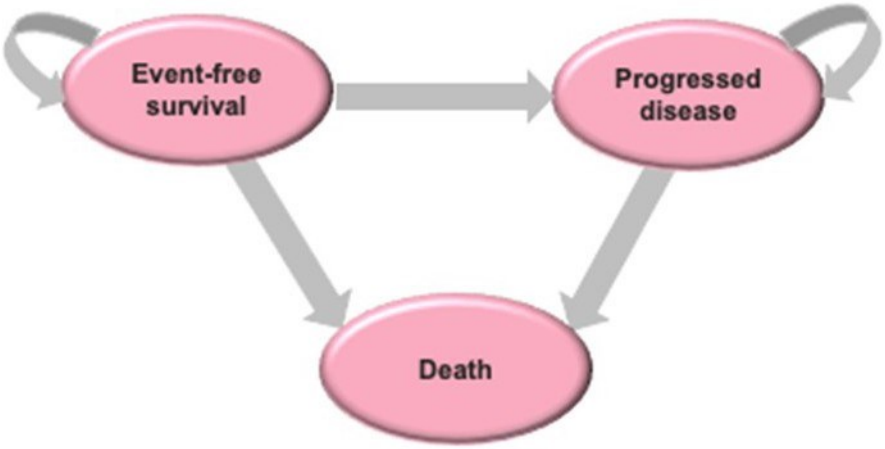
The structure and the health states are in line with the primary objectives of the treatment in R/R ALL: avoiding disease progression, avoiding worsening in quality of

life and extending survival. In addition, this model structure is in line with previous technology appraisals submitted to NICE in R/R B-cell ALL (79,80).

While the survival impact of allo-SCT is not explicitly considered in the model structure (as no SCT-related health state is included), the impact of allo-SCT from a costing and quality of life perspective is accounted for. For each treatment in the model, the impact of allo-SCT is accounted for upfront by weighting the cost and utility impact associated with subsequent allo-SCT by the reported proportion of patients receiving allo-SCT, as observed in the different studies (TOWER, INO-VATE, PACE). Although 14 patients received SCT in the ZUMA-3 mITT Phase 1 and Phase 2 combined trial (14/78=17.9%), no KTE-X19 patients are assumed to receive allo-SCT in the model. KTE-X19 expected positioning is for patients who have either relapsed following SCT or are considered unlikely to be able to achieve an SCT. According to UK clinical experts, no patients would receive a second allo-SCT and allo-SCT is not expected to be given as consolidation following a CAR T-cell therapy (see section B.3.5.3.1). Sensitivity analyses which censored patients who had received an SCT in ZUMA-3 showed no difference in survival outcomes in both the earlier and later data cut (Figure 22).

In the *de novo* model, for the patients in the KTE-X19 arm who underwent leukapheresis but did not go on to receive KTE-X19 infusion in ZUMA-3, rather than modelling this as an initial decision tree, this was instead accounted for by using cost multipliers. This is consistent with the approach used in TA559 and in TA677.

Figure 33: Partitioned survival model structure



B.3.2.2.1 Features of the de novo analysis

The analysis was conducted from the perspective of the NHS and personal social services (PSS) in England. The base-case analysis thus considered only direct healthcare costs, whilst broader societal costs were explored in a scenario analysis. The model spans a lifetime horizon. Given that the mean age of the patients at the start of the analysis was 43 years, a time horizon of 57 years was deemed sufficient to align with the maximum life expectancy of patients. A 20-year time horizon was explored in scenario analysis. Costs and outcomes were discounted at an annual rate of 3.5%, in line with the NICE reference case (101). Different discount rates were explored in the scenario analysis given that KTE-X19 has the potential to restore patients with a short life expectancy to near-full health over an extended period.

A summary of the key features of *de novo* economic analysis and their justification is provided in Table 36. A comparison is provided with the features of previous appraisals in R/R ALL including both adult and paediatric populations.

Table 36: Features of the economic analysis

	Previous appraisals				Current appraisal	
Feature	**TA450 Blinatumomab**	**TA541 Inotuzumab ozogamicin**	**TA451 Ponatinib**	**TA554 Tisagenlecleucel**	**Chosen values**	**Justification**
Time horizon	50 years (lifetime horizon)	60 years (lifetime horizon)	47 years (lifetime)	88 years (lifetime horizon)	57 years (lifetime horizon)	Long enough to reflect differences in costs and outcomes between the technologies being compared, in line with the reference case (101) The time horizon has been chosen considering the cohort mean age of 43 years at baseline.
Treatment waning effect?	Not applied	Not applied	Not applied	Not applied	Not applied	Lack of data to support a treatment waning effect.
Source of utilities	Mapped from EORTC QLQ-C30 data collected in the TOWER study	INO-VATE 1022 study for the no CR/CRi and no HSCT health state and the CR/CRi and no HSCT state. For the HSCT and post-HSCT state time-dependent utilities were based on Kurosawa et al. 2015 (102). Utility for progressed disease was sourced from Aristides et al. 2015 (103).	The company assumed that utilities for BP-CML reported in Szabo et al. (104)	Kelly et al (2015) (105) study where existing mapping functions were applied to convert generic quality-of-life measures (SF-36 and CHRIs) to preference-based utility estimates (iHUI2 and EQ-5D).	EQ-5D values collected prospectively in the ZUMA-3 study. For the comparator arms.	The cost-effectiveness model has been supplemented with data from ZUMA-3 as this is the key clinical study of KTE-X19. EQ-5D data from ZUMA-3 is thus the most appropriate source for utilities as it is in the population of interest and does not require mapping or any other conversion.

Source of costs			An expert survey was conducted to provide relevant and up-to-date healthcare resource use estimates. Costs were sourced from NHS Reference Costs 2014 to 2015 for monitoring and follow-up, with the exception of palliative care costs, which were sourced from Marie Curie Cancer Care.		Electronic market information tool (eMIT) (106), NHS Reference costs 2019/20 (107), PSSRU 2020 (108), TA554.	Generic drug costs were sourced from eMIT. All other cost inputs were sourced from NHS reference costs, PSSRU unit costs and the literature. Where possible, costs were obtained from UK national resources to reflect the UK NHS/PSS perspective. HRU frequency was based on TA554 as it was felt that given the similar patient populations and that the model in the present submission is aligned with TA554, this was the most appropriate source of HRU.

Key: TA, technical appraisal

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention: KTE-X19

KTE-X19 is a single-infusion product, for autologous and intravenous use only, administered at a target dose of 1 x 10^6 anti-CD19 CAR T-cells/kg. Prior to infusion, patients are treated with a nonmyeloablative conditioning regimen consisting of fludarabine 25 mg/m^2/day administered intravenously (IV) for 3 days starting 4 days before planned infusion and cyclophosphamide 900 mg/m^2/day administered intravenously (IV) for 1 day 2 days before planned infusion. Bridging chemotherapy (administered after leukapheresis and before conditioning chemotherapy) is recommended for all patients, particularly those with high disease burden at baseline.

The dosing for both the pre-infusion conditioning chemotherapy and KTE-X19 is based on the doses used in ZUMA-3 Phase 1 and Phase 2 combined.

B.3.2.3.2 Comparators

The comparators considered in the cost-effectiveness model represent the current SoC for patients with R/R ALL in the UK. The comparators align with the most recent (July 2021) NICE pathway for treating relapsed or refractory acute lymphoblastic leukaemia (29), clinical expert opinion and the final NICE scope for KTE-X19. The comparator technologies were differentiated for the 3 different patient populations:

- **Overall population (irrespective of Ph expression):** inotuzumab ozogamicin and FLAG-IDA
- **Ph- population:** blinatumomab, inotuzumab ozogamicin, and FLAG-IDA
- **Ph+ population:** ponatinib, inotuzumab ozogamicin, and FLAG-IDA.

1 Inotuzumab ozogamicin

As per NICE TA541 (81), inotuzumab ozogamicin is recommended as an option for treating R/R CD22 positive B-cell precursor ALL in adults. Patients who have Ph+ disease should have received at least 1 tyrosine kinase inhibitor.

Inotuzumab dosing reflected in the model was in line with INO-VATE study (26). Inotuzumab is administered IV at a dose of 0.8 mg/m^2 on day 1, 0.5mg/m^2 on day 8 and day 15 in cycle 1 (21-day cycle). From cycle 2 onwards (28-day cycles) it is administered 0.8 mg/m^2 or 0.5 mg/m^2 on day 1, 0.5 mg/m^2 on day 8 and day 15. Treatment may continue up to 6 cycles. In the model it was assumed that patients on inotuzumab would receive on average 3 cycles of therapy, in line with the INO-VATE study results (the median number of cycles received in INO-VATE for inotuzumab patients was 3).

2 Blinatumomab

As per NICE TA450 (80), blinatumomab is recommended as an option for treating Ph- R/R B-cell ALL in adults. Blinatumomab dosing in the model was in line with the TOWER study (25). Blinatumomab is administered IV at a dose of 9 µg/day during week 1 of cycle 1 then 28 µg/day for the remainder of the cycle and during subsequent cycles (28-day cycles) followed by a treatment-free interval of 2 weeks. In the model, it was assumed that patients on blinatumomab would receive on average 1.45 cycles, in line with Von Stackelberg et al. (2016) and TA554 (79,109).

3 Ponatinib

As per NICE TA451, ponatinib is recommended as an option for treating Ph+ R/R ALL when either:

- the disease is resistant to dasatinib
- the subject is intolerant to dasatinib (or)
- when a T315I gene mutation is present.

Ponatinib dosing reflected in the model was in line with PACE study (110). Ponatinib is administered orally at a daily dose of 45 mg/day. In the model, it was assumed that patients on ponatinib would be treated until disease progression (the ponatinib EFS curve was used as proxy to reflect patients on treatment) or for a maximum of 3 months, in line with the ponatinib SmPC (111). Based on UK clinical expert opinion, ponatinib was assumed to be given in combination with chemotherapy. In the absence of clinical data to inform outcomes, this was accounted for within the costs

only. As no information regarding the precise regimen could be identified, we assumed the costs of FLAG-IDA in the economic model

4 FLAG-IDA

According to clinical expert opinion, FLAG-IDA is the most commonly used salvage chemotherapy regimen for treating adults with R/R B-cell ALL and this regimen was used as the basis for drug costs. The dosing of each FLAG-IDA therapy is provided below:

- Fludarabine: 30 mg/m^2 for 5 consecutive days per 28-day cycle
- Cytarabine: 2 g/m^2 for 6 consecutive days per 28-day cycle
- Filgrastim: 0.005 mg/kg for 9 total days
- Idarubicin: 8 mg/m^2 for 3 days.

In the model, it was assumed that patients on FLAG-IDA would be treated until disease progression (FLAG-IDA EFS curve used as proxy to reflect patients on treatment) or for a maximum of 4 28-day cycle, in line with UK clinical practice.

B.3.3 Clinical parameters and variables

The model has been constructed to analyse a number of different combinations of population, comparator, ITC data and survival analyses. An overview of the different types of analyses available in the model and the choice of base case and sensitivity analyses is provided in Table 37.

Table 37: Summary of approach to modelling of clinical parameters

Population	Comparator	Type of ITC	KTE-X19 dataset	Survival analyses (KTE-X19 and comparators)
Overall	Inotuzumab	• Naïve ITC (base case) • MAIC	mITT ZUMA-3 Phase 1 and Phase 2 combined (n=78)	• SPM or spline models (EFS and OS) with cure assumption from 3 years onwards (base case) – see section B.3.3.3 for more details • MCM
	FLAG-IDA	• Naive ITC (base case) • MAIC		
Ph-	Blinatumomab	• SCHOLAR-3 matched IPD (base case) • Naive ITC • MAIC	mITT ZUMA-3 Phase 1 and Phase 2 combined, Ph- patients only (n=61)	• SPM or spline models (EFS and OS) with cure assumption from 3 years onwards (base case) – see section B.3.3.3 for more details • MCM
	FLAG-IDA	• Naïve ITC (base case) • MAIC		
	Inotuzumab	• Naive ITC (base case) • MAIC		
Ph+	Ponatinib	• Naive ITC (base case)	mITT ZUMA-3 Phase 1 and Phase 2 combined (n=78)	• SPM or spline models (EFS and OS) with cure assumption from 3 years onwards (base case) – see section B.3.3.3 for more details
	FLAG-IDA	• Naïve ITC (base case) • MAIC		

	Inotuzumab	• Naive ITC (base case) • MAIC		• MCM

Key: IPD: individual patient-level data; ITC, indirect treatment comparison; MCM, mixture-cure model; mITT, modified intention-to-treat; SPM, standard parametric model

B.3.3.1 Baseline characteristics

The baseline characteristics for the modelled population are provided in Table 38. These parameters were informed by the baseline characteristics of the patients who received CAR T-cell infusion: mITT in the ZUMA-3 Phase 2 trial and in the subgroup of patients who received the same CAR T-cell dose in the ZUMA-3 Phase 1 trials of KTE-X19 (Phase 1 and Phase 2 combined dataset). The mITT population was used in the model base case in order to predict outcomes specific to those patients receiving KTE-X19.

The patients enrolled in Phase 1 and Phase 2 combined ZUMA-3 were considered appropriate to support the analysis, as discussed in sections B.2.3.2. The patient baseline characteristics adopted in the base case economic analysis are reported in Table 38.

Table 38: Patient baseline characteristics in the base case economic analysis

Model parameter	Value	Source
Mean age	43.2	ZUMA-3 (mITT Phase 1 and Phase 2 combined)
Percentage male	53.8%	ZUMA-3 (mITT Phase 1 and Phase 2 combined)
Mean weight	81.00 kg	ZUMA-3 (mITT Phase 1 and Phase 2 combined)
Mean height	169.8 cm	ZUMA-3 (mITT Phase 1 and Phase 2 combined)
Mean BSA	1.92 m^2	ZUMA-3 (mITT Phase 1 and Phase 2 combined)

Key: BSA, body surface area; mITT, modified intention-to-treat
Source: ZUMA-3 CSR (56)

The mean age, proportion of females and England life tables (2018-2020) were used to calculate general population background mortality (112). The mean age was also used to calculate age-related utility decrements. The mean weight and mean body surface area were used to calculate treatment dosage for those treatments whose posology is based on weight or body surface area.

Baseline characteristics from the overall ZUMA-3 population, irrespective of Ph expression, were adopted for all the subgroups included in the economic analysis: overall population, Ph- subgroup, and Ph+ subgroup. Clinical experts had confirmed that Ph status was unlikely to affect the clinical effectiveness of KTE (35,71).

B.3.3.2 Clinical efficacy inputs

The primary efficacy outcomes adopted within the economic model were EFS and OS. These endpoints allowed us to define health state occupancy in the partitioned survival model.

The ZUMA-3 trial was designed as a single-arm trial and was thus used to inform EFS and OS for KTE-X19 only. An SLR was conducted to identify relevant published data for the comparators in adult patients with R/R B-cell ALL (see section B.2.1). For each of the modelled comparators, pseudo IPD for EFS and OS were generated using the algorithm by Guyot et al. (2012) (113), after having digitised the published KM plots and using associated event information.

As explained in section B.2.9, a number of ITC approaches were used to compare the efficacy of KTE-X19 with the comparators in the scope, including naïve ITCs, MAICs and a synthetic control arm, SCHOLAR-3 SCA-3, for blinatumomab. KTE-X19 is expected to be positioned for patients who have either failed or are unlikely to achieve SCT, whereas the comparators are used as bridging therapy to allow patients to receive a potentially curative allo-SCT. They are therefore expected to be used in subtly different populations in clinical practice. As 100% of the ZUMA-3 patients are generalisable to its anticipated UK positioning, ZUMA-3 should provide the target population for any adjustments. As explained in section B.2.9, naïve comparisons were therefore considered to be the most representative base case for all comparators other than blinatumomab, for which an adjusted comparison to the ZUMA-3 population was available from SCHOLAR-3 SCA-3. In the latter analysis the blinatumomab IPD had been matched to the appropriate target population, that of ZUMA-3. As the OS HR point estimate in the naïve ITC against blinatumomab was identical to that from the SCHOLAR-3 adjusted comparison, this provided further justification that the results from naïve comparisons might also be more reliable than the MAICs for the other comparators.

Analysis of the IPD informing the naïve ITC and MAIC demonstrated the proportional hazards assumption to be violated in both the naïve and adjusted comparisons (71), therefore all survival analyses for the economic model were carried out by fitting survival curves independently to each comparator.

Table 39 provides an overview of the sources used to inform intervention and comparators' clinical efficacy in each subgroup. Rationale for these choices, summarised above, has also previously been provided in section B.2.9.

Table 39: Summary of data sources adopted for different subgroups in the economic model – base case

Subgroup	Comparator	Data sources	ITC versus KTE-X19
Overall	KTE-X19	mITT ZUMA-3 Phase 1 and Phase 2 combined	-
	Inotuzumab	INO-VATE intervention arm	Naïve comparison
	FLAG-IDA	INO-VATE/TOWER pooled comparator arms	Naïve comparison
Ph -	KTE-X19	mITT ZUMA-3 Phase 1 and Phase 2 combined, Ph- subgroup	-
	Blinatumomab	SCHOLAR-3 SCA-3	SCA-3 constructed as synthetic control arm
	FLAG-IDA	INO-VATE/TOWER pooled comparator arms	Naïve comparison
	Inotuzumab	INO-VATE intervention arm	Naïve comparison
Ph +	KTE-X19	mITT ZUMA-3 Phase 1 and Phase 2 combined	-
	Ponatinib	PACE	Naïve comparison
	FLAG-IDA	INO-VATE/TOWER pooled comparator arms	Naïve comparison
	Inotuzumab	INO-VATE intervention arm	Naïve comparison

Key: mITT, modified intention to treat; SCA, synthetic control arm

B.3.3.2.1 KTE-X19

Consistent with the patient baseline characteristics, EFS and OS inputs for KTE-X19 were based on the analysis of patients who received CAR T-cell infusion, mITT (n=78: ZUMA-3 Phase 2 n=55 and ZUMA-3 Phase 1 n=23). The IPD from ZUMA-3 Phase 1 and Phase 2 combined were directly adopted to inform KTE-X19 EFS and OS. Relapse-free survival (RFS) was used as a proxy for EFS as this was the endpoint in ZUMA-3.

In the base case, only data for patients who successfully received CAR T-cell infusion (mITT dataset) was used to provide EFS and OS inputs in the economic

model. This approach accurately reflected the clinical benefits of KTE-X19 without the confounding of those patients that did not receive CAR T-cell infusion (i.e., received other treatments).

Different assumptions were applied to estimate EFS and OS for patients who failed to receive CAR T-cell infusion based on the reasons for failing to receive KTE-X19 as observed in ZUMA-3:

- Proportion of patients who received CAR T-cell infusion followed KTE-X19 EFS and OS curves (incurring corresponding treatment costs and outcomes)
- Proportion of patients who failed to received CAR T-cell infusion due to adverse events followed FLAG-IDA EFS and OS curves (incurring corresponding treatment costs and outcomes)
- Proportion of patients who failed to received CAR T-cell infusion due to other reasons (e.g. manufacturing failure) followed relevant comparators' EFS and OS curves based on the subgroup under evaluation (incurring corresponding treatment costs and outcomes).

The assumption of modelling patients who failed to receive CAR T-cell infusion due to adverse events as being treated with FLAG-IDA was the same suggested by the ERG in NICE TA554. It allowed representation of the poor prognosis of patients failing to receive CAR T-cell infusion due to adverse events.

Two scenario analyses were performed to test the above assumption:

- Proportion of patients who failed to received CAR T-cell infusion (regardless of the reason) followed FLAG-IDA EFS and OS curves (incurring corresponding treatment costs and outcomes)
- Proportion of patients who failed to received CAR T-cell infusion (regardless of the reason) followed relevant comparators' EFS and OS excluding FLAG-IDA (incurring corresponding treatment costs and outcomes).

Table 40 provides the distribution of patients in KTE-X19 arm.

Table 40: Distribution of patients in KTE-X19 arm (mITT analysis)

Subgroup cost-effectiveness analysis	ZUMA-3 dataset informing KTE-X19	KTE-19	Inotuzumab	Blinatumomab	Ponatinib	FLAG-IDA
Overall	mITT Phase 1 and Phase 2 combined	78.8%	10.1%	NA	NA	11.1%
Ph-	mITT Phase 1 and Phase 2 combined	78.8%	5.0%	5.0%	NA	11.1%
Ph+	mITT Phase 1 and Phase 2 combined	78.8%	5.0%	NA	5.0%	11.1%

Key: mITT, modified intention-to-treat; NA, not applicable
Source: ZUMA-3 CSR (56)

Although Ph expression is not expected to affect efficacy of KTE-X19, efficacy data for the Ph- subgroup in ZUMA-3(n=61, 78% of the total cohort of n=78) were implemented to inform KTE-X19 EFS and OS. The same approach was not taken for the Ph+ subgroup as the sample size of the corresponding subgroup from mITT ZUMA-3 Phase 1 and Phase 2 combined (n=17, 22% of the total cohort of n=78) was considered too small to inform KTE-X19 EFS and OS data.

B.3.3.2.2 Inotuzumab ozogamicin

INO-VATE PFS and OS published KM curves were used to reproduce inotuzumab pseudo-IPD (74). INO-VATE enrolled R/R ALL patients irrespective of Ph expression and did not provide disaggregated efficacy results for Ph- and Ph+ subgroups that could be utilized for survival analyses. Therefore, the overall INO-VATE population was used to reflect inotuzumab EFS and OS absolute outcomes in the economic analysis for all three subgroups.

B.3.3.2.3 Blinatumomab

Two sources of clinical data were available for blinatumomab in the economic model; matched IPD from the SCA-3 cohort of the SCHOLAR-3 study and published data from the TOWER (25) study:

- The SCHOLAR-3 methodology has been described in section B.2.9.3 and in the separate SCHOLAR-3 CSR (72). Briefly, the SCA-3 cohort consisted of

patients from historical trials who were blinatumomab-naive. The rationale for this analysis was that SCA-3 patients would generally have better outcomes than patients who had previously failed blinatumomab, leading to a bias against the matched ZUMA-3 patients.

- TOWER EFS and OS published KM curves were used to reproduce blinatumomab pseudo-IPD (25). TOWER enrolled R/R ALL patients who were Ph-.

As explained in section B.2.9, the unadjusted ZUMA-3 population in the SCHOLAR-3 analysis is the most generalisable to its intended positioning in UK clinical practice. Therefore, SCA-3 was used to inform EFS and OS absolute outcomes in the economic analysis for the Ph- subgroup. Note that, although the SCHOLAR-3 ITC utilised the Phase 2 mITT dataset for the analysis of KTE-X19 against blinatumomab (see section B.2.9.3), in the economic model, for consistency with other comparators, the KTE-X19 Phase 1 and 2 combined mITT dataset is used for the comparison with blinatumomab, with a sensitivity analysis using the Phase 2 mITT.

B.3.3.2.4 Ponatinib

PACE PFS and OS published KM curves were used to reproduce ponatinib pseudo-IPD as described in the MAIC report (71,110). PACE enrolled R/R ALL patients who were Ph+, thus, the overall PACE population was used to inform EFS and OS absolute outcomes in the economic analysis for the Ph+ subgroup.

While in ZUMA-3 RFS was used (see section B.3.3.2.1), in PACE PFS was defined as the interval from the first dose of study treatment until progression or death. Thus, the PACE PFS curve was used as a proxy for EFS. This was deemed to be an appropriate approach by the health economics and clinical experts in the one-to-one interviews, given the publicly available comparative data.

B.3.3.2.5 FLAG-IDA

Comparator data from INO-VATE and TOWER EFS and OS published KM curves were used to reproduce pseudo-IPD (25,74). The pseudo-IPD from the two datasets was pooled to inform FLAG-IDA EFS and OS in the economic analysis for the overall population, the Ph- subgroup, and the Ph+ subgroup.

In the INO-VATE and TOWER trials, the chemotherapy regimen given to patients in the control arms was based on investigator's choice. Out of the 162 patients allocated to the INO-VATE control arm, 102 (63%) were treated with FLAG, 38 (23%) were treated with MXN/Ara-C, and 22 (14%) were treated with HIDAC. Out of the 109 patients treated in the TOWER (25) control arm, 49 (45%) were treated with FLAG with or without idarubicin, 19 (17%) were treated with HIDAC, 22 (20%) were treated with high-dose methotrexate-based regimens, and 19 (17%) were treated with clofarabine-based regimens. Consequently, the source used to inform FLAG-IDA in the economic model reflected a blend of different salvage chemotherapy regimens. However, there are no clear superior salvage chemotherapy regimens used in the treatment of R/R B-cell ALL in adults. The preference for one course of therapy over others depends on several factors such as safety profile, local clinical practice, and physician preference. For the economic analysis, it was thus assumed that the salvage chemotherapies (investigated in INO-VATE and TOWER and used to reflect FLAG-IDA EFS and OS) were no different in terms of treatment effect.

The combined INO-VATE and TOWER population was thus used to inform the FLAG-IDA EFS and OS absolute outcome in the economic analysis for the overall population, the Ph- subgroup, and the Ph+ subgroup.

B.3.3.3 Survival inputs and assumptions

As the follow-up periods of the studies used to inform intervention and comparators' EFS/PFS and OS curves (ZUMA-3, INO-VATE, TOWER, and PACE) were shorter than the model time horizon, extrapolation of EFS/PFS and OS observed data was required. A range of models were fitted to the KTE-X19 and comparator arm EFS/PFS and OS, in line with NICE DSU TSD 14 and 21 (114,115). Since the proportional hazard assumption was violated in the comparison of KTE-X19 versus relevant comparators (71), independent models were adopted.

EFS was primarily defined as time from randomisation until the date of relapse after achieving CR, CRi or CRh within a set number of weeks post treatment initiation. Patients that progressed in this period were assumed to have an EFS duration of 1 day, resulting in a significant number of patients being assigned an event at day 1. To avoid convergence issues due to the shape of the EFS KM curve, survival

models were only fit amongst responders. The estimated survival curves were later weighted in the economic model to account for patients that did not achieve a response following treatment initiation at cycle 1. This does not apply for ponatinib, since PFS curves were used.

The modelled parametric curves included standard parametric models such as exponential, Weibull, log-logistic, lognormal, Gompertz, and generalised gamma functions and flexible models, such as spline models. The spline models were fitted based on the algorithm by Royston and Parmar (2002) (116). A series of one-, two-, and three-knot restricted cubic spline models using hazard, odds and normal scales were explored. The location of the knots was chosen based on the quantiles of log uncensored survival times, as per the default settings in the *flexsurv* package in R. Although flexible models have good statistical fit to observed KM data with complex hazard functions, such models often fail to accurately reflect the clinical mechanisms underlying the observed hazard functions and predict unrealistic long-term data. Therefore, in addition to the above models, mixture cure models (MCMs) were fitted using the *flexsurvcure* package in R where the cure fraction is calculated using a logarithmic model. This type of model represents the population as a combination of two subpopulations: one reflects non-cured patients, who have a risk of experiencing an event defined by a standard parametric function, whilst the other reflects cured patients, who have a risk of experiencing an event as per the general population.

In line with NICE DSU TSD 14 (114) and TSD 21 (115), parametric survival models, splines models and MCMs were considered for all treatments arms and were compared and assessed using the below goodness-of-fit criteria:

- Akaike information criterion (AIC) and Bayesian information criterion (BIC), where smaller AIC/BIC values indicate a better statistical fit;
- A visual inspection of the fitted curves, where the fitted models were overlaid on the KM curves assessing how closely the model data matches reported trial survival data;
- Whether the predicted cure fractions for the comparators were in line with the proportion of patients reported to have survived following receipt of an allo-SCT

- Clinical plausibility of long-term extrapolations beyond the trial period based on clinical experts' opinion and relevant published external data where possible

As stated in NICE DSU TSD 21 (115), MCMs are used in cases where there is supporting evidence that a proportion of patients treated with the intervention will be effectively 'cured', and as such, are subject to background mortality. However, NICE DSU TSD 21 also affirms that performing MCM on small datasets raises issues around the practicability and plausibility of being able to estimate cure fraction. A sufficient number of patients at risk are thus needed in the tail of the distribution. The results using MCMs showed a wide variation in cure rates in this analysis (see Appendix N), therefore the data were considered too immature to provide robust results using MCMs and these will only be referred to briefly henceforth.

As discussed in detail in B.3.2.2, patients alive from the 3-year time-point are assumed to be cured and incur an increased risk of death (excess mortality) compared to the general population. An SMR of 1.09 was applied to the background mortality (section B.3.3.3). The SMR of 1.09 has been sourced from a study in DLBCL, Maurer et al., 2014 (98).

Although the comparators are not standalone curative treatments, given their intended use as bridging therapies to allo-SCT, a well-established curative treatment in ALL (96), the use of a cure assumption (parametric model followed by adjusted general population mortality from 3 years) was also deemed appropriate for the comparators. To accommodate this assumption, the economic model enables the combination of a parametric model (standard or spline) for a period of time defined by the user followed by general population mortality with an excess risk of death applied. This approach enabled the inclusion of a clinically validated cure assumption after fitted parametric models that did not require the estimation of a proportion of cured patients from immature data.

Therefore, in the base case, the hybrid approach was adopted for all the endpoints and comparators from 3 years onwards. The survival of patients considered to be effectively 'cured' was reflected through age- and gender- matched background mortality calculated using the England life tables (2018-2020) (112). In the base

case, a mortality adjustment was applied using a SMR of 1.09 based on the literature (Maurer et al., 2014 (98)) and in line with previous NICE TA in DLBCL (97) (see section B.3.2.2). An alternative assumption regarding the SMR (SMR of 2.5) from the NICE STA for inotuzumab in R/R ALL (81) was explored in a scenario analysis.

Age- and gender-specific general population mortality, modelled through England life tables (2018-2020) (112), was also used in the model to ensure that the estimated and extrapolated risk of death (OS) of the modelled cohort at any timepoint was not inferior to the risk of death of the matched general population. In addition, it was ensured that the modelled event-free patients would not overestimate the modelled alive patients by directly capping the EFS curves with the OS curve.

B.3.3.3.1 Summary of curve selection

Table 41 provides a summary of the survival functions adopted in the base case up to the timepoint of cure (3 years in the base case). The details of the survival analyses performed for each comparator/endpoint are provided in the following sections.

Table 41: Summary of curve selection – base case*

Subgroup	Treatment arm	EFS/PFS	OS
Overall	KTE-X19 (overall)	Lognormal	Lognormal
	Inotuzumab	1-knot hazard spline	2-knot normal spline
	FLAG-IDA	Generalised gamma	Generalised gamma
Ph-	KTE-X19 (Ph-)	Lognormal	Lognormal
	Inotuzumab	*Same as overall subgroup*	
	FLAG-IDA	*Same as overall subgroup*	
	Blinatumomab	1-knot hazard spline	Lognormal
Ph+	KTE-X19	*Same as overall subgroup*	
	Inotuzumab	*Same as overall subgroup*	
	FLAG-IDA	*Same as overall subgroup*	
	Ponatinib	Lognormal	Lognormal

Key: EFS, event-free survival; OS, overall survival; PFS, progression-free survival
* **Note**: in the base case, all the treatment arms' EFS/PFS and OS follow a hybrid approach (cure assumption from 3 years onwards)

B.3.3.3.2 Overall R/R B-cell ALL population

For the overall population, unadjusted KTE-X19 KM curves were used to inform the comparison versus inotuzumab and FLAG-IDA in the cost-effectiveness model. The

INO-VATE intervention arm informed inotuzumab EFS and OS, while pooled INO-VATE and TOWER comparator arms informed FLAG-IDA EFS and OS.

The base case approach combined a parametric model with adjusted general population mortality from 3 years onwards. Note that in the NICE TA for inotuzumab in R/R ALL (TA541) cure was conditional on having received SCT and MRD-negativity and cure fractions were not reported. Therefore a 3-year cure applied to all patients receiving inotuzumab in this model can be considered optimistic.

1 KTE-X19, EFS

Figure 67 through Figure 69 in Appendix N present the various models fitted to the EFS patient level data for KTE-X19 (naïve). The AIC/BIC statistics are presented in Table 138 and in Table 139, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 34: Modelled* KTE-X19 EFS, cure assumption at 3 years – lognormal

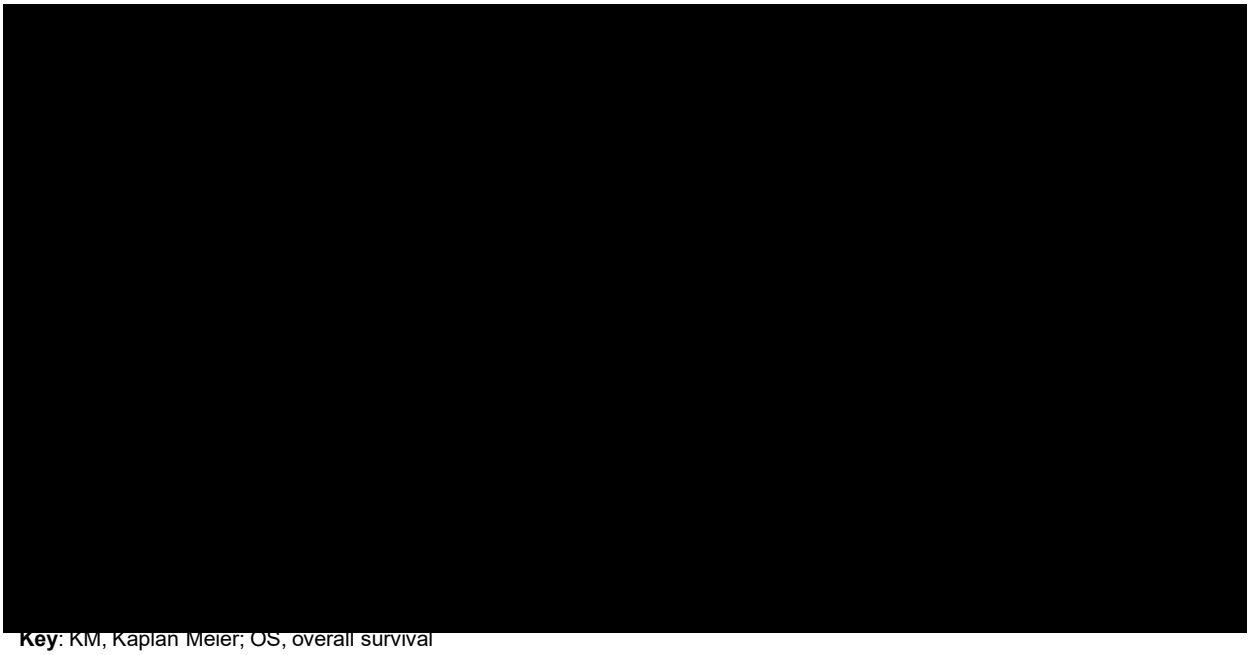
Key: EFS: event-free survival; KM, Kaplan Meier
*Note that the modelled KTE-X19 EFS curve include those patients who did not receive CAR T-cell infusion and are assumed to receive one of the comparators

2 KTE-X19, OS

Figure 70 through Figure 72 in Appendix N present the various models fitted to the OS patient level data for KTE-X19 (naïve). The AIC/BIC statistics are presented in Table 140 and Table 141, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 35: Modelled* KTE-X19 OS, cure assumption at 3 years – lognormal



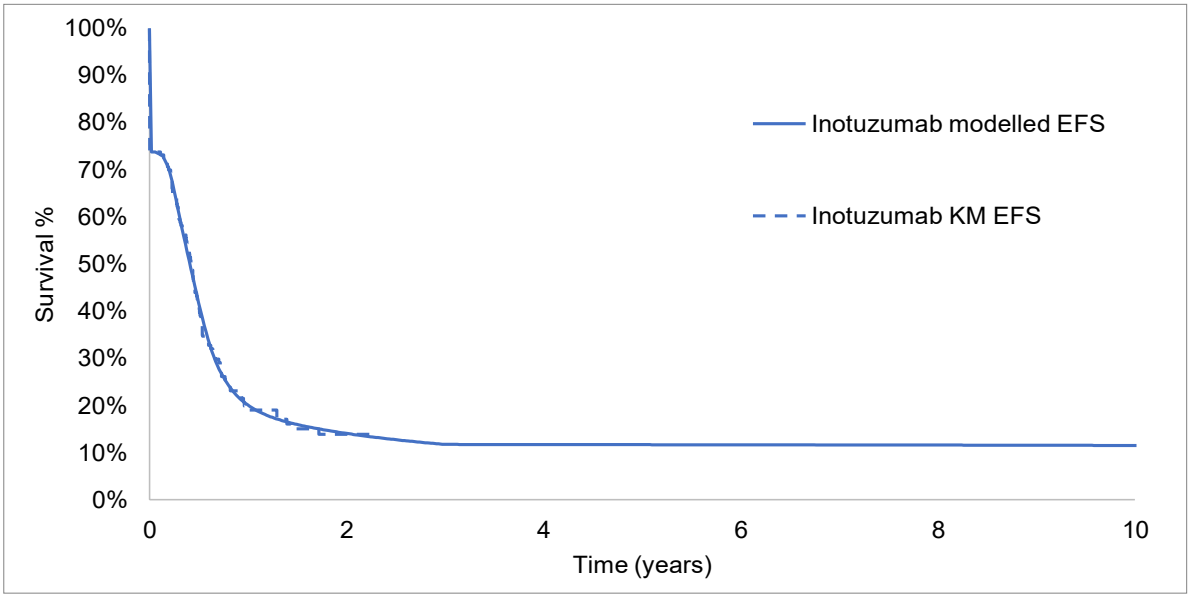
Key: KM, Kaplan Meier; OS, overall survival
*Note that the modelled KTE-X19 OS curve include those patients who did not receive CAR T-cell infusion and are assumed to receive one of the comparators.

3 Inotuzumab, EFS

Figure 73 through Figure 75 in Appendix N present the various models fitted to the EFS patient level data from the INO-VATE intervention arm. The AIC/BIC statistics are presented in Table 142 and in Table 143, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the 1-knot hazard spline model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 36: Modelled inotuzumab EFS, cure assumption at 3 years – 1-knot hazard spline



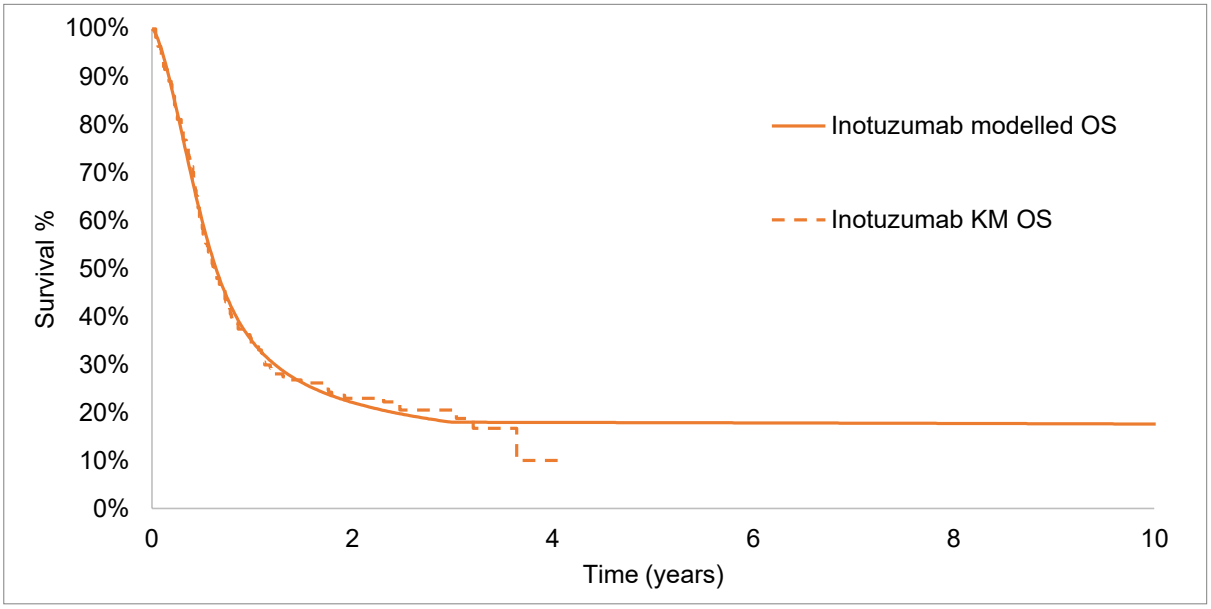
Key: EFS, event-free survival; KM, Kaplan Meier

4 Inotuzumab, OS

Figure 76 through Figure 78 in Appendix N present the various models fitted to the OS patient level data from the INO-VATE intervention arm. The AIC/BIC statistics are presented in Table 144 and Table 145, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the 2-knot normal spline model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 37: Modelled inotuzumab OS, cure assumption at 3 years – 2-knot normal spline



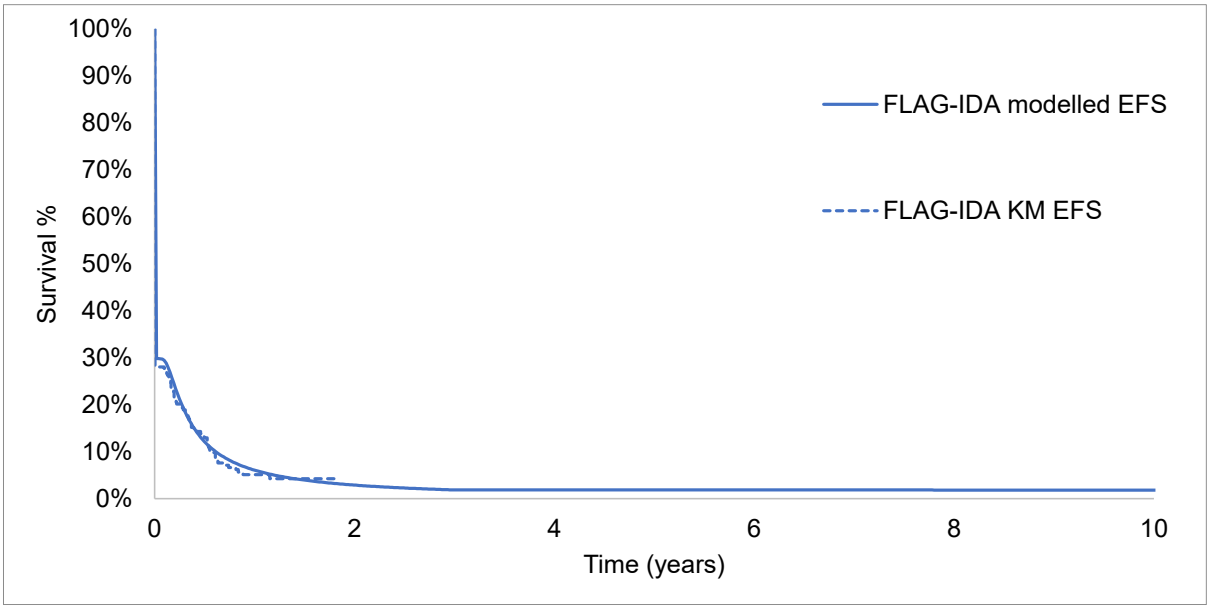
Key: KM, Kaplan Meier; OS, overall survival

5 FLAG-IDA, EFS

Figure 79 through Figure 81 in Appendix N present the various models fitted to the EFS patient level data for INO-VATE and TOWER pooled control arms. The AIC/BIC statistics are presented in Table 146 and Table 147, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the generalised gamma standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 38: Modelled FLAG-IDA EFS, cure assumption at 3 years – generalised gamma



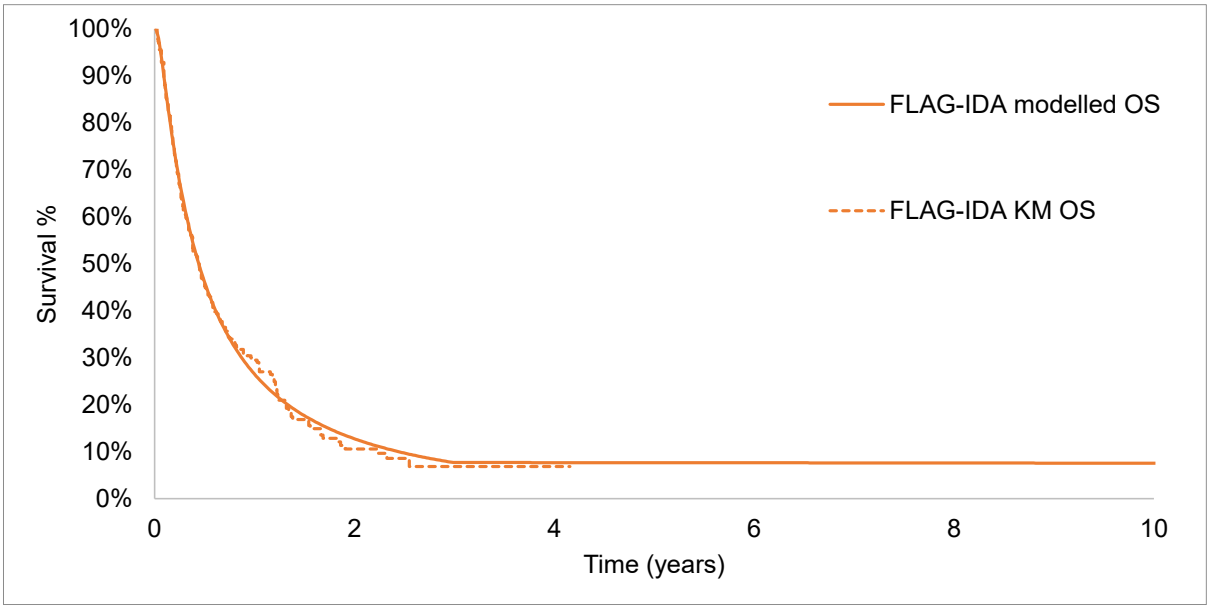
Key: EFS, event-free survival; KM, Kaplan Meier

6 FLAG-IDA, OS

Figure 82 through Figure 84 in Appendix N present the various models fitted to the OS patient level data for INO-VATE and TOWER pooled control arms. The AIC/BIC statistics are presented in Table 148 and Table 149, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the generalised gamma standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 39: Modelled FLAG-IDA OS, cure assumption at 3 years – generalised gamma



Key: KM, Kaplan Meier; OS, overall survival

B.3.3.3.3 Ph- R/R B-cell ALL population

For the Ph- population, unadjusted KTE-X19 KM curves from the ZUMA-3 Ph- subgroup (mITT Phase 1 and Phase 2 combined dataset) were used to inform the comparison versus inotuzumab, FLAG-IDA, and blinatumomab in the cost-effectiveness model. Since inotuzumab and FLAG-IDA outcomes were not differentiated by Ph expression, the same data and curve selection as the overall population was used (see section B.3.3.3.2). The SCHOLAR-3 SCA-3 dataset, with the exclusion of patients receiving salvage chemotherapy, was used to inform the blinatumomab EFS and OS in the economic model.

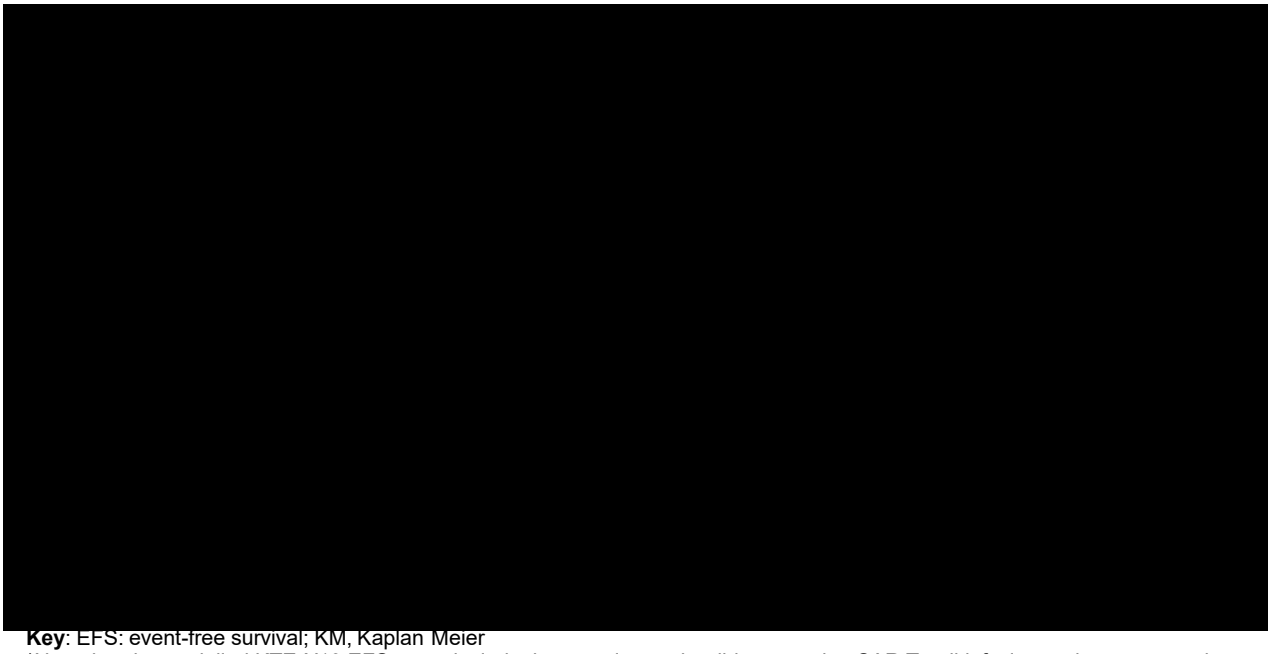
Consistent with the overall population, the base case approach combined a parametric model with adjusted general population mortality from 3 years onwards for all comparators in this subgroup.

7 KTE-X19, EFS (Ph-)

Figure 85 through Figure 87 in Appendix N present the various models fitted to the EFS patient level data for KTE-X19 (naïve). The AIC/BIC statistics are presented in Table 150 and in Table 151, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 40: Modelled* KTE-X19 EFS (Ph-), cure assumption at 3 years – lognormal



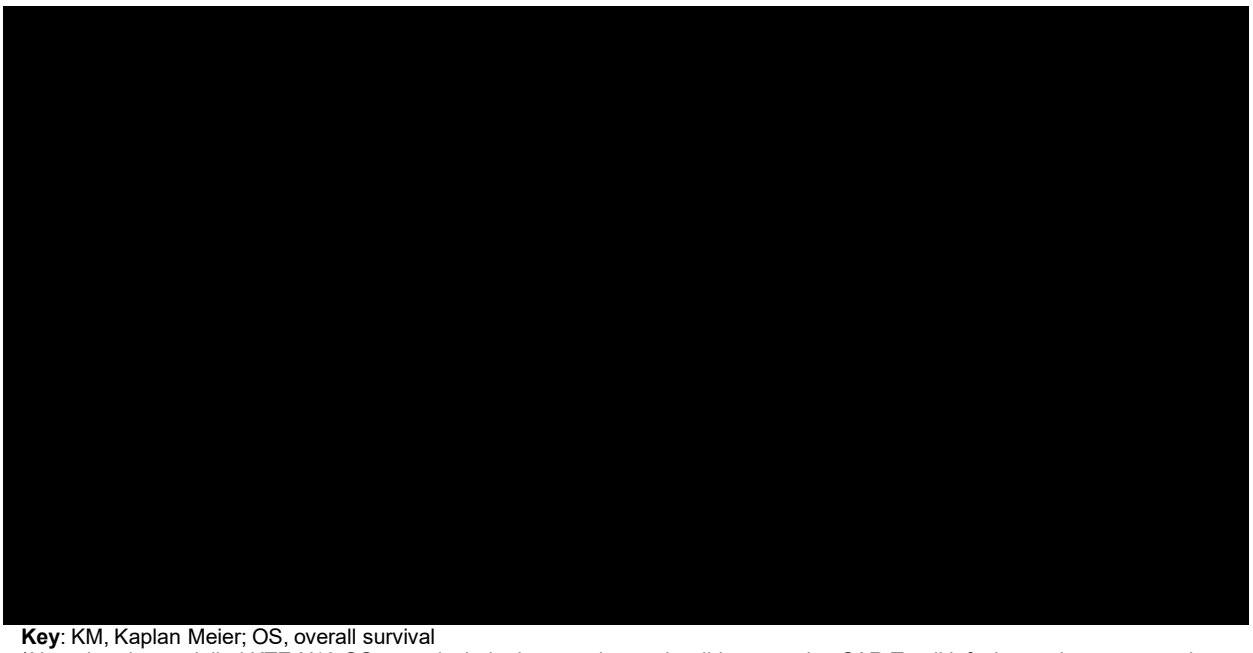
Key: EFS: event-free survival; KM, Kaplan Meier
*Note that the modelled KTE-X19 EFS curve include those patients who did not receive CAR T-cell infusion and are assumed to receive one of the comparators

8 KTE-X19, OS (Ph-)

Figure 88 through Figure 90 in Appendix N present the various models fitted to the OS patient level data for KTE-X19 (naïve). The AIC/BIC statistics are presented in Table 152 and Table 153 , Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 41: Modelled* KTE-X19 OS (Ph-), cure assumption at 3 years – lognormal



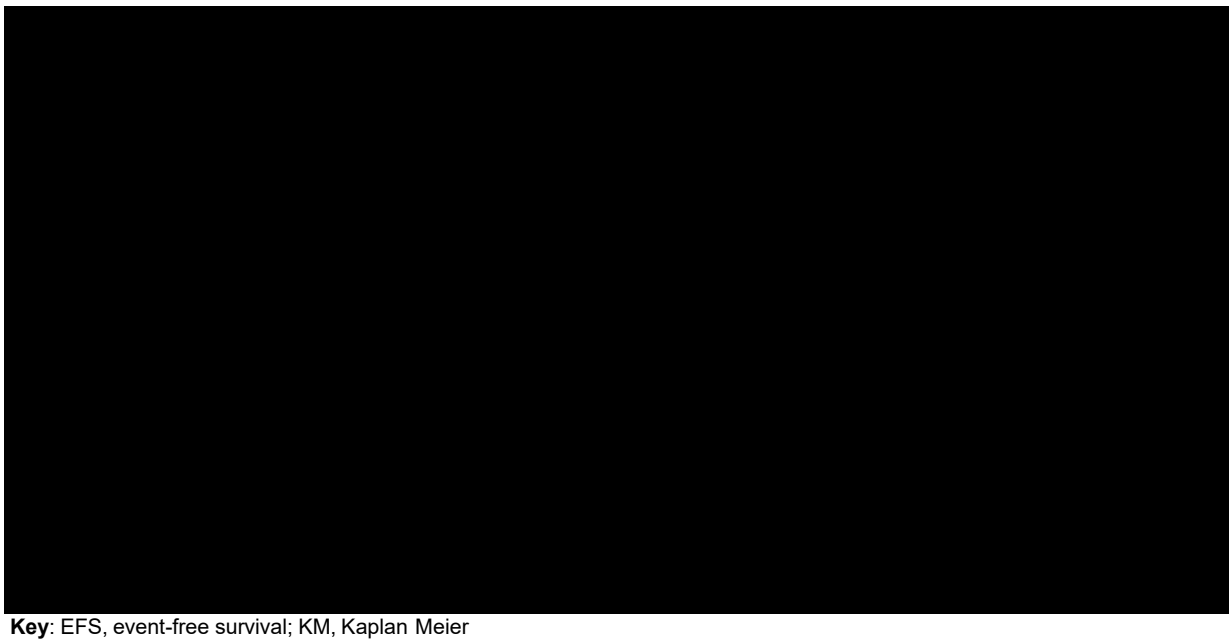
Key: KM, Kaplan Meier; OS, overall survival
*Note that the modelled KTE-X19 OS curve include those patients who did not receive CAR T-cell infusion and are assumed to receive one of the comparators

9 Blinatumomab, EFS

Figure 91 through Figure 93 in Appendix N present the various models fitted to the EFS patient level data from SCHOLAR-3 SCA-3. The AIC/BIC statistics are presented in Table 154 and Table 155, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the 1-knot hazard spline model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 42: Modelled blinatumomab EFS, cure assumption at 3 years – 1-knot hazard spline



Key: EFS, event-free survival; KM, Kaplan Meier

10 Blinatumomab, OS

Figure 94 through Figure 96 in Appendix N present the various models fitted to the OS patient level data for SCHOLAR-3 SCA-3. The AIC/BIC statistics are presented in Table 156 and Table 157, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 43: Modelled blinatumomab OS, cure assumption at 3 years – lognormal

Key: KM, Kaplan Meier; OS, overall survival

B.3.3.3.4 Ph+ R/R B-cell ALL population

For the Ph+ population, unadjusted KTE-X19 KM curves were used to inform the comparison versus inotuzumab, FLAG-IDA, and ponatinib in the cost-effectiveness model. Since the ZUMA-3 Ph+ subgroup was deemed too small to be used for survival analyses, the same data (mITT ZUMA-3 Phase 1 and Phase 2 combined, n=78) and curve selection as the overall population was used (see section B.3.3.3.2). Since inotuzumab and FLAG-IDA outcomes were not differentiated by Ph expression, the same data and curve selection as the overall population was used (see section B.3.3.3.2). PACE informed ponatinib PFS and OS absolute outcomes.

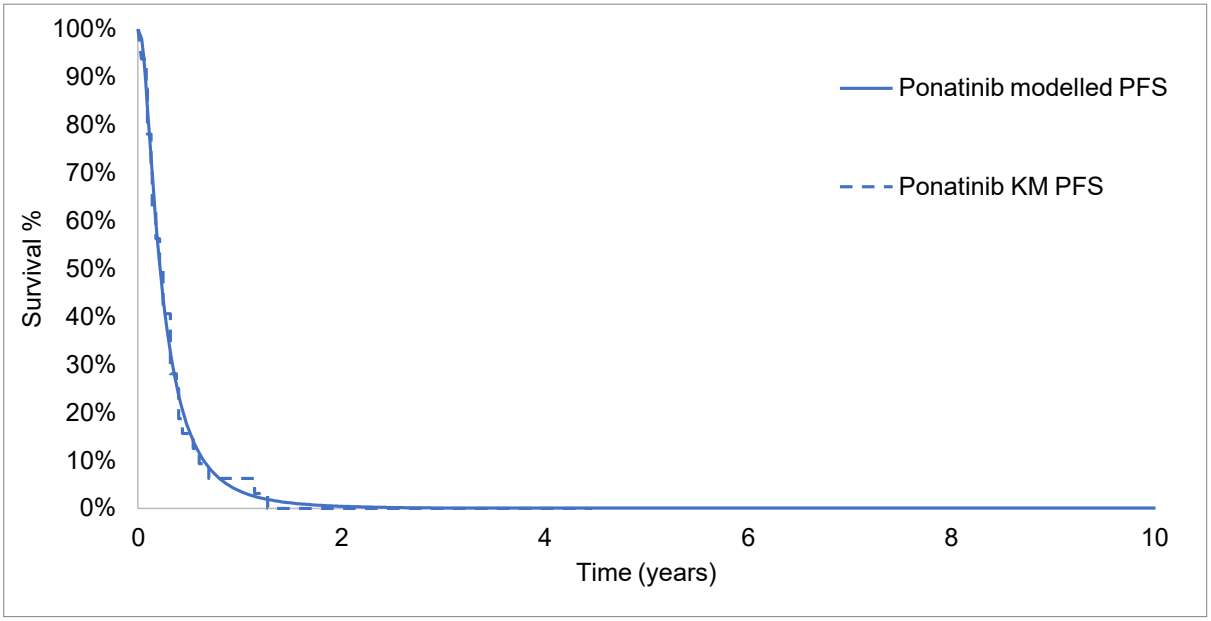
Although ponatinib is not a curative treatment, given its intended use as a bridging therapy to allo-SCT, a well-established curative treatment in ALL, the use of a cure assumption (parametric model followed by adjusted general population mortality from 3 years) was deemed appropriate.

11 Ponatinib, PFS

Figure 97 through Figure 99 in Appendix N present the various models fitted to the PFS patient level data for PACE arm. The AIC/BIC statistics are presented in Table 158 and Table 159, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 44: Modelled ponatinib PFS, cure assumption at 3 years – lognormal



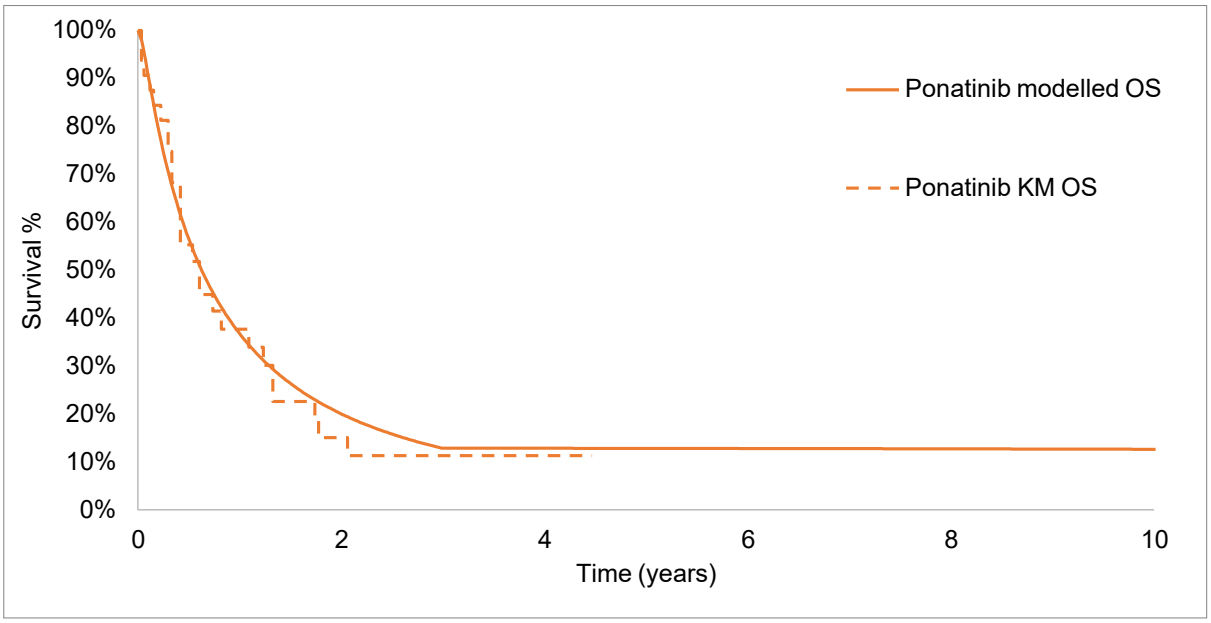
Key: KM, Kaplan Meier; PFS, progression-free survival

12 Ponatinib, OS

Figure 100 through Figure 102 in Appendix N present the various models fitted to the OS patient level data for PACE arm. The AIC/BIC statistics are presented in Table 160 and Table 161, Appendix N.

Based on the smaller AIC/BIC and the visual fit to the KM data, the lognormal standard parametric model followed by adjusted general population mortality from 3 years was adopted in the base case.

Figure 45: Modelled ponatinib OS, cure assumption at 3 years – lognormal



Key: KM, Kaplan Meier; OS, overall survival

B.3.3.4 Adverse events

The incidence of adverse events (AEs) for individual treatments was informed by individual clinical trials. For KTE-X19, these included grade 3 or 4 AEs occurring post-infusion in ≥5% of the population (ZUMA-3 mITT Phase 1 and Phase 2 combined, with Phase 1 target dose obtained from the publication) (42). For blinatumomab, grade ≥3 AEs observed during TOWER that occurred in ≥5% of adults in the first cycle of therapy were used in the model (25). Since the INO-VATE study reported serious AEs that occurred in ≥2% of the safety population (26), these figures were used in the model to reflect inotuzumab safety profile. Treatment-emergent AEs of any grade occurring in ≥20% of the total population were taken from the phase 2 PACE trial for the ponatinib arm (110). In order to be consistent with the efficacy data, the adverse event rates for the FLAG-IDA arm was pooled from the control arms of the INO-VATE (inotuzumab) and TOWER (blinatumomab) trials. AEs rates for each treatment arm are reported in Table 42.

Table 42: Adverse events rates included in the model

Adverse event	KTE-X19	Inotuzumab	Blinatumomab	Ponatinib	FLAG-IDA
CRS	[redacted]	NR	3.0%	NR	NR
Anaemia	[redacted]	NR	19.5%	18.8%	14.7%
Neutropenia	[redacted]	NR	28.5%	21.9%	24.2%
Platelet count decreased	[redacted]	NR	NR	NR	NR
Thrombocytopenia	[redacted]	NR	17.6%	18.8%	15.9%
Encephalopathy	[redacted]	NR	NR	NR	NR
Febrile neutropenia	[redacted]	11.6%	NR	NR	10.7%
Hypophosphatemia	[redacted]	NR	NR	NR	NR
Hypotension	[redacted]	NR	NR	NR	0.8%
Leukopenia	[redacted]	NR	6.7%	NR	3.6%
Lymphocyte count decreased	[redacted]	NR	NR	NR	NR
Neutrophil count decreased	[redacted]	NR	NR	NR	NR
Pyrexia	[redacted]	1.2%	5.6%	NR	2.0%
White blood cell count decreased	[redacted]	NR	NR	NR	NR

Adverse event	KTE-X19	Inotuzumab	Blinatumomab	Ponatinib	FLAG-IDA
Alanine aminotransferase increased	[redacted]	NR	NR	NR	NR
Device related infection	[redacted]	NR	3.4%	NR	0.4%
Hyperglycaemia	[redacted]	NR	NR	NR	NR
Hypertension	[redacted]	NR	NR	9.4%	NR
Hypokalaemia	[redacted]	NR	NR	NR	NR
Hypoxia	[redacted]	NR	NR	NR	NR
Pneumonia	[redacted]	5.5%	NR	NR	NR
Respiratory failure	[redacted]	1.2%	NR	NR	2.4%
Rash	[redacted]	NR	NR	6.3%	NR
Diarrhea	[redacted]	NR	NR	3.1%	NR
Septic shock	[redacted]	1.8%	NR	NR	1.2%
Sepsis	[redacted]	2.4%	NR	NR	4.0%
Neutropenic sepsis	[redacted]	1.8%	NR	NR	1.6%
Abdominal pain	[redacted]	NR	NR	6.3%	NR
VOD	[redacted]	11.6%	NR	NR	1.2%
Decrease in appetite	[redacted]	NR	NR	NR	NR

Adverse event	KTE-X19	Inotuzumab	Blinatumomab	Ponatinib	FLAG-IDA
Increase in blood bilirubin	[redacted]	NR	NR	NR	1.2%
Fungal pneumonia	[redacted]	NR	NR	NR	1.2%
Subdural hematoma	[redacted]	NR	NR	NR	1.2%
Hypertransaminasaemia	[redacted]	NR	8.2%	NR	2.8%
Infection pathogen unspecified	[redacted]	NR	15.0%	NR	13.9%
Bacterial infectious disorders	[redacted]	NR	7.1%	NR	8.3%
Viral infectious disorders	[redacted]	NR	1.5%	NR	NR
Fungal infectious disorders	[redacted]	NR	4.9%	NR	3.6%
Lipase increase	[redacted]	NR	NR	6.3%	NR
Constipation	[redacted]	NR	NR	3.1%	NR
Acute kidney injury	[redacted]	NR	NR	NR	NR
Pulmonary edema	[redacted]	NR	NR	NR	NR
Bacteraemia	[redacted]	NR	NR	NR	NR

Key: CRS, cytokine release syndrome; VOD, veno-occlusive disease

B.3.4 Measurement and valuation of health effects

Each state in the model is associated with a utility weight specific to that state. In the base case, utility weights for the EFS and PD health states are calculated from analyses of HRQoL data from ZUMA-3, described below.

B.3.4.1 Health-related quality-of-life data from clinical trials

The ZUMA-3 trial collected HRQoL data using the EQ-5D-5L. The EQ-5D is a standardised and validated generic instrument; the preference elicitation is based on a time trade-off algorithm, in line with the NICE reference case (117). For the UK analysis, the EQ-5D-5L values were cross-walked to the EQ-5D-3L, in accordance with the NICE reference case, using the algorithm by van Hout et al. (118). An analysis was undertaken on the cross-walked EQ-5D-5L to support the economic modelling efforts, full details of which are available in the separate *post-hoc* Patient Reported Outcomes analysis report (119).

Since only the phase 2 of ZUMA-3 trial collected EQ-5D data, only participants from the mITT phase 2 cohort (n=55) could be included. EQ-5D-5L scores were collected at screening, day 0, day 28, month 3, month 6, month 9, month 12, and month 15. Descriptive statistics on the EQ- 5D-5L values generated using patient-level EQ-5D-5L data from the ZUMA-3 trial were calculated by the following categories, corresponding to the model health states:

- Pre-injection: this comprised any visits that were prior to the first injection (i.e., the screening visit and Day 0); this served as a reference category in models
- Post-injection, pre-relapse: this comprised any visits that were after injection and prior to the date of relapse; if the patient did not relapse, all post-injections visits would fall into this category; conversely, if patients never responded, all visits were counted in the post relapse category
- Post relapse: this included all visits on the date of relapse or after; note this category also includes all post-injection visits for patients who never responded.

Cross-walked EQ-5D-5L indices (UK) and EQ-5D-5L VAS scores were analysed as continuous dependent variables at each assessment. The number of subjects in the analysis set used and number of subjects having a non-missing value of that endpoint were reported by model-based time period and whether the patient was experiencing a grade 3 or 4 TEAE at the time of reporting.

Two analysis populations were used. The first analysis (model 1) included all observations (screening, Day 0, Day 28, Month 3, Month 6, Month 9, Month 12, Month 15 visits), stratified by time-dependent time-period and Grade 3 or 4 TEAE categories. The second analysis (model 2) collapsed down cases where there was more than one observation within a time period and AE category by taking the mean index score for that patient across the multiple observations within the time period. In order to avoid any skewed results arising from those patients who had more than one visit within a certain time period, model 2 informs the base-case health state utilities (disutilities associated with adverse events are informed by the literature in the base case; see section B.3.4.5).

Each of the calculated cross-walked EQ-5D-5L indices was the dependent variable in 4 separate mixed model for repeated measures (MMRM) model series. Covariates included in the MMRM were model-based time-period and grade 3 or 4 TEAE, each treated as discrete variables. After attempting unstructured (UN) and autoregressive (AR) covariance structures, a compound symmetry (CS) covariance structure was used due to model convergence issues. For each MMRM, the model output included parameter estimates and least square means estimates for indices by model-based time period. Descriptive statistics of the EQ-5D utility values and the total sample size by the considered health state categories are shown in Table 43. Outputs of the MMRM model using the UK value set are shown in Table 44. The base-case health state utilities, as informed by model 2, are presented in Table 45: these health state utilities are age-adjusted in the submitted base case (see section B.3.4.3). The ZUMA-3 adverse event disutilities are explored in scenario analysis, while these are informed by the literature in the base case (see section B.3.4.5).

Table 43: EQ-5D Indices by injection, relapse, and AE status (all observations in each time period) in ZUMA-3 trial phase 2

	Pre-injection			Post-injection, pre-relapse						Post-relapse					
	No AE			No AE			AE			No AE			AE		
EQ-5D-5L index	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
UK	[redacted]														

[a] Active grade 3 or 4 treatment-emergent AE (time dependent)
Key: AE, adverse event; CI, confidence interval; REF, reference group; SD, standard deviation; US, United States
Note Mixed models run with CS Covariance structure.
Source: PRO analysis report (119).

Table 44: EQ-5D-5L Index (UK Crosswalk Value Set) by Injection, Relapse, and AE Status

		Model 1: All observations		Model 2: Collapsed observations	
Variable or Statistic	**Level**	**Estimate (SE)**	**p-value**	**Estimate (SE)**	**p-value**
Intercept		[redacted]			
Time Point Classification	Post-injection, pre-relapse				
	Post-relapse				
	Pre-injection	REF		REF	
Active AE at time of measurement [a]	Y				
	N	REF		REF	
Least squares mean estimate		Estimate (95% CI)		Estimate (95% CI)	
Pre-injection					
Post-injection, pre-relapse					
Post-relapse					

[a] Active grade 3 or 4 treatment-emergent AE (time dependent)
Key: AE, adverse event; SE, standard error; CI, confidence interval; UK, United Kingdom; REF, reference group
Note Mixed models run with CS Covariance structure.
Source: PRO analysis report (119).

Table 45: Base-case health state utilities: ZUMA-3

Health state	Mean utility value	Source (ZUMA-3)
Event-free survival	[redacted]	Intercept value plus post-injection, pre-relapse parameter value from model 2
Progressed disease	[redacted]	Intercept value plus post-relapse parameter value from model 2

B.3.4.2 Mapping

The EQ-5D-5L utilities from ZUMA-3 data were mapped to EQ-5D-3L in alignment with the NICE reference case (117). The utility index scores were mapped using the EuroQol data set of cross-walked values for each of the possible EQ-5D-5L response sets with UK preference weighting using the van Hout et al. (2012) method (118).

B.3.4.3 General population utility

Patients alive at the 3-year time-point in the model are assumed to be cured and incur general population utility (see section B.3.2.2). General population utility was modelled using the approach detailed in Ara and Brazier 2010 (120). This paper provides a regression model which can be used to calculated general population health state utility values, with adjustments applied for age and gender, as specified in the equation below.

$$EQ - 5D = \alpha + \beta_1 Male + \beta_2 Baseline\ age + \beta_3 Baseline\ age^2 + \varepsilon$$

The coefficient values for the intercept term (α) and the age and gender (male) covariates are provided in the publication (120). The proportion male (54%) and baseline age (43.23 years) are informed by ZUMA-3 baseline characteristics. General population utility is also used in the model to account for age-related utility decrements for the EFS and PD health states.

B.3.4.4 Health-related quality-of-life studies

A systematic search was conducted to identify relevant health-related quality-of-life data. The methods and results of this SLR are presented in Appendix H. 10 publications were identified which reported on HRQoL or utilities. The utility values applied in the model base-case are however sourced from ZUMA-3 instead as these utility values were collected prospectively from the trial population and this was therefore deemed the most appropriate source.

B.3.4.5 Adverse reactions

Utility decrements associated with adverse events were incorporated in the cost-effectiveness model by multiplying the utility decrement by the duration to determine a one-off value, applied in the first cycle of the model. Disutilities associated with adverse events are informed by the literature in the base case, while these are informed by ZUMA-3 (see section B.3.4.1) in a scenario analysis.

In line with TA554 (79), utility decrements were applied for the pre-treatment hospitalisation period for patients receiving blinatumomab or FLAG-IDA. The utility decrement of -0.42 was based on estimates provided by Sung et al., 2003 (121) and adjusted for the duration of days in hospital (9.2 and 21 for blinatumomab and FLAG-IDA respectively). This resulted in a one-off disutility of -0.01 and -0.02 for blinatumomab and FLAG-IDA, respectively.

The utility decrements associated with the AEs listed in Table 42 are presented below, along with the duration in days and source. For CRS, the utility value in the base case is assumed to be 0 (since the base case utility for EFS is [redacted], this equals to a utility decrement of [redacted]). An alternate value of -0.23 by Howell et al. (122) can be used to inform CRS related disutility, and it is explored in scenario analysis.

For the proportion of patients receiving subsequent allo-SCT (section B.3.5.3), patients were assumed to have additional utility decrements in order to capture the impact of any potential complications or AEs associated with allo-SCT. A utility decrement of -0.57, derived from Sung et al, (121) was applied for a duration of one year; this value is in line with previous NICE submissions (79).

Table 46: Utility decrements associated with adverse events included in the model

Adverse event	Utility decrement	Duration (days)	Source
CRS (base case)	[redacted]	4.3	Assumption
CRS (scenario)	-0.23	4.3	Howell et al., 2020 (122)
Anaemia	-0.12	14.9	Swinburn 2010 (123)
Neutropenia	-0.09	13.2	Nafees et al., 2008 (124)
Platelet count decreased	-0.05	11.9	TA416 (125)
Thrombocytopenia	-0.09	20.1	Nafees et al., 2008 (124)
Encephalopathy	-0.22	5.86	TA416 (126)
Febrile neutropenia	-0.09	6.2	Nafees et al., 2008 (124)
Hypotension	-0.07	2.3	TA510 (127)
Leukopenia	-0.09	11.8	Nafees et al., 2008 (124)
Lymphocyte count decreased	-0.07	19.0	TA510 (128)
Neutrophil count decreased	0.00	9.8	TA520 (129)
Pyrexia	-0.11	1.2	Beusterien et al., 2010 (130)
White blood cell count decreased	-0.05	16.9	In line with TA520 (131)
Alanine aminotransferase increased	0.00	20.0	Assumption
Device related infection	-0.05	4.3	Assumed same as dyspnoea
Hyperglycaemia	-0.06	7.5	Nafees et al., 2016 (130)
Hypertension	-0.07	4.0	Assumed same as hypotension
Hypocalcaemia	-0.20	1.0	Assumed same as hypokalaemia
Hypokalaemia	-0.20	1.0	TA510 (128)
Hypophosphatemia	-0.07	3.37	TA510 (128)
Hypoxia	-0.22	2.4	Lachaine et al., 2015 (132)
Pneumonia	-0.22	11.3	Stein et al., 2018 (133)
Respiratory failure	-0.22	1.6	Assumption same as pneumonia

Rash	-0.06	7.0	Stein et al., 2018 (133)
Diarrhoea	-0.05	7.0	Nafees et al., 2008 (124)
Septic shock	-0.20	6.0	Tolley et al., 2013 (134)
Sepsis	-0.20	15.1	Tolley et al., 2013 (134)
Neutropenic sepsis	-0.20	15.1	Assumption same as sepsis
Abdominal pain	-0.05	7.0	Assumption same as diarrhoea
VOD	-0.21	28.0	TA541 (81)
Decrease in appetite	0.00	0.0	Assumption
Increase in blood bilirubin	0.00	0.0	Assumption
Fungal pneumonia	-0.19	11.3	Assumption same as pneumonia
Subdural hematoma	-0.22	5.9	Assumption same as encephalopathy in line with TA559 (94)
Hypertransaminasemia	0.00	20.0	Assumption
Infection pathogen unspecified	-0.22	15.1	Assumption same as sepsis
Bacterial infectious disorders	-0.22	15.1	Assumption same as sepsis
Viral infectious disorders	-0.22	15.1	Assumption same as sepsis
Fungal infectious disorders	-0.22	15.1	Assumption same as sepsis
Lipase increase	0.00	20.0	Assumption
Constipation	-0.05	7.0	Assumption same as diarrhoea
Bacteraemia	-0.20	14.8	Assumption same as sepsis

Key: CRS, cytokine release syndrome; VOD, veno-occlusive disease

B.3.4.6 Scenario analyses

Scenario analyses were conducted to explore the impact of applying different utility values for the PD health state and for the cured patients. These utility values are reported in the table below. The utility values were varied individually to observe the isolated impact of each change in health state utility values upon the ICER.

Table 47: Health state utility values applied in scenario analyses

Health state	Mean utility value	Source
PD	0.35	Blinatumomab SMC submission in R/R ALL (135)
	0.75	Tisagenlecleucel SMC submission (136)
Cured	0.76	Kurosawa et al. (45), in line with TA541 (4)
	0.86	Blinatumomab SMC submission in R/R ALL (135)

B.3.4.7 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the cost-effectiveness analysis is presented in the table below.

Table 48: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case health-state utilities				
Pre-infusion	[redacted]	[redacted]	ZUMA-3 (Health-related quality-of-life data from clinical trials, page, Table 45, page 175)	Prospective utility data measured in trial population of interest
Event-free survival	[redacted]	[redacted]	ZUMA-3 (Health-related quality-of-life data from clinical trials, page, Table 45, page 175)	Prospective utility data measured in trial population of interest
Progressed disease (base-case)	[redacted]	[redacted]	ZUMA-3 (Health-related quality-of-life data from clinical trials, page, Table 45, page 175)	Prospective utility data measured in trial population of interest
Progressed disease (scenario)	0.35	(0.22, 0.49)	Blinatumomab SMC submission in	Literature

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
			R/R ALL (135) (Scenario analyses, Table 47, page 179)	
Progressed disease (scenario)	0.75	(0.41, 0.97)	Tisagenlecleucel SMC submission (137)	Literature
Cured patients (base-case)	General population utility	N/A	(General population utility, page 175)	Assumption
Cured (scenario)	0.86	(0.38, 1.00)	Blinatumomab SMC submission (Scenario analyses, Table 47, page 179)	Literature
Cured (scenario)	0.76	(0.42, 0.97)	Kurosawa et al. (45), in line with TA541 (4) (Scenario analyses, Table 47, page 179)	Literature
Adverse event utility decrements				
Pre-treatment hospitalisation				
Blinatumomab	-0.01	(-0.01, -0.02)	Sung 2003 (121)	Literature
Salvage chemotherapy	-0.02	(-0.02, 0.03)	Sung 2003 (121)	Literature
Treatment-related adverse events				
CRS (base case)	[redacted]	[redacted]	(Adverse reactions, page 176)	Assumption
CRS (scenario)	-0.23	(-0.15, -0.33)	Howell 2020 (122) (Adverse reactions, page 176)	Literature
Anaemia	-0.12 (-0.02)	(-0.08, -0.17)	Swinburn 2010 (123) (Adverse reactions, page 176)	Literature
Neutropenia	-0.09 (-0.02)	(-0.06,-0.13)	Nafees 2008 (124) (Adverse reactions, page 176)	Literature

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Platelet count decreased	-0.05 (-0.01)	(-0.03, -0.07)	TA416 (126) (Adverse reactions, page 176)	Literature
Thrombocytopenia	-0.09 (-0.02)	(-0.06, -0.13)	Nafees 2008 (124) (Adverse reactions, page 176)	Literature
Encephalopathy	-0.22 (-0.04)	(-0.14, -0.31)	TA416 (126) (Adverse reactions, page 176)	Literature
Febrile neutropenia	-0.09 (-0.02)	(-0.06, -0.13)	Nafees 2008 (124) (Adverse reactions, page 176)	Literature
Hypotension	-0.07 (-0.01)	(-0.05, -0.10)	TA510 (128) (Adverse reactions, page 176)	Literature
Leukopenia	-0.09 (-0.02)	(-0.06, -0.13)	Nafees 2008 (124) (Adverse reactions, page 176)	Literature
Lymphocyte count decreased	-0.07 (-0.01)	(-0.05, -0.10)	TA510 (128) (Adverse reactions, page 176)	Literature
Neutrophil count decreased	0.00 (0.00)	(0.00, 0.00)	TA520 (131) (Adverse reactions, page 176)	Assumption of no disutility due to the very mild nature of this event
Pyrexia	-0.11 (-0.02)	(-0.07, -0.16)	Beusterien 2010 (130) (Adverse reactions, page 176)	Literature
White blood cell count decreased	-0.05 (-0.01)	(-0.03, -0.07)	In line with TA520 (131) (Adverse reactions, page 176)	Literature
Alanine aminotransferase increased	0.00 (0.00)	(0.00, 0.00)	(Adverse reactions, page 176)	Assumption of no disutility due to the mild nature of this event

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Device related infection	-0.05 (-0.01)	(-0.03, -0.07)	(Adverse reactions, page 176)	Assumed same as dyspnoea
Hyperglycaemia	-0.06 (-0.01)	(-0.04, -0.09)	Nafees 2016 (130) Assumed same as dyspnoea	Assumed same as hypotension
Hypertension	-0.07 (-0.01)	(-0.05, -0.10)	(Adverse reactions, page 176)	Assumed same as hypotension
Hypocalcaemia	-0.20 (-0.04)	(-0.13, -0.28)	(Adverse reactions, page 176)	Assumed same as hypokalaemia
Hypokalaemia	-0.20 (-0.04)	(-0.13, -0.28)	TA510 (128) (Adverse reactions, page 176)	Literature
Hypophosphatemia	-0.07 (-0.01)	(-0.05, -0.10)	TA510 (128) (Adverse reactions, page 176)	Literature
Hypoxia	-0.22 (-0.04)	(-0.14, -0.31)	Lachaine 2015 (132) (Adverse reactions, page 176)	Literature
Pneumonia	-0.22 (-0.04)	(-0.14, -0.31)	Stein et al., 2018 (133) (Adverse reactions, page 176)	Literature
Respiratory failure	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumed same as pneumonia
Rash	-0.06 (-0.01)	(-0.04, -0.09)	Stein et al., 2018 (133) (Adverse reactions, page 176)	Literature
Diarrheal	-0.05 (-0.01)	(-0.03, -0.07)	Nafees 2008 (124) (Adverse reactions, page 176)	Literature
Septic shock	-0.20 (-0.04)	(-0.13, -0.28)	Tolley 2013 (134) (Adverse reactions, page 176)	Literature

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Sepsis	-0.20 (-0.04)	(-0.13, -0.28)	Tolley 2013 (134) (Adverse reactions, page 176)	Literature
Neutropenic sepsis	-0.20 (-0.04)	(-0.13, -0.28)	(Adverse reactions, page 176)	Assumed same as sepsis
Abdominal pain	-0.05 (-0.01)	(-0.03, -0.07)	(Adverse reactions, page 176)	Assumption same as diarrhoea
VOD	-0.21 (-0.04)	(-0.13, -0.30)	TA541 (81) (Adverse reactions, page 176)	Literature
Decrease in appetite	0.00 (0.00)	(0.00, 0.00)	(Adverse reactions, page 176)	Assumption of no disutility due to the very mild nature of this event
Increase in blood bilirubin	0.00 (0.00)	(0.00, 0.00)	(Adverse reactions, page 176)	Assumption of no disutility due to the very mild nature of this event
Fungal pneumonia	-0.19 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumed same as pneumonia
Subdural hematoma	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumption same as encephalopathy in line with TA559 cc
Hypertransaminasemia	0.00 (0.00)	(0.00, 0.00)	(Adverse reactions, page 176)	Assumption of no disutility due to the very mild nature of this event
Infection pathogen unspecified	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumption same as sepsis
Bacterial infectious disorders	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumption same as sepsis
Viral infectious disorders	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumption same as sepsis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Fungal infectious disorders	-0.22 (-0.04)	(-0.14, -0.31)	(Adverse reactions, page 176)	Assumption same as sepsis
Lipase increase	0.00 (0.00)	(0.00, 0.00)	(Adverse reactions, page 176)	Assumption of no disutility due to the very mild nature of this event
Constipation	-0.05 (-0.01)	(-0.03, -0.07)	(Adverse reactions, page 176)	Assumed same as diarrhoea
Bacteraemia	-0.20 (-0.04)	(-0.13, -0.28)	(Adverse reactions, page 176)	Assumed same as sepsis
Allo-SCT utility decrement	-0.57 (-0.11)	(-0.34, -0.78)	Sung et al., 2003 (121) (Adverse reactions, page 176)	Literature

Key: AR, adverse reaction; HS, health state

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The economic analysis was conducted from the perspective of the NHS and PPS and therefore only direct healthcare costs were considered in the model base-case.

The economic SLR identified 12 publications reporting on healthcare resource utilisation (HRU) use in R/R B-cell ALL (Appendix I). None of these studies were however deemed relevant as only one study included data for the UK (Zhang et al. 2018 (138)). The resource use estimates in this study were informed by KOL opinion, as opposed to more reliable methods such as resource use measured prospectively. Resource use in the present analysis is thus informed by HRU and assumptions applied in previous appraisals in this disease area (79), (80), (81).

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug administration costs

The drug administration costs applied in the model are presented in Table 49. These costs refer to all treatments under evaluation as well as to costs associated with pre-infusion phase (KTE-X19 arm only).

Table 49: Drug administration costs used in the economic model

Mode of administration	Unit cost	Source
Oral	£211	Deliver Exclusively Oral Chemotherapy, currency code SB11Z, weighted average of outpatient, day case and other services. National Schedule of NHS Costs - Year 2019-20 (107)
Intravenous infusion	£303	Deliver more complex parenteral chemotherapy at first attendance, currency code SB13Z, outpatient (107)
Subcutaneous injections	£31	Cost per working hour for band 4 hospital-based nurses, PSS Research Unit, 2020 (139)
Average cost of hospitalisation per day	£550	Acute Lymphoblastic Leukaemia with CC score 0-5+, weighted average of currency codes SA24G-SA24J, Day case (107)
Community nurse home visit	£99	Specialist Nursing, cancer related adult face to face visit, currency code N10AF (107)

ICU stay	£1,620	Non-specific, general adult critical care patients predominate, weighted average of currency codes XC01Z- XC07Z (107)

Key: ICU, intensive care unit; NHS, national health service; PSS, Personal Social Services

B.3.5.1.2 Pre-treatment costs

As a CAR T-cell therapy, KTE-X19 is associated with costs prior to receiving an infusion. The following pre-treatment costs were applied in the first cycle of the model for patients receiving KTE-X19:

1 Leukapheresis

It was assumed that all KTE-X19 patients would receive leukapheresis to obtain T-cells. The cost of leukapheresis was estimated to be £1,549.81 based on the NICE TA559 (94), where a weighted average of NHS reference cost codes SA34Z - Peripheral Blood Stem Cell Harvest (£1,233.22) and SA18Z - Bone Marrow Harvest (£1,857.22) were used (107). Following the same approach using the most recently published NHS reference costs (2019-2020) resulted in a unit cost of £1,953.38. As a scenario analysis, the cost of leukapheresis was supplemented with the NHS reference cost for currency code SA43Z – Leucopheresis (£3,068.40) as in TA554 (79).

In order to reflect the clinical trial and the anticipated clinical setting, a correcting factor was applied to account for patients that have received leukapheresis but failed to receive the CAR T-cell infusion. For the base case, in line with mITT ZUMA-3 Phase 1 and Phase 2 combined dataset, the correcting factor (1.27) was calculated as proportion of patients that received leukapheresis in the ITT population (n=99) over number of patients that received leukapheresis in the mITT population (n=78, this corresponds to the entire group receiving CAR T-cell infusion).

When accounting for correcting factor, the total leukapheresis costs increased from £1,953.38 to £2,479.29.

2 Conditioning chemotherapy: to prepare patients to receive treatment

Based on the ZUMA-3 trial, it is expected that patients would receive a single round of conditioning chemotherapy, while waiting for their CAR T-cell infusion. Conditioning chemotherapy was assumed to be given for only 3 consecutive days (55). Based on TA554 (79), it was assumed that 65% of patients would receive this in the inpatient setting, whilst the remaining 35% would receive in the outpatient setting.

The following conditioning chemotherapies, in line with ZUMA-3 trial, were included in the economic analysis:

- Fludarabine: at a recommended dose of 25 mg/m^2/day for 3 consecutive days
- Cyclophosphamide: at a recommended dose of 900 mg/m^2/day for 1 day.

In order to reflect the clinical trial and the anticipated clinical setting, a correcting factor was applied to account for patients that have received conditioning chemotherapy but failed to receive the CAR T-cell infusion. For the base case, in line with mITT ZUMA-3 Phase 1 and Phase 2 combined dataset, the correcting factor (1.05) was calculated as proportion of patients that received conditioning chemotherapy in the ITT population (n=82) over number of patients that received conditioning chemotherapy in the mITT population (n=78, this corresponds to the entire group receiving CAR T-cell infusion).

Table 50 and Table 51 provide the details related to conditioning chemotherapy drug and administration costs.

3 Bridging chemotherapy: to stabilise disease while waiting for the infusion

Within the ZUMA-3 trial, the provision of bridging chemotherapy was left to investigator discretion and therefore a wide range of bridging chemotherapy regimens were received by patients. Therefore, in the economic model, a weighted average of bridging chemotherapy regimens was assumed based on the distributions observed in mITT ZUMA-3 Phase 1 and Phase 2 combined dataset. It

was assumed that all patients received bridging chemotherapy in the outpatient setting, as validated by UK clinical expert opinion in NICE appraisal TA554 (79). To determine costs, important patient characteristics such as height and weight were based on that of the mITT ZUMA-3 Phase 1 and Phase 2 combined dataset. Total bridging chemotherapy (drug and administration) costs were estimated to be £1,258.06.

In order to reflect the clinical trial and the anticipated clinical setting, a correcting factor was applied to account for patients that have received bridging chemotherapy but failed to receive the CAR T-cell infusion. For the base case, in line with mITT ZUMA-3 Phase 1 and Phase 2 combined dataset, the correcting factor (1.25) was calculated as proportion of patients that received bridging chemotherapy in the ITT population (n=91) over number of patients that received bridging chemotherapy in the mITT population (n=73).

When accounting for correcting factor, the total bridging chemotherapy costs increased from £1,258.06 to £1,568.27.

Table 50: Conditioning chemotherapy drug costs

Regimen	Unit cost	Recommended dose	Total dose	Average dose per KTE-X19 infusion	Total cost per dose	Unit cost source
Cyclophosphamide	£8.23/500 mg £13.55/1000 mg £27.50/2000 mg	900 mg/m^2	1731 mg	1	£27.10	eMIT (106)
Fludarabine	£20.28/50 mg	25 mg/m^2	48 mg	3	£60.85	(106)
Correcting factor						1.05%
Total conditioning chemotherapy drug costs						**£92.46**

Table 51: Conditioning chemotherapy administration costs

Hospital setting	Unit cost	Proportion	Number of days	Total administration	Unit cost source
Inpatient	£550	65.0%	7	£2502.89	Weighted average, Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J, Day case, National Health Service reference costs 2019/2020
Outpatient	£302.53	35.0%	3	£317.66	Deliver more complex parenteral chemotherapy at first attendance, outpatient (SB13Z), National Health Service reference costs 2019/2020
Correcting factor					1.05%
Total conditioning chemotherapy administration costs					**£2,965.19**

Table 52: KTE-X19 bridging therapy costs

Regimen	Frequency	Unit cost	Dosing	Number of admins	Total acquisition costs	Total administration costs	Source
Dexamethasone	48.72%	£8.49	20 mg IV 3 – 4 days per week	6	£8.49	£210.82	eMIT (106)
Vincristine (non-liposomal)	37.18%	£3.43	1 – 2 mg IV weekly	1	£13.70	£432.19	(106)
Fludarabine	15.38%	£20.28	30 mg/m^2 IV days 1 – 2	3	£101.42	£864.37	(106)
Methotrexate	16.67%	£5.83	250 mg/m^2 day 1	1	£5.83	£432.19	(106)
Vincristine (liposomal)	20.51%	£6.48	2.25 mg/m^2 weekly	1	£32.41	£432.19	(106)
Cytarabine	28.21%	£5.58	0.5 g/m^2 IV 4 doses on days 2 and 3	3	£22.32	£864.37	(106)
Cyclophosphamide	14.10%	£8.18	150 mg/m^2 for 3 days	4	£24.54	£366.82	(106)
Mercaptopurine	11.54%	£11.25	50 – 75 mg/m^2/day	10	£22.50	£244.55	NHS drug tariff, October 2021 (140)
Doxorubicin	10.26%	£20.02	50 mg/m^2 once	1	£980.98	£302.53	(106)
Idarubicin	7.69%	£87.36	6 mg/m^2	3	£873.60	£864.37	NHS indicative price, BNF 2021 (141)
Hydroxyurea	5.13%	£9.54	15 – 50 mg/kg/day daily	10	£9.54	£210.82	(106)
Etoposide	2.56%	£15.99	100 mg/m^2 for days 1 – 5 every 3 – 4 weeks	7	£15.99	£2,160.93	(106)

B.3.5.1.3 Treatment costs

1 KTE-X19

The cost of a single, one-time infusion of KTE-X19 is [redacted] after the PAS is applied. Based on data from the mITT ZUMA-3 Phase 1 and Phase 2 combined dataset, patients who received a KTE-X19 infusion were hospitalised for an average of [redacted] days, with an average of [redacted] days spent in the intensive care unit (ICU), in addition to hospitalisation for pre-treatment (56). This data was used to inform the resource use in the administration cost calculations for KTE-X19, as summarised in the table below.

Table 53: KTE-X19 infusion and administration costs

Input	Cost	Source
Drug acquisition costs		
KTE-X19 infusion	[redacted]	KITE (includes PAS)
Drug administration costs		
Cost of hospitalization (non-ICU)	£550	NHS reference costs 2019/20 Weighted average, Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J Day case
Average length of stay (non-ICU), days	[redacted]	mITT ZUMA-3 Phase 1 and Phase 2 combined
Cost of ICU stay	£1,620	NHS reference costs 2019/20 Weighted average, Adult Critical Care XC01Z- XC07Z
Average length of stay, ICU, days	[redacted]	mITT ZUMA-3 Phase 1 and Phase 2 combined
Total administration costs	**£14,765**	

Key: ICU, intensive care unit; NHS, national health service

2 Inotuzumab

The unit cost of inotuzumab is £8,048 per 1 mg (140). Inotuzumab is administered 0.8 mg/m^2 on day 1, 0.5 mg/m^2 on day 8 and 0.5 mg/m^2 on day 15 of a 21-day cycle. From cycle 2 onwards, inotuzumab is administered 0.8 mg/m^2 or 0.5 mg/m^2 on day 1, 0.5 mg/m^2 on day 8 and 0.5 mg/m^2 on day 15 of a 28-day cycle (section B.3.2.3.2). It was assumed that dosing in subsequent cycles would be the same as in cycle 1, that is on day 1 of the 2nd (or any subsequent) cycle, the dose used in the

cost calculations was 0.8 mg/m^2. Inotuzumab treatment may continue up to 6 cycles. Since the storage conditions for inotuzumab after the opening of the vial preclude any vial sharing (according to SmPC, any unused vial can only be stored in a fridge for up to 4 hours and cannot be frozen (30)), vial wastage was assumed on a per administration basis. In the model it was assumed that patients on inotuzumab would receive on average 3 cycles of therapy, in line with INO-VATE study results (INO-VATE reported a 3 median number of cycles for patients on inotuzumab).

Table 54: Inotuzumab drug acquisition costs

Cycle	Recommended dose	Total dose	Number of vials required	Cost per administration
Cycle 1 – 21 days	0.8 mg/m^2	1.55 mg	2	£16,096
	0.5 mg/m^2	0.97 mg	1	£8,048
	0.5 mg/m^2	0.97 mg	1	£8,048
Cycle 2 onwards – 28 days	0.8 mg/m^2	1.55 mg	2	£16,096
	0.5 mg/m^2	0.97 mg	1	£8,048
	0.5 mg/m^2	0.97 mg	1	£8,048

Inotuzumab is assumed to be administered on an inpatient basis for the first 9.5 days of the cycle 1, in line with the ERG preferred approach in NICE appraisal TA541 (81). For the remainder of cycle 1 and for cycle 2 onwards, patients receive inotuzumab on an outpatient basis.

Table 55: Inotuzumab administration costs

Input	Unit cost/resource use	Source
Cycle 1		
Cost of hospitalization (non-ICU) for first ten days	£550	Weighted average, NHS reference costs 2018/19 Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J Day case
Average length of stay (non-ICU), days	9.5	TA541 (81)
Cost of administration	£303	Deliver more complex parenteral chemotherapy at first attendance,

		outpatient, Currency code: SB13Z. NHS reference costs 2019-2020
Administrations in cycle 1	1	Number of administrations required to complete cycle 1 after 9.5 days in inpatient setting
Total administration costs cycle 1	**£5,528**	
Cycle 2 onwards		
Cost of administration	£303	Deliver more complex parenteral chemotherapy at first attendance, outpatient, Currency code: SB13Z. NHS reference costs 2019-2020
Administrations in cycle 2 onwards	3	
Total administration costs cycle 2 onwards	**£908**	

Key: ICU, intensive care unit; NHS, national health service

3 Blinatumomab

Blinatumomab costs £2,017 per 38.5 µg vial, of which only 28 µg are usable (142). It is administered as a continuous IV infusion over 4 weeks, with 9 µg/day for the first 7 days of cycle 1, then 28 µg/day for the remainder of cycle 1 and 28 µg/day for subsequent cycles. Between each cycle there is a treatment-free interval of 2 weeks. Patients who have no signs of cancer after 2 full cycles of treatment may be treated with up to 3 additional cycles. Based on the UK clinical opinion presented during the NICE TA554 for tisagenlecleucel in R/R ALL (which included adult dosing) (79), vial wastage was assumed on a per administration basis. The duration of treatment with blinatumomab was calculated from treatment exposure reported in von Stackelberg et al., 2016 (109). The study reported that 96% of patients received one cycle of treatment, 31% of patients received two cycles, 10% of patients received three cycles, and 4% of patients received 5 cycles. This represents an average of 1.45 treatment cycles per patient. The drug acquisition costs are reported in Table 56.

Blinatumomab is assumed to be administered on an inpatient basis for the first 10 days of the cycle 1, resulting in 10-days of in-patient costs. For the remainder of the cycle, patients receive blinatumomab on an outpatient basis via a pump, which requires a change of bag every three days in the outpatient setting. For cycle 2+, patients continue receiving blinatumomab via a pump, incurring the daily cost of the

pump and a bag change every three days in the outpatient setting. The drug administration costs for blinatumomab are presented in Table 57.

Table 56: Blinatumomab acquisition costs

Cycle	Number of days	Dose per day (µg)	Number of vials	Total cost
Cycle 1, days 1 – 7	7	9	7	£14,119
Cycle 1, days 8 – 28	21	28	21	£42,357
Cycle 2+, days 1 – 28	28	28	28	£56,476

Table 57: Blinatumomab administration costs

Input	Unit cost/resource use	Source
Cost of hospitalization (non-ICU)	£550	Weighted average, NHS reference costs 2018/19 Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J Day case
Average length of stay (non-ICU), days	10.0	Blinatumomab SmPC
Daily pump cost	£4.18	Inflated from the 2014/15 cost reported in NICE TA450 (143)
IV cost in outpatient setting	£303	NHS Reference costs 2019/2020
Total administration costs	**£8,338.87**	

Key: ICU, intensive care unit; NHS, national health service; SmPC, summary of product characteristics

4 Ponatinib

The recommended dose for ponatinib is 45 mg QD for a 3-month cycle where patients with minor cytogenetic response (MCyR) are then treated with allo-SCT. If there is no response in the first cycle, treatment is discontinued. Ponatinib is assumed to be given for a maximum of 91 days (144). In the model, ponatinib acquisition and administration costs are applied as long as patients remain in EFS health state (EFS used as a proxy for time-on-treatment). The acquisition costs for ponatinib were sourced from the BNF (145) and are reported in Table 58. Adjusting for the pack size (30) and weekly cycle length (7 days), this results in a cost per model cycle of £1,178 (7*5050/30). Additionally, since ponatinib is assumed to be

given in combination with FLAG-IDA, additional acquisition costs were included, resulting in additional £3,642 each 4 weeks (see section B.3.5.1.3.5).

Although ponatinib is orally administered, there are still some administration costs that apply to this treatment due to the supervision and monitoring of patients that is required. The administration cost was calculated on a per cycle basis as the unit cost of oral administration (£211) by the cycle length in days (7) divided by the number of tablets per pack (30). This resulted in a total administration cost per cycle of £49 (7*210/30). Additionally, the administration costs for FLAG-IDA were also included, resulting in additional £9,241 each 4 weeks (see section B.3.5.1.3.5).

Table 58: Ponatinib acquisition costs applied in the model

Pack size	Dose per pack	Unit cost	Source	Cost per weekly cycle
30	45 mg	£5,050	BNF	£1,178.33

5 FLAG-IDA

Dosing for FLAG-IDA is line with UK clinical practice and is comprised of:

- Fludarabine: 30 mg/m^2 for 5 consecutive days per 28-day cycle for up to 4 cycles;
- Cytarabine: 2 g/m^2 for 6 consecutive days per 28-day cycle for up to 4 cycles;
- Filgrastim: 0.005 mg/kg for 9 total days
- Idarubicin: 8 mg/m^2 for 3 days per 28-day cycle.

As per NICE TA for tisagenlecleucel in R/R ALL (TA554), vial sharing was not considered in the base case.

The acquisition cost of the various treatments that comprise this regimen are reported in Table 59. The acquisition costs applied in the model are calculated based on weight-adjusted dosing and are presented in Table 60. The maximum treatment duration for FLAG-IDA was estimated to be 4 cycles, in line with UK clinical practice, with 17 days administered on an inpatient basis (80). The costs associated with the administration of FLAG-IDA are summarised in Table 61.

Table 59: FLAG-IDA acquisition costs

Treatment	Vial/pack size	Concentration per vial/unit	Unit cost	Source
Fludarabine	2 ml	50 mg	£20.28	eMIT (106)
Cytarabine	1	1000 mg	£5.58	(106)
Filgrastrim	5	1 mg	£250.75	NHS drug tariff, October 2021 (140)
Idarubicin	1	5 mg	£87.36	NHS indicative price, BNF 2021 (141)
	1	10 mg	£174.72	

Table 60: FLAG-IDA acquisition costs applied in the model

Treatment	Recommended dose	Weight-adjusted dose	Drug cost per administration	Number of administrations per treatment cycle
Fludarabine	30 mg/m^2 for 5 consecutive days per 28-day cycle up to 4 cycles	58.00 mg	£41	5
Cytarabine	2 g/m^2 for 6 consecutive days per 28-day cycle up to 4 cycles	3,866.53 mg	£22	6
Filgrastrim	0.005 mg/kg for 9 days	0.4049 mg	£251	9

Idarubicin	8 mg/m^2 (3 days per treatment cycle)	15.47 mg	£349	3
Total treatment costs (per cycle)	**£3,642**			

Table 61: FLAG-IDA administration costs applied in the model

Input	Unit cost/resource use	Source
Cost of hospitalisation (non-ICU)	£550	Weighted average, NHS reference costs 2018/19 Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J Day case
Average length of stay (non-ICU), days	17	TA450 (80)
Total administration costs (per cycle)	**£9,241**	

Key: ICU, intensive care unit; NHS, national health service

B.3.5.2 Health-state unit costs and resource use

Health state costs were comprised of monitoring and follow-up costs such as outpatient consultant visits, clinical tests and procedures. The frequency of monitoring and follow-up was assumed to vary for KTE-X19 and comparators in the EFS health state. Healthcare resource use (HRU) frequency was based on the tisagenlecleucel NICE submission for R/R B-cell ALL (TA554) (79). Since patients alive at 3 years were assumed to be cured, it was assumed that these patients would incur lower healthcare resource costs. HRU frequency, unit costs and total health state costs are presented in Table 62 to Table 64. All unit costs were derived from NHS reference costs 2019-2020 (107).

Table 62: Health state costs for KTE-X19, EFS health state

Item	Unit cost	Weekly frequency (Y1)	Weekly frequency (Y2)	Weekly frequency (After Y3)	Weekly frequency (Cured)	Cost source
Consultant visit	£401.78	0.23	0.08	0.04	0.02	NHS Reference Costs 2019-2020: Consultant Led, WF01D-370
Haematology panel	£2.53	0.31	0.08	0.04	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS05, Haematology114
CSF	£464.86	0.02	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, HC72A-303
Bone marrow aspirate	£252.40	0.06	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, SA33Z-303, Clinical haematology114
Bone marrow biopsy	£252.40	0.06	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, SA33Z-303, Clinical haematology115
ECG	£328.55	0.02	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, EY51Z-303, Clinical haematology114
Serum test	£1.81	0.10	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS03, Integrated blood services114
B-cell and T-cell test	£2.53	0.15	0.04	0.04	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS05, Haematology 114
Coagulation panel	£1.81	0.06	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS03, Integrated blood services114
Chemistry panel	£1.20	0.31	0.08	0.04	0.00	NHS Reference Costs 2019-2020: Direct accessed patient services, DAPS04, Clinical biochemistry114
Weekly cost		**£138.44**	**£31.18**	**£15.64**	**£7.70**	

Table 63: Health state costs for comparators, EFS health state

Item	Unit cost	Weekly frequency (Y1)	Weekly frequency (Y2)	Weekly frequency (After Y3)	Weekly frequency (Cured)	Cost source
Consultant visit	£401.78	0.11	0.08	0.04	0.02	NHS Reference Costs 2019-2020: Consultant Led, WF01D-370
Haematology panel	£2.53	0.11	0.08	0.04	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS05, Haematology114
CSF	£464.86	0.02	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, HC72A-303
Bone marrow aspirate	£252.40	0.06	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, SA33Z-303, Clinical haematology114
Echocardiogram	£328.55	0.02	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, EY50Z-303, Clinical haematology114
Liver function test	£1.20	0.11	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS04, Clinical biochemistry114
ECG	£328.55	0.02	0.00	0.00	0.00	NHS Reference Costs 2019-2020: Outpatient procedures, EY51Z-303, Clinical haematology114
Weekly cost		**£72.97**	**£30.99**	**£15.50**	**£7.70**	

Key: CSF, cerebrospinal fluid; ECG, echocardiogram; EFS, event-free survival; NHS, National Health Service

Table 64: Health state costs, all treatments, progressed disease health state

Item	Unit cost	Weekly frequency	Cost source
Consultant visit	£401.78	0.11	NHS Reference Costs 2019-2020: Consultant Led, WF01D-370
Haematology panel	£2.53	0.11	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS05, Haematology114
CSF	£464.86	0.02	NHS Reference Costs 2019-2020: Outpatient procedures, HC72A-303
Bone marrow aspirate	£252.40	0.02	NHS Reference Costs 2019-2020: Outpatient procedures, SA33Z-303, Clinical haematology114
Echocardiogram	£328.55	0.02	NHS Reference Costs 2019-2020: Outpatient procedures, EY50Z-303, Clinical haematology114
Liver function test	£1.20	0.11	NHS Reference Costs 2019-2020: Directly accessed patient services, DAPS04, Clinical biochemistry114
Weekly cost		**£66.67**	

Key: CSF, cerebrospinal fluid; NHS, National Health Service

B.3.5.3 Subsequent treatment costs

The economic analysis assumed that patients could receive either subsequent treatments or allo-SCT, based on respectively trial data. Distribution of subsequent treatments was based on the ZUMA-3 trial (Phase 1 and Phase 2 combined) (Table 65). However, patients were assumed to not be re-treated with their initial therapy and therefore the distribution was re-weighted to remove the re-treatment therapy in the case of blinatumomab, inotuzumab and ponatinib. Patients who received salvage chemotherapy initially were assumed to receive the same frequency of subsequent treatment as KTE-X19. The list of subsequent treatment considered in the economic model is line with the UK treatment pathway for patients with relapsed/refractory ALL disease.

Subsequent treatment costs are applied as a one-off weighted cost upon progression (i.e., when leaving EFS health state) and are detailed in Table 66.

B.3.5.3.1 Subsequent allo-SCT

The economic analysis assumed that in lieu of subsequent treatment, some patients may receive a subsequent allo-SCT after initial treatment. The rates of subsequent allo-SCT were obtained from the same sources that informed adverse events and are outlined in Table 67.

Based on clinical expert opinion, no allo-SCTs were assumed for the KTE-X19 arm. As explained in section B.3.2.2, according to UK clinical experts, no patients would receive a second allo-SCT and allo-SCT is not expected to be given as consolidation following a CAR T-cell therapy (see section B.3.5.3.1). All of the patients in the ZUMA-3 study who received an SCT did so as consolidation following KTE-X19 and not following treatment with subsequent therapies. In addition, the KM OS plot (July 2021 data cut) stratified by subsequent SCT and OCR demonstrates that OS benefit appears independent of whether subsequent SCT was carried out (see B.2.6.1.1, Data from the most recent data cutoff (23/07/21) provides longer-term evidence on the effect of allo-SCT consolidation of KTE-X19 (Figure 22). Of note is that sensitivity analysis of median OS stratified by censoring at allo-SCT demonstrate that survival appeared to be independent of subsequent SCT based on the Phase 2 mITT

population (56). This supports the curative, standalone potential of KTE-X19 (Figure 22).

The inclusion of ZUMA-3 allo-SCT is explored in scenario analyses. 14 over 78 patients received allo-SCT in the mITT ZUMA-3 Phase 1 and Phase 2 combined dataset.

Table 65: Health state costs, all treatments, progressed disease health state

Subsequent treatment					
Initial regimen	**Inotuzumab + ponatinib**	**Inotuzumab**	**Cyclophosphamide + dexamethasone**	**Blinatumomab**	**Source**
KTE-X19	10.26%	7.69%	11.54%	7.69%	mITT ZUMA-3 Phase 1 and Phase 2 combined
Blinatumomab	13.11%	9.83%	14.74%	0.00%	Assumption same as ZUMA-3, with blinatumomab re-distributed
Inotuzumab	0.00%	0.00%	19.23%	12.82%	Assumption same as ZUMA-3, with inotuzumab re-distributed
Ponatinib	0.00%	11.06%	16.59%	11.06%	Assumption same as ZUMA-3, with ponatinib re-distributed
FLAG-IDA	10.26%	7.69%	11.54%	7.69%	Assumption same as ZUMA-3

Table 66: Subsequent therapy one-off costs

Initial regimen	Weighted acquisition cost	Weighted administration cost
KTE-X19	£24,967	£3,750
Blinatumomab	£23,853	£3,908
Inotuzumab	£10,505	£1,264
Ponatinib	£19,740	£2,924
FLAG-IDA	£24,967	£3,750

Table 67: Subsequent allo-SCT distribution

Initial regimen	Proportion receiving allo-SCT	Source
KTE-X19	0.0%	Assumption (see body text for justification)
Blinatumomab	13.21%	SCHOLAR-3 SCA-3
Inotuzumab	48.20%	INO-VATE
Ponatinib	46.88%	PACE
FLAG-IDA	22.93%	Pooled standard of care arm INO-VATE and TOWER*
*A pooled allo-SCT distribution was used for the most conservative estimate of allo-SCT rates for salvage chemotherapy. The overall survival hazard ratios for KTE-X19 vs. salvage chemotherapy are estimated at 0.31 and 0.33 for pooled (i.e., INO-VATE and TOWER) and INO-VATE individually, respectively. Though the INO-VATE trial is longer, only three-months are needed to see a complete response from allo-SCT which is available in both trials. Thus, the lower overall estimate for allo-SCT use for salvage chemotherapy was used for a more conservative estimate.		

Key: SCT, stem cell transplant

The costs associated with a subsequent allo-SCT were considered in three parts: stem cell harvesting, the cost of the allo-SCT procedure, and the cost of up to 24 months follow-up after the allo-SCT procedure. The cost of harvesting and the allo-SCT procedure were based on NHS Reference Costs 2019 – 2020. The cost associated with follow-up was based on NHS Blood and Transplant costs in 2014 (inflated 2019 – 2020) and were weighted based on the proportion of patients alive at different time periods.

Table 68: Subsequent allo-SCT cost

Component	Cost	Source
Stem cell harvesting	£4,699.80	NHS Reference Costs 2019-2020: weighted average of elective inpatient SA18Z bone marrow harvest and SA34Z peripheral blood stem cell harvest
Allo-SCT procedure	£66,744.65	NHS Reference Costs 2019-2020: weighted average of elective inpatient paediatric bone marrow transplant and peripheral blood stem cell transplant (SA20B – SA23B, S38B, SA39B)
Follow-up, up to 24 months post allo-SCT	£46,307.00	NHS Blood and Transplant 2014, weighted average based on proportion alive that received an allo-SCT (Table 69)

Key: NHS, national health service; SCT, stem cell transplant

Table 69: Subsequent allo-SCT follow-up cost breakdown

Component	Cost (2012-2013)	Proportion alive	Weighted cost 2019-2020
Follow-up 1 (up to 6 months)	£28,390	90.00%	£46,307.00
Follow-up 2 (6 -12 months)	£19,502	48.00%	
Follow-up 3 (12-24 months)	£14,073	31.00%	

Key: SCT, stem cell transplant

B.3.5.4 Adverse reaction unit costs and resource use

Unit costs of adverse events were sourced from the most recent NHS reference costs (2019/2020) (107) and are presented in Table 72. Unit costs were combined with the adverse event rates reported in section (Table 42) and applied as one-off costs in in the cycle during which the AE occurred. The total one-off adverse event costs applied for each treatment arm are presented in Table 73.

CRS is an AE that is specific to treatment with both KTE-X19 and blinatumomab and is associated with substantial resource use. CRS event costs were calculated assuming a mean duration of 4.3 days in ICU (based on data from ZUMA-3) in addition to the acquisition cost of tocilizumab and were applied to the proportion of patients experiencing CRS. Treatment with tocilizumab was assumed to be given at a dose of 8 mg/kg daily. CRS AE costs are summarized in Table 70.

Table 70: CRS AE cost

Component	Unit cost	Duration	Source
ICU stay	£1,620	4.3 days	Weighted average, NHS reference costs 2019/20 Adult Critical Care XC01Z- XC07Z
Tocilizumab	£913/vial	8 mg/kg for 10 days	NHS drug tariff, October 2021 (140)
Total	**£7,878.57**		

Key: AE, adverse event; CRS, cytokine release syndrome; ICU, intensive care unit; NHS, National Health Service

VOD is also associated with substantial resource use. VOD costs were calculated based on NHS policy and the NICE submission for inotuzumab ozogamicin (81). It

was assumed that to treat VOD, 85% of patients would require an ICU stay, and the remaining 15% would require high dependency care. Costs were inflated to 2020 costs. All patients with VOD were assumed to require treatment with defibrotide for a mean duration of treatment of 23 days. VOD AE costs are summarized in Table 71.

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 Terminal care costs

All patients are assumed to incur a palliative care cost before death. This includes costs related to hospital care in the 90 days prior to death, based on Georghiou and Bardsley (146). Terminal care costs comprise district nurse time, nursing and residential care, hospital care and Marie Curie nursing costs. A one-off terminal care cost of £8,437 after adjustment for inflation using the consumer price index (CPI) weights for health (147) was applied to patients upon entry to the death health state.

Table 71: VOD AE Cost

Component	Unit Cost	Duration	Source
Hospital stay	£2,156.73	28.5 days	TA541 (81)
Defibrotide	£365/vial	23 days	MIMS
Total	**£153,768.72**		

Key: MIMS, Monthly Index of Medical Specialties; VOD, veno-occlusive disease

Table 72: Unit costs of adverse events included in the model

Adverse event	Unit cost	Source
CRS	£7,878.57	Cost is estimated as a combination of ICU stay and treatment with tocilizumab (Table 70)
Anaemia	£333.89	Weighted average of Day Case Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia (SA01G– SA01K), Haemolytic Anaemia (SA03G–SA03H), Iron Deficiency Anaemia (SA04G–SA04L) and Megaloblastic Anaemia (SA05G–SA05J), NHS reference costs 2019/20 (107)
Neutropenia	£332.11	Weighted average of DC Agranulocytosis (SA35A–E) (107)
Platelet count decreased	£367.76	Assumed same as thrombocytopenia
Thrombocytopenia	£367.76	Weighted average of DC thrombocytopenia SA12G- K (107)
Encephalopathy	£2,845.54	Weighted average of NES & NEL Cerebrovascular Accident, Nervous System Infections or Encephalopathy AA22C-G (107)

Febrile neutropenia	£1,533.37	Weighted average of NEL & NES - Other haematological or Splenic disorders (SA08G-J) (107)
Hypophosphatemia	£617.05	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions (107)
Fluid overload	£617.05	Weighted average of the codes: KC05G, KC05H, KC05J, KC05K, KC05L, KC05M, KC05N for Fluid or Electrolyte Disorders, without Interventions (107)
Hypotension	£457.41	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J) (107)
Leukopenia	£457.41	
Lymphocyte count decreased	£457.41	
Neutrophil count decreased	£332.11	Assume same as neutropenia
Pyrexia	£396.50	Weighted average of DC Fever of Unknown origin with and without intervention WJ07B-C (107)
White blood cell count decreased	£457.41	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J) (107)
Alanine aminotransferase increased	£380.38	DC liver failure disorders without interventions, GC01F (107)
Device related infection	£1,017.17	Weighted average of NES HE81B-C Infection or Inflammatory Reaction, due to, Internal Orthopaedic Prosthetic Devices, Implants or Grafts, with CC Score 0-5 (107)
Hyperglycaemia	£457.41	Weighted average of DC - Other haematological or Splenic disorders (SA08G-J) (107)
Hypertension	£334.75	Hypertension, Day case, EB04Z (107)
Hypokalaemia	£617.05	Weighted average NES Fluid or Electrolyte Disorders, without Interventions, with CC Score 0-10+ KC05G-N (107)

Hypoxia	£712.96	Weighted average of DC - Respiratory Failure with single and multiple without Interventions, with CC Score 0-11+ DZ27N-U (107)
Pneumonia	£792.30	Weighted average of NES - Lobar, Atypical or Viral Pneumonia, with Multiple Interventions, with CC 0-14+ ScoreDZ11K-V (107)
Respiratory failure	£712.96	Weighted average of DC - Respiratory Failure with single and multiple without Interventions, with CC Score 0-11+ DZ27N-U (107)
Rash	£369.68	Weighted average of DC Skin Disorders without Interventions, with CC Score 0-1-19+ JD07E-K (107)
Diarrhea	£573.23	Weighted average DC Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions, with CC Score 0-2 FD10D-M (107)
Septic shock	£1,503.19	DC Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1 WH07D (107)
Sepsis	£1,503.19	
Neutropenic sepsis	£1,503.19	Assumed same as sepsis
Abdominal pain	£2,720.03	NEL Abdominal Pain with Interventions FD05A (107)
VOD	£153,768.72	In line with TA541, based on the SMC submission for defibrotide, where VOD is treated with defibrotide (£3,650 for the 10 vials with 200mg/2.5ml) and is administered at a dose of 6.25mg/kg every 6 hours for 21 days. 86% of patients will require an ICU and 15% will require high dependency care (Table 71)
Decrease in appetite	£338.68	Specialist Eating Disorder Services, Outpatient Attendances, admitted patient and community service nurse, codes: SPHMSEDSAAPC, SPHMSEDSACC, SPHMSEDSAOP (107)
Increase in blood bilirubin	£457.07	NES Toxic Effect of Other Substance with CC Score 1-2+ WH03A -B (107)
Fungal pneumonia	£792.30	Assume same as pneumonia

Subdural hematoma	£936.26	Weighted average DC Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury, with CC Score 0-2-15+AA26C-AA26H (107)
Hypertransaminasaemia	£380.38	Assume same as ALT increase
Infection pathogen unspecified	£666.13	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+-15+WH07A-WH07G (107)
Bacterial infectious disorders	£666.13	
Viral infectious disorders	£666.13	
Fungal infectious disorders	£666.13	
Lipase increase	£813.00	Assume 1 Day Case, total HRGs, NHS reference costs (107) in line with TA451(82)
Constipation	£573.23	Assume same as diarrhoea
Acute kidney injury	£415.47	Weighted average, DC Acute Kidney Injury without Interventions, with CC Score 0-3 LA07M-LA07P (107)
Pulmonary edema	£432.50	Weighted average DC Pulmonary Oedema without Interventions, with CC Score 0-5 DC DZ20F- DZ20E (107)
Bacteraemia	£1,503.19	DC Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1 WH07D (107)

Key: CRS: cytokine release syndrome; NHS, National Health Service; NR: not reported; VOD: veno-occlusive disease

Table 73: Total one-off adverse event costs used in the model

Treatment	Total one-off cost
KTE-X19	[redacted]
Inotuzumab	£18,140.98
Blinatumomab	£768.71
Ponatinib	£515.34
FLAG-IDA	£2,541.32

Table 74: Terminal care costs

Item	Unit cost	Year	Unit cost – 2020	Source
District nurse	£278	2010/2011	£346	Georghiou and Bardsley
Nursing and residential care	£1,000	2009/2010	£1,285	
Hospital care – inpatient	£550	2010/2011	£684	
Hospital care – final 3 months of life	£4,500	2011/2012	£5,437	
Marie Curie nursing service	£550	2010/2011	£684	
Total	£6,878		£8,437	

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Please see Table 137 in Appendix M for the summary of input parameters.

B.3.6.2 Assumptions

A list of the assumptions applied in the model base-case and justifications for these assumptions is provided in Table 75.

Table 75: List of assumptions for the base case analysis

Assumption	Justification	Source/Exploration in scenario analysis
Patients in the KTE-X19 arm who did not receive infusion due to AE were assumed to receive FLAG-IDA, while the remaining patients that did not receive infusion were assumed to receive comparator therapies	Patients that fail to receive infusion due to AE are expected to have poor prognosis, and thus they are assumed to follow salvage chemotherapy EFS and OS curves. The remaining patients who fail to receive infusion for other reasons (manufacture failure, eligibility criteria etc.) are not assumed to have poor prognosis and thus can be assumed to be treated with inotuzumab, blinatumomab, or ponatinib (depending on the subgroup under evaluation).	ERG preference in NICE TA554 (79)
Patients who remain alive after 3 years in the model were considered to be effectively cured, but with a heightened risk of mortality versus the general population.	It has been established that patients with ALL who remain alive in the mid-term can be considered effectively cured (96). The concept of cure following CAR-T treatment has been accepted as plausible by NICE in other indications (94), (97), (95).	Cure timepoint explored in sensitivity analyses. SMR post-cure explored in scenario analyses (SMR of 2.5, as per TA541 (81), rather than 1.09 from TA567 (97).
Naïve ITCs are used over MAICs to inform relative efficacy between KTE-X19 and comparators (where no synthetic control arm was available)	KTE-X19 is positioned for patients who have either failed or are unlikely to achieve SCT. The ZUMA-3 study is generalisable to the likely positioning of KTE-X19 in the UK NHS. Comparators are primarily bridging treatments to SCT and thus studies such as TOWER and INO-VATE are not representative of the patients likely to be selected for treatment with KTE-X19 in the	MAICs are explored in sensitivity analyses where naïve ITCs were preferred.

	UK NHS. As the target population in the MAICs is different to that of KTE-X19, a MAIC analysis would not reflect the likely patient population relevant to KTE-X19.	
KTE-X19 clinical efficacy is informed by ZUMA-3 mITT Phase 1 and Phase 2 combined in the Ph- subgroup economic analysis	For consistency with the other comparisons, the model uses the Phase 1 and Phase 2 combined data rather than the Phase 2 used in the SCHOLAR-3 SCA-3 analysis presented in the ITC section. The baseline characteristics are similar for the Phase 1 and Phase 2 combined dataset compared to the isolated Phase 2 dataset. Adopting the Phase 1 and Phase 2 combined dataset would thus be unlikely to affect the matching process in the SCHOLAR-3 study	A scenario is explored whereby the ZUMA-3 Phase 2 dataset informs the KTE-X19 arm.
Subsequent treatment options for KTE-X19 patients	No allo-SCT was assumed for KTE-X19. Clinical experts stated that in the UK no allo-SCT would be given following treatment with a CAR T-cell. OS outcome stratified by subsequent SCT and OCR demonstrates that OS benefit appears independent from subsequent SCT (see B.2.6.1.1, Data from the most recent data cutoff (23/07/21) provides longer-term evidence on the effect of allo-SCT consolidation of KTE-X19 (Figure 22). Of note is that sensitivity analysis of median OS stratified by censoring at allo-SCT demonstrate that survival appeared to be independent of subsequent SCT based on the Phase 2 mITT population (56). This	Costs of allo-SCT in the KTE-X19 arm included in a sensitivity analysis

	supports the curative, standalone potential of KTE-X19. (Figure 22)	

Key: AE, adverse event; ALL, acute lymphoblastic lymphoma; EFS, event-free survival; ITC, indirect treatment comparison; KM, Kaplan-Meier; mITT, modified intention-to-treat; NHS, national health service; OCR, complete remission rate; OS, overall survival; R/R, relapsed/refractory; SCA, synthetic control arm; SCT, stem cell transplant; SmPC, summary of product characteristics; SMR, standardised mortality ratio

B.3.7 Base-case results

Given the availability of MAICs, which would change the costs and QALYs in the KTE-X19 arm, only pairwise results are presented for each comparison below. Clinical outcomes and disaggregated results from the model are presented in Appendix J.

B.3.7.1 Overall population

In the comparison versus inotuzumab (using a naïve comparison), it can be seen in Table 76 that although KTE-X19 is associated with higher costs it is also associated with substantial life-year and QALY gains, with an incremental gain of 4.053 LYs and [redacted] QALYs. The ICER of £18,353 lies considerably below the willingness to pay (WTP) threshold of £50,000/QALY for end-of-life (EoL) therapies.

In the comparison versus FLAG-IDA (using a naïve comparison) it can be seen in Table 76 that although KTE-X19 is associated with higher costs it is also associated with substantial life-year and QALY gains, with an incremental gain of 6.210 LYs and [redacted] QALYs. As FLAG-IDA is largely comprised of generic drugs, the cost increase is substantial when compared with the comparisons versus novel agents, but as expected the QALY gains are substantially greater with the novel agents. The ICER of £33,449 per QALY lies below the WTP threshold of £50,000/QALY for EoL therapies. These results should, however, be considered alongside clinician feedback that few patients are offered this option given both its poor effectiveness and poor toxicity profile. The latter is of particular importance in the expected positioning of KTE-X19, as many patients will have already been through a burdensome SCT and/or relapsed following multiple lines of therapy.

Table 76: Base-case results (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.411	[redacted]	-	-	-	-
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	4.053	[redacted]	£18,353
FLAG-IDA	[redacted]	2.200	[redacted]	[redacted]	6.210	[redacted]	£33,449

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.7.2 Ph- population

The base-case cost-effectiveness results for the Ph- population are presented in Table 77. In the base-case comparison versus blinatumomab, individual blinatumomab-naïve patients in the SCHOLAR-3 SCA-3 cohort, were matched to ZUMA-3 patients, regardless of whether they were blinatumomab naïve or experienced. Despite the inherent bias against KTE-X19 in this comparison, it can be seen in Table 77 that KTE-X19 is more costly (incremental costs of [redacted]) but also more effective against blinatumomab. KTE-X19 is associated with an incremental QALY gain of [redacted] QALYs and 4.825 LYs vs. blinatumomab. The ICER for KTE-X19 vs. blinatumomab is £29,317 per QALY.

The pairwise results in this population for KTE-X19 vs. FLAG-IDA and inotuzumab follow a similar pattern, as KTE-X19 is again both more costly but also more effective against these comparators. Compared to FLAG-IDA, KTE-X19 is associated with an incremental cost of [redacted] in the Ph- population and incremental QALY gain of [redacted] QALYs and 5.702 LYs. The ICER for KTE-X19 vs. FLAG-IDA is £29,317. The incremental costs for KTE-X19 vs. inotuzumab are [redacted], with an incremental gain of [redacted] QALYs and 3.545 LYs. The subsequent ICER is £14,636 per QALY for KTE-X19 vs. inotuzumab.

The cost-effectiveness results for KTE-X19 in this population indicate that KTE-X19 is likely to be considered cost-effective against all comparators given that all of the ICERs lie below the WTP threshold of £50,000/QALY for EoL therapies.

Table 77: Base-case results (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	7.902	[redacted]	-	-	-	-
Blinatumomab	[redacted]	3.077	[redacted]	[redacted]	4.825	[redacted]	£29,317
FLAG-IDA	[redacted]	2.200	[redacted]	[redacted]	5.702	[redacted]	£35,634
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	3.545	[redacted]	£19,709

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.7.3 Ph+ population

The cost-effectiveness results for KTE-X19 in the Ph+ population are presented in Table 78. In the comparison against ponatinib, a naïve comparison was carried out between the ZUMA-3 overall population and patients recruited to the PACE trial. It can be seen in Table 78 that although KTE-X19 is associated with higher costs (incremental costs of [redacted]) it is also associated with substantially higher LYs (incremental gain of 4.987 LYs) and QALYs (incremental gain of [redacted] QALYs). These gains are substantial within the context of Ph+ patients, who have a particularly poor prognosis with few treatment options at this point in the treatment pathway. The ICER of £28,001 lies below the WTP threshold of £50,000/QALY for EoL therapies.

Consistent with the results in the overall population, KTE-X19 is more costly but also more effective against inotuzumab and FLAG-IDA, resulting in ICERs of £17,723 per QALY vs. inotuzumab and £33,143 per QALY vs. FLAG-IDA. The ICERs for inotuzumab and FLAG-IDA in the Ph+ population are however slightly lower than those observed in the overall population (£18,353 and £33,449 per QALY for inotuzumab and FLAG-IDA respectively). No INO-VATE or TOWER subgroup data were used for these analyses hence the total costs and QALYs for inotuzumab and FLAG-IDA remain as per the overall population comparison. Conversely, unadjusted patient data from the overall ZUMA-3 population are used which leads to lower incremental costs but higher incremental life years and QALYs for KTE-19 in the Ph+ comparisons compared with those for the overall population.

Table 78: Base-case results (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.361	[redacted]	-	-	-	-
Ponatinib	[redacted]	3.374	[redacted]	[redacted]	4.987	[redacted]	£28,001
FLAG-IDA	[redacted]	2.200	[redacted]	[redacted]	6.161	[redacted]	£33,143
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	4.004	[redacted]	£17,723

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Deterministic sensitivity analysis

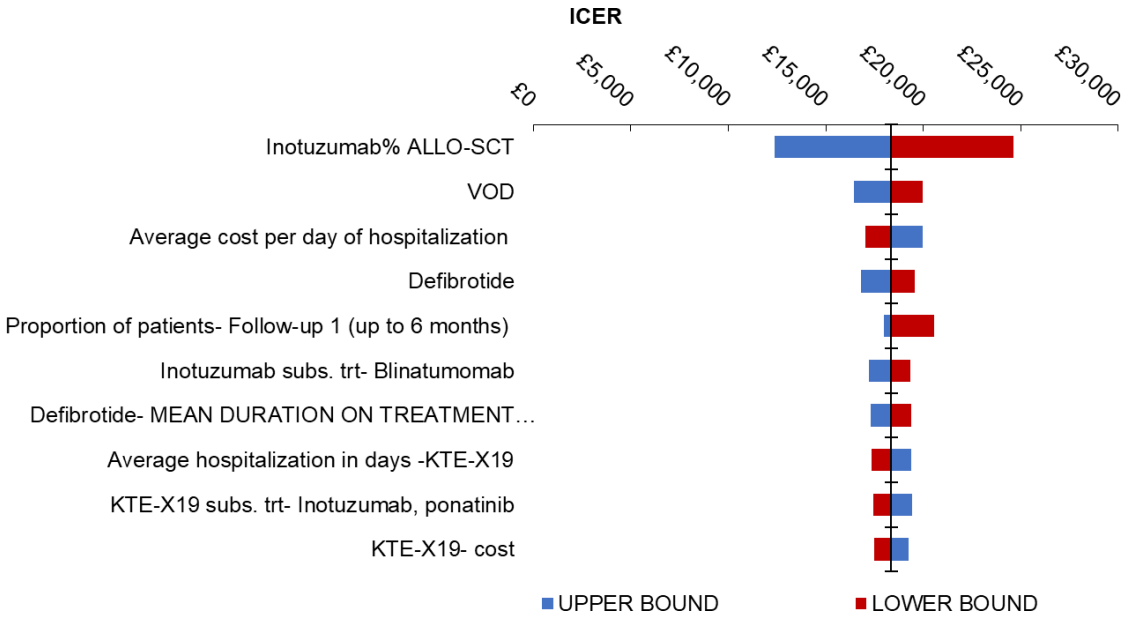
One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. Only parameters which could be varied independently were varied in one-way sensitivity analyses (OWSA). The OWSA thus excluded survival modelling parameters but included utility values derived from the ZUMA-3 EQ-5D regression analyses. The lower and upper bounds for the latter were determined by the upper and lower confidence intervals of the regression coefficients in combinations with the associated variance-covariance matrix. Uncertainty estimates have been provided in Appendix M, the majority of which were underpinned by an assumption of a standard error of the mean of 20%. The OWSA results are presented in tornado diagrams (Figure 46 to Figure 53) where each parameter (y axis) is ranked (highest to lowest) by its impact on the model result. Only the 20 parameters that had the largest impact on the results are included in the tornado diagrams.

The most influential parameter across all the comparisons was the proportion of patients receiving an SCT in the comparator arm. When varied between its upper and lower bounds, this parameter led to differences in the ICERs ranging from £3,284 to £14,653 per QALY. Other influential parameters include the number of inpatient days for FLAG-IDA patients, the incidence of VOD (in the KTE-X19 vs. inotuzumab comparisons) and the proportion of blinatumomab patients allocated to inotuzumab and ponatinib as subsequent treatments.

Table 79: OWSA results, overall population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab % ALLO-SCT	30%	67%	£24,614	£12,373	£12,241
VOD incidence	7%	16%	£19,965	£16,445	£3,520
Average cost per day of hospitalization	£345	£803	£17,050	£19,957	£2,907
Defibrotide drug cost	£202	£575	£19,541	£16,821	£2,720
Proportion of patients-Follow-up 1 (up to 6 months)	33%	100%	£20,557	£17,970	£2,587
Inotuzumab subs. trt-Blinatumomab	8%	18%	£19,315	£17,217	£2,098
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£19,399	£17,308	£2,091
Average hospitalization in days -KTE-X19	13	30	£17,323	£19,384	£2,061
KTE-X19 subs. trt-Inotuzumab, ponatinib	7%	15%	£17,440	£19,439	£2,000
KTE-X19- cost	£310,632	£321,652	£17,479	£19,235	£1,756

Figure 46: OWSA results, overall population, inotuzumab

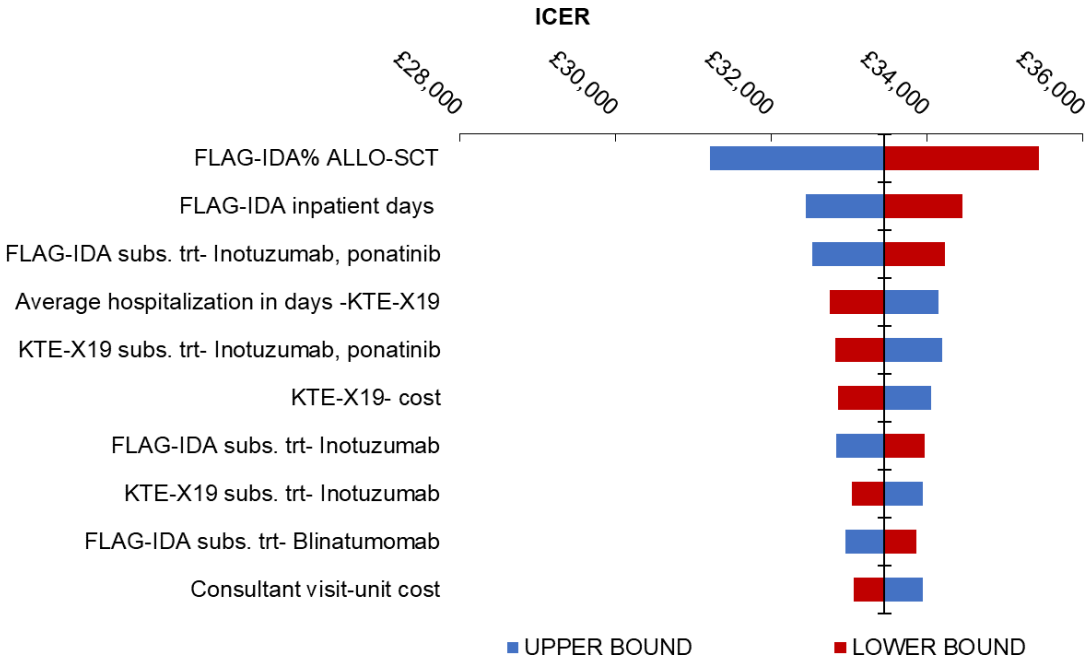


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant

Table 80: OWSA results, overall population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£35,440	£31,208	£4,232
FLAG-IDA inpatient days	10	23	£34,459	£32,440	£2,018
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£34,224	£32,529	£1,695
Average hospitalization in days -KTE-X19	13	30	£32,747	£34,152	£1,404
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£32,827	£34,189	£1,363
KTE-X19- cost	£310,632	£321,652	£32,854	£34,050	£1,196
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£33,968	£32,829	£1,139
KTE-X19 subs. trt- Inotuzumab	5%	11%	£33,032	£33,948	£916
FLAG-IDA subs. trt- Blinatumomab	5%	11%	£33,866	£32,951	£915
Consultant visit-unit cost	£230	£621	£33,056	£33,951	£895

Figure 47: OWSA results, overall population, FLAG-IDA

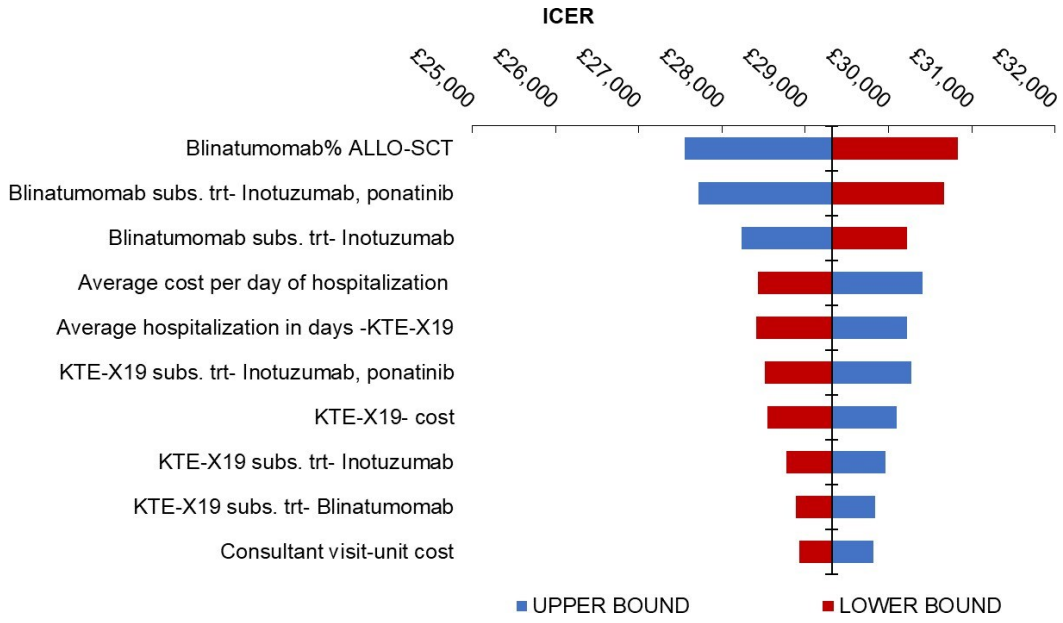


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant

Table 81: OWSA results, Ph- population, blinatumomab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Blinatumomab% ALLO-SCT	8%	19%	£30,835.73	£27,551.34	£3,284.38
Blinatumomab subs. trt- Inotuzumab, ponatinib	8%	19%	£30,670.97	£27,719.44	£2,951.53
Blinatumomab subs. trt- Inotuzumab	6%	14%	£30,223.39	£28,239.34	£1,984.04
Average cost per day of hospitalization	£345	£803	£28,432.76	£30,405.18	£1,972.42
Average hospitalization in days -KTE-X19	13	30	£28,407.09	£30,227.51	£1,820.43
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£28,510.34	£30,276.39	£1,766.06
KTE-X19- cost	£310,632	£321,652	£28,545.36	£30,095.90	£1,550.54
KTE-X19 subs. trt- Inotuzumab	5%	11%	£28,776.58	£29,963.69	£1,187.11
KTE-X19 subs. trt- Blinatumomab	5%	11%	£28,883.03	£29,836.43	£953.40
Consultant visit-unit cost	£230	£621	£28,925.71	£29,816.34	£890.64

Figure 48: OWSA results, Ph- population, blinatumomab

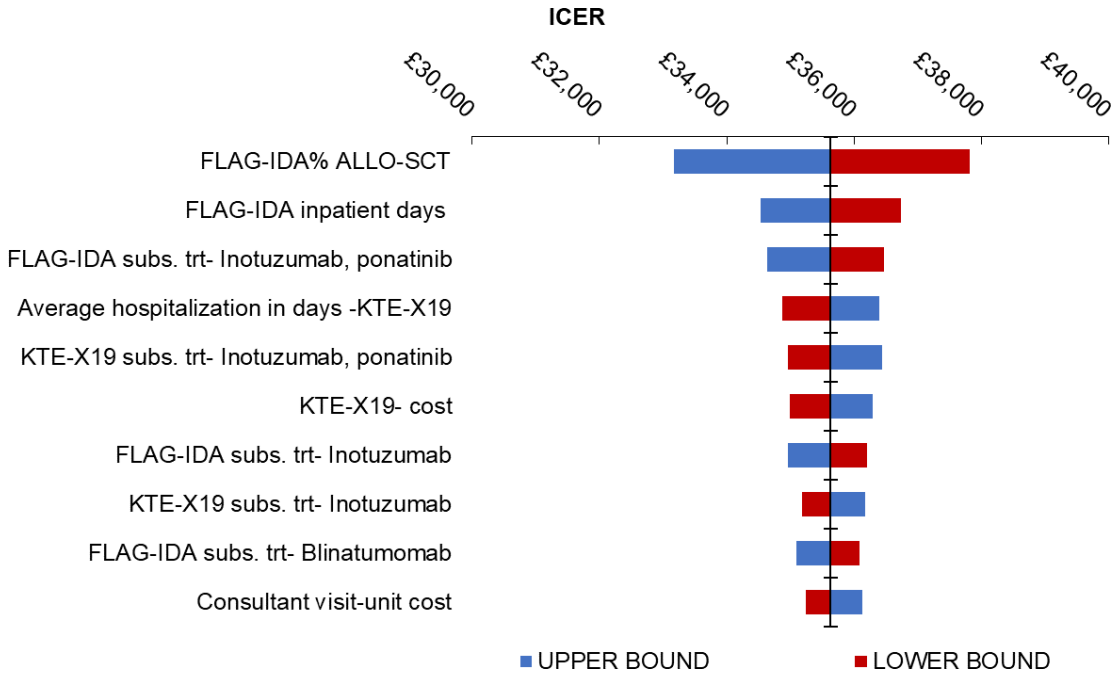


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 82: OWSA results, Ph- population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£37,819	£33,177	£4,642
FLAG-IDA inpatient days	10	23	£36,738	£34,529	£2,209
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£36,475	£34,634	£1,841
Average hospitalization in days -KTE-X19	13	30	£34,871	£36,396	£1,525
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£34,958	£36,437	£1,480
KTE-X19- cost	£310,632	£321,652	£34,987	£36,286	£1,299
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£36,197	£34,960	£1,237
KTE-X19 subs. trt- Inotuzumab	5%	11%	£35,181	£36,175	£995
FLAG-IDA subs. trt- Blinatumomab	5%	11%	£36,087	£35,093	£994
Consultant visit-unit cost	£230	£621	£35,241	£36,134	£893

Figure 49: OWSA results, Ph- population, FLAG-IDA

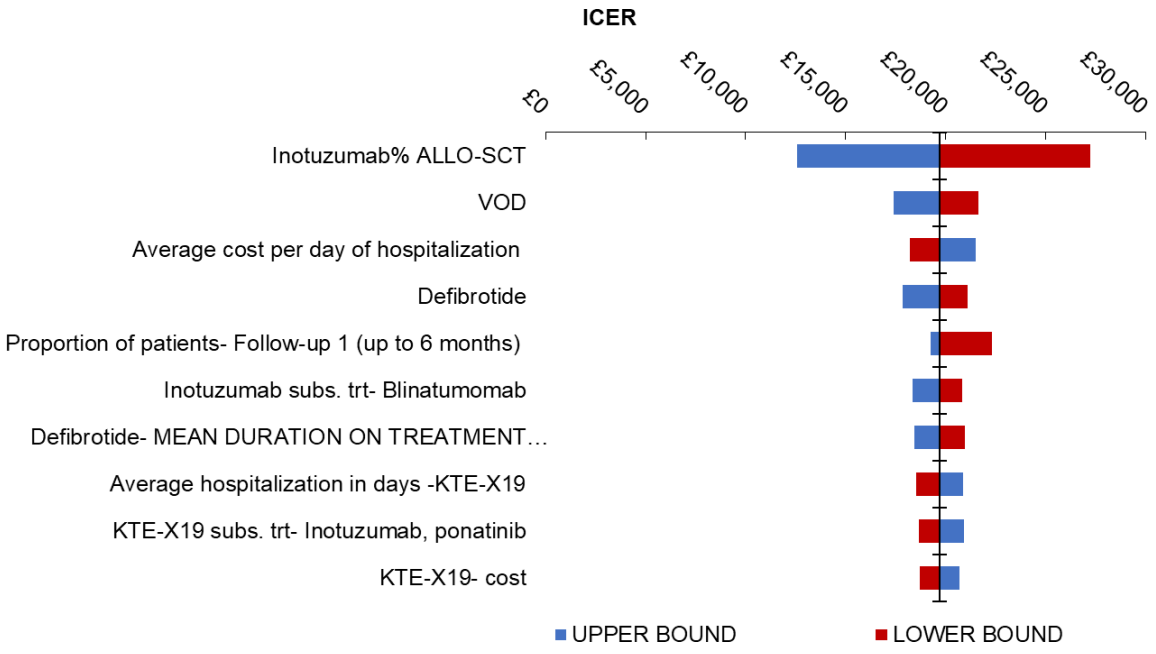


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 83: OWSA results, Ph- population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	30%	67%	£27,233	£12,580	£14,653
VOD incidence	7%	16%	£21,635	£17,428	£4,207
Average cost per day of hospitalization	£345	£803	£18,229	£21,529	£3,300
Defibrotide drug cost	£202	£575	£21,130	£17,877	£3,252
Proportion of patients-Follow-up 1 (up to 6 months)	33%	100%	£22,311	£19,257	£3,054
Inotuzumab subs. trt-Blinatumomab	8%	18%	£20,859	£18,352	£2,507
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£20,959	£18,459	£2,500
Average hospitalization in days -KTE-X19	13	30	£18,543	£20,875	£2,332
KTE-X19 subs. trt-Inotuzumab, ponatinib	7%	15%	£18,675	£20,938	£2,262
KTE-X19- cost	£310,632	£321,652	£18,720	£20,707	£1,986

Figure 50: OWSA results, Ph- population, inotuzumab

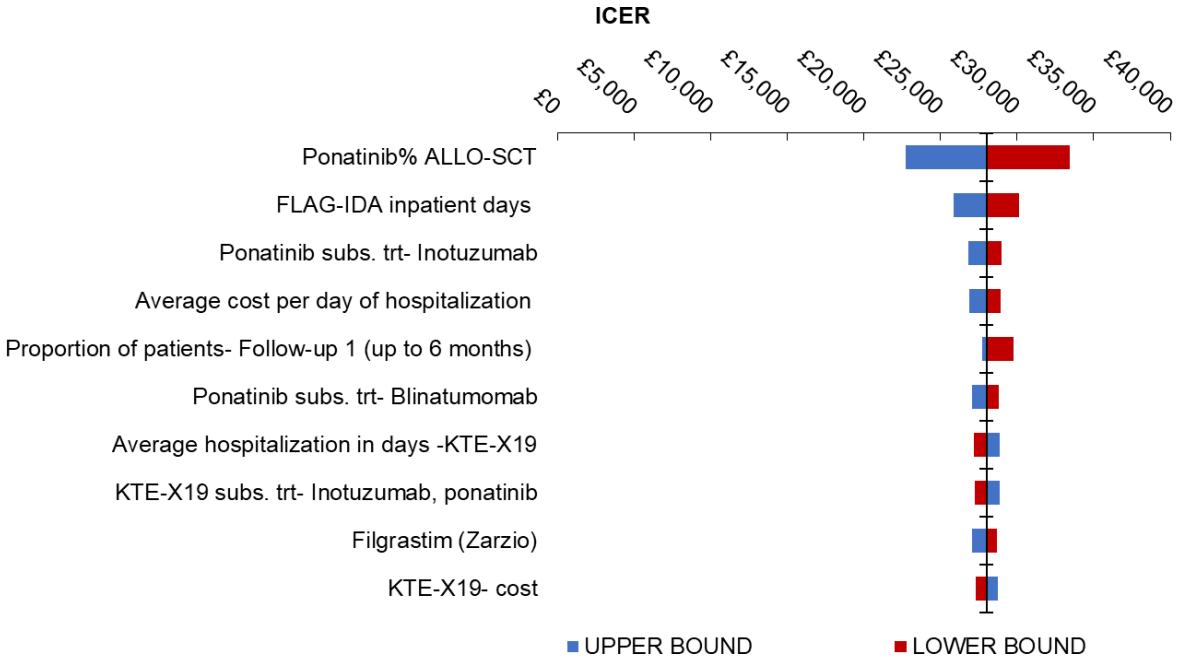


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant; VOD, veno-occlusive disease.

Table 84: OWSA results, Ph+ population, ponatinib

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Ponatinib% ALLO-SCT	29%	65%	£33,428	£22,704	£10,724
FLAG-IDA inpatient days	10	23	£30,126	£25,877	£4,249
Ponatinib subs. trt- Inotuzumab	7%	16%	£28,977	£26,844	£2,133
Average cost per day of hospitalization	£345	£803	£28,931	£26,858	£2,072
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£29,753	£27,697	£2,056
Ponatinib subs. trt- Blinatumomab	7%	16%	£28,785	£27,072	£1,713
Average hospitalization in days -KTE-X19	13	30	£27,156	£28,847	£1,690
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£27,248	£28,896	£1,648
Filgrastim (Zarzio) drug costs	£120	£428	£28,689	£27,065	£1,624
KTE-X19- cost	£310,632	£321,652	£27,285	£28,724	£1,440

Figure 51: OWSA results, Ph+ population, ponatinib

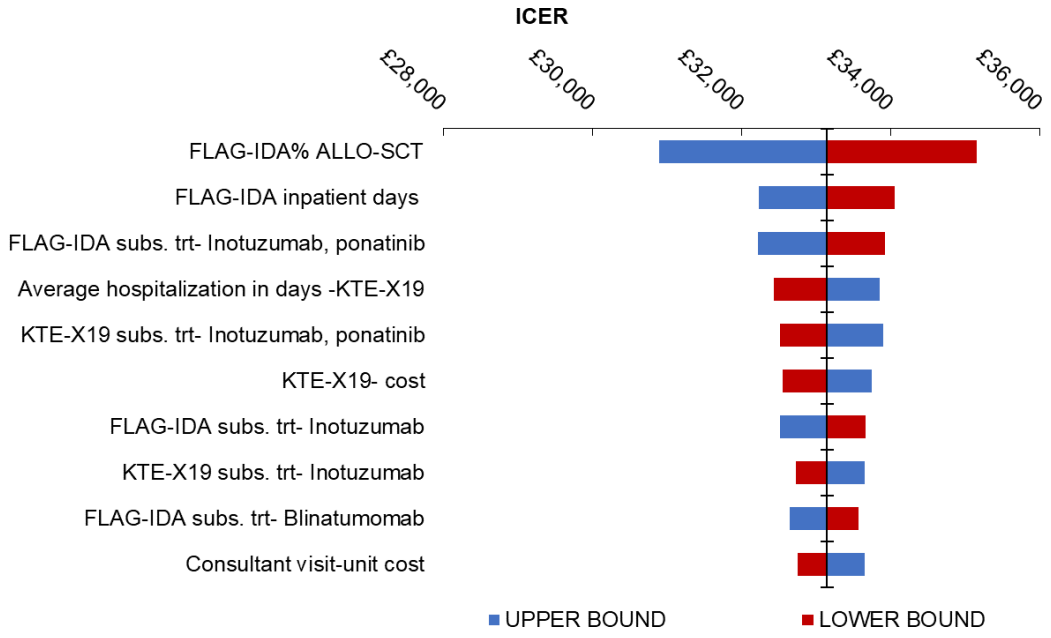


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 85: OWSA results, Ph+ population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£35,148	£30,887	£4,260
FLAG-IDA inpatient days	10	23	£34,056	£32,231	£1,824
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£33,924	£32,216	£1,709
Average hospitalization in days -KTE-X19	13	30	£32,436	£33,851	£1,416
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£32,513	£33,893	£1,380
KTE-X19- cost	£310,632	£321,652	£32,543	£33,749	£1,206
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£33,667	£32,518	£1,149
KTE-X19 subs. trt- Inotuzumab	5%	11%	£32,721	£33,649	£928
FLAG-IDA subs. trt- Blinatumomab	5%	11%	£33,564	£32,641	£922
Consultant visit-unit cost	£230	£621	£32,749	£33,646	£897

Figure 52: OWSA results, Ph+ population, FLAG-IDA

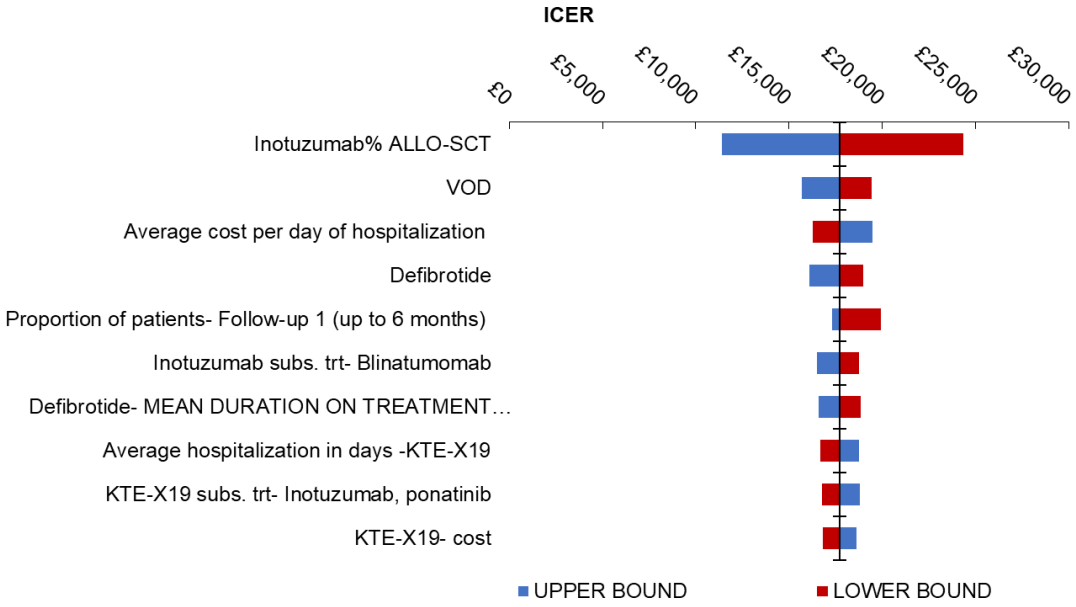


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 86: OWSA results, Ph+ population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	30%	67%	£24,365	£11,383	£12,982
VOD incidence	7%	16%	£19,445	£15,683	£3,762
Average cost per day of hospitalization	£345	£803	£16,273	£19,505	£3,231
Defibrotide drug costs	£202	£575	£18,993	£16,084	£2,909
Proportion of patients-Follow-up 1 (up to 6 months)	33%	100%	£19,956	£17,334	£2,622
Inotuzumab subs. trt-Blinatumomab	8%	18%	£18,751	£16,508	£2,242
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£18,841	£16,605	£2,236
Average hospitalization in days -KTE-X19	13	30	£16,680	£18,765	£2,086
KTE-X19 subs. trt-Inotuzumab, ponatinib	7%	15%	£16,794	£18,827	£2,033
KTE-X19- cost	£310,632	£321,652	£16,838	£18,615	£1,777

Figure 53: OWSA results, Ph+ population, inotuzumab



Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

B.3.8.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values and a distribution was assigned to these parameters. These uncertainty estimates are provided in section B.3.6.1, the majority of which were underpinned by an assumption of a standard error of the mean of 20% for the upper and lower bound values. Exceptions to this include parameters obtained from survival and the ZUMA-3 EQ-5D regressions, which were covaried in the PSA as constrained by their respective variance-covariance matrices. 1,000 simulations were run for the probabilistic sensitivity analysis (PSA), by which time the ICERs had converged to a stable mean, represented by the probabilistic ICERs.

The probabilistic cost-effectiveness results are reported in Table 88 to Table 90. The probabilistic results are closely aligned with the deterministic results, as the ICERs across all subgroups and comparators rise only slightly. The highest probabilistic ICER obtained for KTE-X19 is in the analysis vs. FLAG-IDA for the Ph- population. At £36,780 per QALY, this value lies closely to the corresponding base-case ICER which is £35,634 per QALY. None of the probabilistic ICERs thus exceed the £50,000/QALY threshold for EoL therapies.

Output from the PSA iterations is presented as scatter points on the cost-effectiveness planes in Figure 54 to Figure 56. All points lie in the northeast quadrants of the plane, indicating that KTE-X19 is more costly and more effective compared to the comparator technologies. Cost-effectiveness acceptability curves (CEACs) are presented in Figure 57 to Figure 59. The CEACs show that the probability of KTE-X19 increases in line with the WTP threshold. Conversely, the CEAC for FLAG-IDA decreases at increased WTP thresholds, across all 3 sub-groups, whilst remaining considerably low for blinatumomab and inotuzumab. The probability that KTE-X19 was the most cost-effective treatment at a WTP threshold of £50,000/QALY was above 90% in all sub-groups other than the Ph- population (Table 87). However, the probability of cost-effectiveness for this sub-group remained high at 87%.

Table 87: Probability that KTE-X19 is the most cost-effective treatment

		Probability that KTE-X19 is the most cost-effective comparator at a WTP of:	
Population	**Comparators**	**£40,000/QALY**	**£50,000/QALY**
Overall	Inotuzumab FLAG-IDA	78%	96%
Philadelphia -	Blinatumomab FLAG-IDA Inotuzumab	63%	87%
Philadelphia +	Ponatinib FLAG-IDA Inotuzumab	75%	94%

Key: QALY, quality-adjusted life years; WTP, willingness to pay

Table 88: Probabilistic results - overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.379	[redacted]	-	-	-	-
Inotuzumab	[redacted]	4.369	[redacted]	[redacted]	4.011	[redacted]	£20,103
FLAG-IDA	[redacted]	2.222	[redacted]	[redacted]	6.158	[redacted]	£34,740

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 89: Probabilistic results - Ph- population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	7.963	[redacted]	-	-	-	-
Blinatumomab	[redacted]	3.124	[redacted]	[redacted]	4.839	[redacted]	£30,646
FLAG-IDA	[redacted]	2.252	[redacted]	[redacted]	5.711	[redacted]	£36,780
Inotuzumab	[redacted]	4.400	[redacted]	[redacted]	3.563	[redacted]	£21,328

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 90: Probabilistic results - Ph+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.397	[redacted]	-	-	-	-
Ponatinib	[redacted]	3.407	[redacted]	[redacted]	4.990	[redacted]	£29,123
FLAG-IDA	[redacted]	2.252	[redacted]	[redacted]	6.144	[redacted]	£34,253
Inotuzumab	[redacted]	4.394	[redacted]	[redacted]	4.003	[redacted]	£19,117

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 54:Scatter plot, overall population

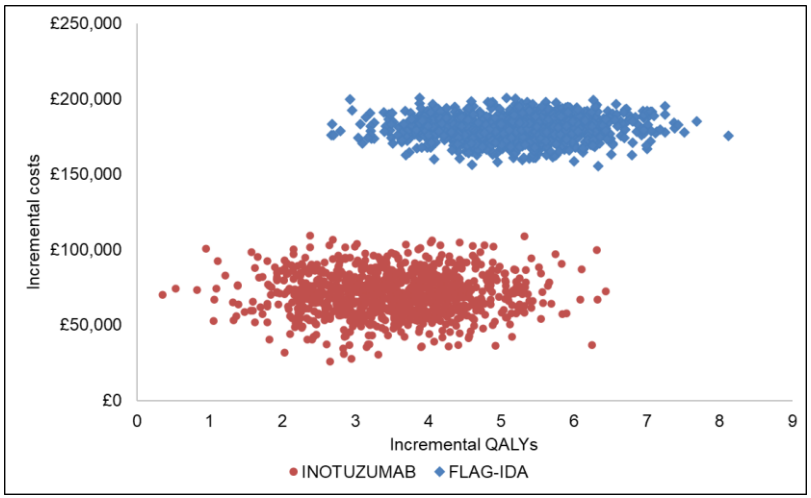


Figure 55: Scatter plot, Ph- population

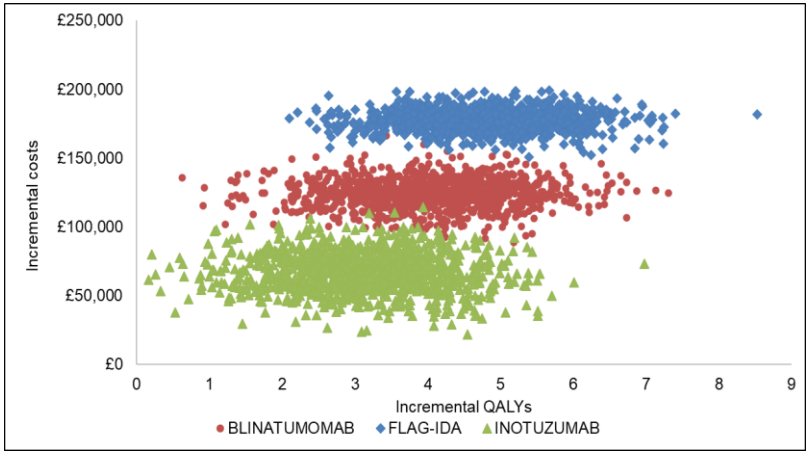


Figure 56: Scatter plot, Ph+ population

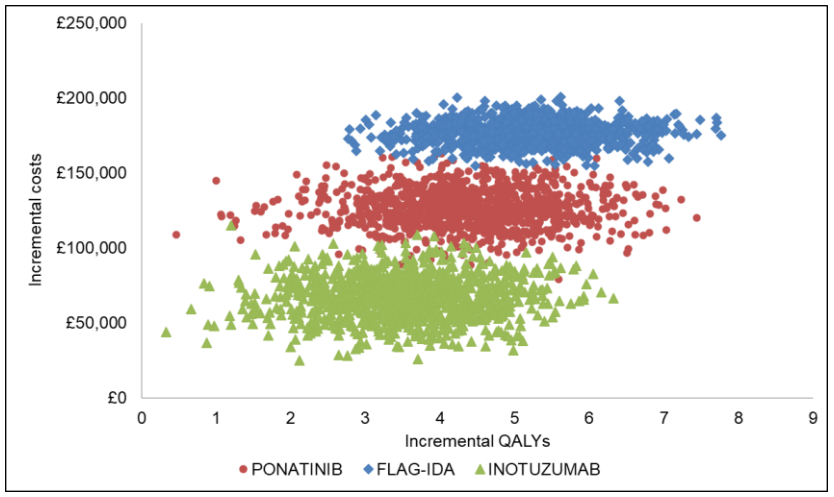


Figure 57: CEAC, overall population

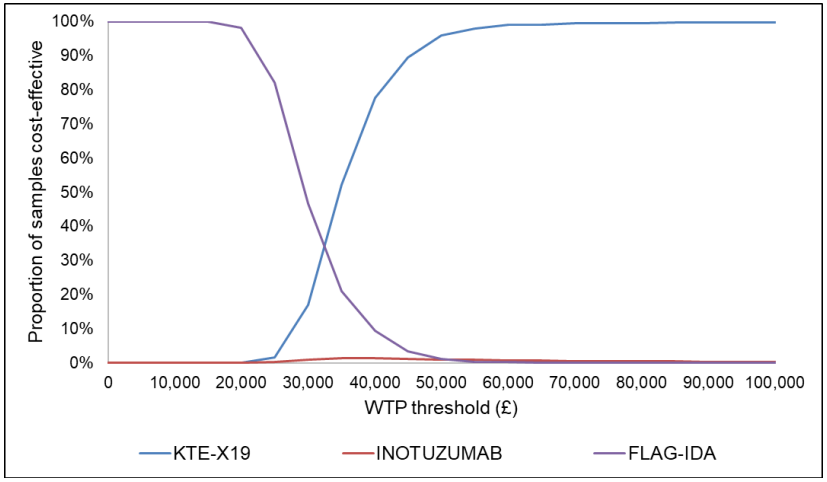


Figure 58: CEAC, Ph- population

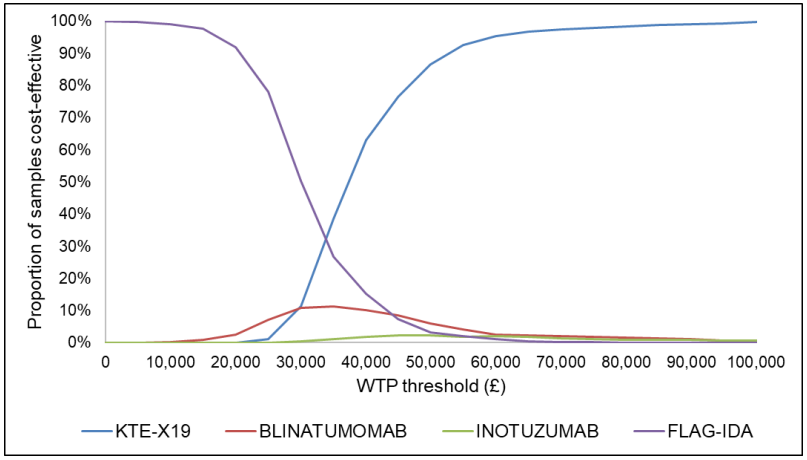
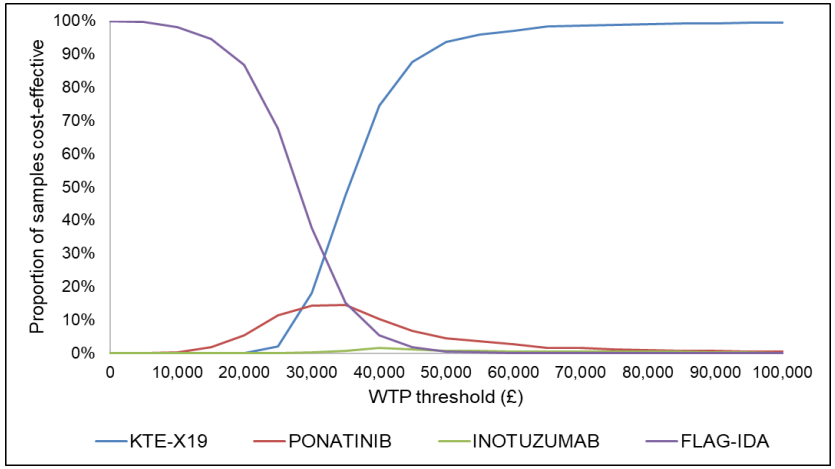


Figure 59: CEAC, Ph+ population



B.3.8.3 Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters underpinning the model base-case was examined through several scenario analyses. The scenarios analyses results are presented in Table 91 to Table 93. The scenarios were explored for each of the 3 populations for which the cost-effectiveness of KTE-X19 has been examined (overall population, Ph- and Ph+). In general, it is notable that very few scenarios led to ICERs above the EoL WTP threshold of £50,000/QALY.

For the analysis considering the overall population, the scenarios that had the largest impact upon the ICER were the selection of a mixture-cure model (MCM) to model EFS and OS for all treatments, using the MAIC to model relative clinical efficacy and when the time horizon was reduced to 20 years. When the best-fitting MCM was selected as opposed to the spline and SPM models as in the base-case, the incremental QALYs for KTE-X19 reduced considerably (from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA). This reduction in incremental QALYs increased the ICERs for KTE-X19 vs. inotuzumab and FLAG-IDA to £52,789 and £58,834 compared to £18,353 and £33,449 in the base-case. These results are unsurprising as they decrease the cure advantage of KTE-X19 versus the comparators. It should be borne in mind that the MCMs were not selected for our base case because the cure fractions varied widely, which strongly suggested lack of enough data to inform this type of survival model (see section B.3.3.3). A similar pattern was observed with the MAIC was selected, as the incremental QALYs reduced from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA. This led to increased ICERs of £28,769 and £50,834 per QALY for KTE-X19 vs. inotuzumab and FLAG-IDA respectively. Again, the MAICs were not deemed to provide the most suitable basis for comparison, as discussed in section B.2.9. Reducing the time horizon from a life-time horizon to 20 years had a similar impact as the incremental costs did not change by much whilst the incremental QALYs reduced from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA. This led to increased ICERs of £24,829 and £46,483 for KTE-X19 vs. inotuzumab and FLAG-IDA respectively, compared to £18,353 and £33,449 in the base-case.

In the analysis of the Ph- subgroup, the scenarios that had the largest impact upon the ICER were the reduction of the time horizon to 20 years and the selection of a log normal SPM function to model EFS and a Weibull function to model OS in the blinatumomab arm. Once again, reducing the time horizon to 20 years reduced the QALY gains associated with KTE-X19, leading to higher ICERs ranging from £26,580 per QALY to £49,487 against the comparators. Opting for alternative parametric functions to model EFS and OS for blinatumomab as opposed to a generalised gamma SPM for both EFS and OS, as in the base-case, reduced the QALY gains considerably in the blinatumomab arm, from [redacted] to [redacted], thus increasing the ICER from £29,317 to £54,945 per QALY.

The scenario analysis results for the Ph+ subgroup were in line with those obtained for the overall population, as the scenarios that had the largest impact upon the ICER were the selection of a MCM for EFS and OS for all treatments and a 20 year when the time horizon for the analysis. In the scenario where the alternative survival functions were adopted for EFS and OS, the ICERs ranged from £51,892 to £63,146 per QALY for KTE-X19 vs. the comparators. This was a considerable increase from the base-case range of £28,001 to £33,143 per QALY. When the time horizon was reduced to 20 years, the ICERs ranged from £23,961 to £46,052 per QALY.

Table 91: Results of scenario analysis – overall population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Inotuzumab**	[redacted]	[redacted]	**£18,353**
			FLAG-IDA	[redacted]	[redacted]	**£33,449**
Time horizon	57 years	20 years	Inotuzumab	[redacted]	[redacted]	£24,829
			FLAG-IDA	[redacted]	[redacted]	£46,483
Discount rate for costs and outcomes (QALYs)	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Inotuzumab	[redacted]	[redacted]	£14,102
			FLAG-IDA	[redacted]	[redacted]	£25,110
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Inotuzumab	[redacted]	[redacted]	£19,608
			FLAG-IDA	[redacted]	[redacted]	£35,119
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Inotuzumab	[redacted]	[redacted]	£17,340
			FLAG-IDA	[redacted]	[redacted]	£30,845
Modelling of clinical efficacy between treatment arms	Naïve comparison	MAIC	Inotuzumab	[redacted]	[redacted]	£28,769
			FLAG-IDA	[redacted]	[redacted]	£50,834
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Inotuzumab	[redacted]	[redacted]	£20,324
			FLAG-IDA	[redacted]	[redacted]	£37,191
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Inotuzumab	[redacted]	[redacted]	£18,849
			FLAG-IDA	[redacted]	[redacted]	£34,396

	General population utility	TA541	Inotuzumab	[redacted]	[redacted]	£20,783
			FLAG-IDA	[redacted]	[redacted]	£38,107
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Inotuzumab	[redacted]	[redacted]	£16,441
			FLAG-IDA	[redacted]	[redacted]	£32,707
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Inotuzumab	[redacted]	[redacted]	£20,137
			FLAG-IDA	[redacted]	[redacted]	£34,134
PD utility source	ZUMA-3	Blinatumomab SMC submission	Inotuzumab	[redacted]	[redacted]	£19,061
			FLAG-IDA	[redacted]	[redacted]	£33,716
		Tisagenlecleucel SMC submission	Inotuzumab	[redacted]	[redacted]	£18,356
			FLAG-IDA	[redacted]	[redacted]	£33,450
KTE-X19 AE disutility source	Literature	ZUMA-3	Inotuzumab	[redacted]	[redacted]	£18,851
			FLAG-IDA	[redacted]	[redacted]	£34,062
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Inotuzumab	[redacted]	[redacted]	£18,344
			FLAG-IDA	[redacted]	[redacted]	£33,438
AE related costs	Included	Excluded	Inotuzumab	[redacted]	[redacted]	£21,888
			FLAG-IDA	[redacted]	[redacted]	£32,873
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Inotuzumab	[redacted]	[redacted]	£21,202
			FLAG-IDA	[redacted]	[redacted]	£36,531

Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Inotuzumab	[redacted]	[redacted]	£52,789
			FLAG-IDA	[redacted]	[redacted]	£58,834
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£18,746
			FLAG-IDA	[redacted]	[redacted]	£34,099
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£17,137
Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£29,960
SCT as subsequent treatment option for KTE-X19 patients	No SCT	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Inotuzumab	[redacted]	[redacted]	£23,711
			FLAG-IDA	[redacted]	[redacted]	£37,368

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model

Table 92: Results of scenario analysis – Ph- population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Blinatumomab**	[redacted]	[redacted]	**£29,317**
			Inotuzumab	[redacted]	[redacted]	**£19,709**
			FLAG-IDA	[redacted]	[redacted]	**£35,634**
Time horizon	57 years	20 years	Blinatumomab	[redacted]	[redacted]	£41,171

			Inotuzumab	[redacted]	[redacted]	£26,580
			FLAG-IDA	[redacted]	[redacted]	£49,487
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Blinatumomab	[redacted]	[redacted]	£21,889
			Inotuzumab	[redacted]	[redacted]	£15,170
			FLAG-IDA	[redacted]	[redacted]	£26,753
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Blinatumomab	[redacted]	[redacted]	£32,746
			Inotuzumab	[redacted]	[redacted]	£22,769
			FLAG-IDA	[redacted]	[redacted]	£34,059
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Blinatumomab	[redacted]	[redacted]	£27,790
			Inotuzumab	[redacted]	[redacted]	£19,529
			FLAG-IDA	[redacted]	[redacted]	£39,257
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Blinatumomab	[redacted]	[redacted]	£32,714
			Inotuzumab	[redacted]	[redacted]	£21,807
			FLAG-IDA	[redacted]	[redacted]	£36,639
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Blinatumomab	[redacted]	[redacted]	£30,173
			Inotuzumab	[redacted]	[redacted]	£20,236
			FLAG-IDA	[redacted]	[redacted]	£39,611
		TA541	Blinatumomab	[redacted]	[redacted]	£33,544
			Inotuzumab	[redacted]	[redacted]	£22,288

			FLAG-IDA	[redacted]	[redacted]	£40,581
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Blinatumomab	[redacted]	[redacted]	£28,479
			Inotuzumab	[redacted]	[redacted]	£18,225
			FLAG-IDA	[redacted]	[redacted]	£35,105
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Blinatumomab	[redacted]	[redacted]	£30,119
			Inotuzumab	[redacted]	[redacted]	£21,132
			FLAG-IDA	[redacted]	[redacted]	£36,132
PD utility source	ZUMA-3	Blinatumomab SMC submission	Blinatumomab	[redacted]	[redacted]	£29,222
			Inotuzumab	[redacted]	[redacted]	£20,467
			FLAG-IDA	[redacted]	[redacted]	£35,825
		Tisagenlecleucel SMC submission	Blinatumomab	[redacted]	[redacted]	£29,317
			Inotuzumab	[redacted]	[redacted]	£19,712
			FLAG-IDA	[redacted]	[redacted]	£35,635
KTE-X19 AE disutility source	Literature	ZUMA-3	Blinatumomab	[redacted]	[redacted]	£30,017
			Inotuzumab	[redacted]	[redacted]	£20,316
			FLAG-IDA	[redacted]	[redacted]	£36,343
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Blinatumomab	[redacted]	[redacted]	£29,304
			Inotuzumab	[redacted]	[redacted]	£19,698
			FLAG-IDA	[redacted]	[redacted]	£35,621

AE related costs	Included	Excluded	Blinatumomab	[redacted]	[redacted]	£28,348
			Inotuzumab	[redacted]	[redacted]	£23,988
			FLAG-IDA	[redacted]	[redacted]	£35,190
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Blinatumomab	[redacted]	[redacted]	£31,056
			Inotuzumab	[redacted]	[redacted]	£22,936
			FLAG-IDA	[redacted]	[redacted]	£38,935
Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Blinatumomab	[redacted]	[redacted]	£58,242
			Inotuzumab	[redacted]	[redacted]	£43,244
			FLAG-IDA	[redacted]	[redacted]	£54,057
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£28,440
			Inotuzumab	[redacted]	[redacted]	£18,973
			FLAG-IDA	[redacted]	[redacted]	£34,731
Parametric function adopted to model EFS and OS for blinatumomab	1-knot spline hazard is used to model EFS, lognormal SPM is used to model OS	Lognormal SPM is used to model EFS, generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£29,426
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Blinatumomab	[redacted]	[redacted]	£29,888
			Inotuzumab	[redacted]	[redacted]	£20,209
			FLAG-IDA	[redacted]	[redacted]	£31,635

Parametric function adopted to model EFS and OS for Blinatumomab	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	Blinatumomab	[redacted]	[redacted]	£54,945
SCT as subsequent treatment option for KTE-X19 patients	Not included	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Blinatumomab	[redacted]	[redacted]	£34,318
			Inotuzumab	[redacted]	[redacted]	£25,841
			FLAG-IDA	[redacted]	[redacted]	£39,943

Table 93: Results of scenario analysis – Ph+ population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Ponatinib**	[redacted]	[redacted]	**£28,001**
			Inotuzumab	[redacted]	[redacted]	**£17,723**
			FLAG-IDA	[redacted]	[redacted]	**£33,143**
Time horizon	57 years	20 years	Ponatinib	[redacted]	[redacted]	£38,474
			Inotuzumab	[redacted]	[redacted]	£23,961
			FLAG-IDA	[redacted]	[redacted]	£46,052
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Ponatinib	[redacted]	[redacted]	£21,219
			Inotuzumab	[redacted]	[redacted]	£13,625
			FLAG-IDA	[redacted]	[redacted]	£24,881
		ZUMA-3 ITT dataset	Ponatinib	[redacted]	[redacted]	£29,183

Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset		Inotuzumab	[redacted]	[redacted]	£18,676
			FLAG-IDA	[redacted]	[redacted]	£34,496
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Ponatinib	[redacted]	[redacted]	£25,837
			Inotuzumab	[redacted]	[redacted]	£16,718
			FLAG-IDA	[redacted]	[redacted]	£30,530
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Ponatinib	[redacted]	[redacted]	£31,091
			Inotuzumab	[redacted]	[redacted]	£19,619
			FLAG-IDA	[redacted]	[redacted]	£36,846
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Ponatinib	[redacted]	[redacted]	£28,778
			Inotuzumab	[redacted]	[redacted]	£18,201
			FLAG-IDA	[redacted]	[redacted]	£34,080
		TA541	Ponatinib	[redacted]	[redacted]	£31,817
			Inotuzumab	[redacted]	[redacted]	£20,064
			FLAG-IDA	[redacted]	[redacted]	£37,755
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Ponatinib	[redacted]	[redacted]	£27,308
			Inotuzumab	[redacted]	[redacted]	£16,441
			FLAG-IDA	[redacted]	[redacted]	£32,707
		All patients who fail to receive infusion are assumed to receive	Ponatinib	[redacted]	[redacted]	£28,690
			Inotuzumab	[redacted]	[redacted]	£18,991

		other comparators (not FLAG-IDA)	FLAG-IDA	[redacted]	[redacted]	£33,577
PD utility source	ZUMA-3	Blinatumomab SMC submission	Ponatinib	[redacted]	[redacted]	£27,973
			Inotuzumab	[redacted]	[redacted]	£18,454
			FLAG-IDA	[redacted]	[redacted]	£33,457
		Tisagenlecleucel SMC submission	Ponatinib	[redacted]	[redacted]	£28,001
			Inotuzumab	[redacted]	[redacted]	£17,725
			FLAG-IDA	[redacted]	[redacted]	£33,145
KTE-X19 AE disutility source	Literature	ZUMA-3	Ponatinib	[redacted]	[redacted]	£28,621
			Inotuzumab	[redacted]	[redacted]	£18,209
			FLAG-IDA	[redacted]	[redacted]	£33,755
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Ponatinib	[redacted]	[redacted]	£27,990
			Inotuzumab	[redacted]	[redacted]	£17,714
			FLAG-IDA	[redacted]	[redacted]	£33,132
AE related costs	Included	Excluded	Ponatinib	[redacted]	[redacted]	£27,046
			Inotuzumab	[redacted]	[redacted]	£21,553
			FLAG-IDA	[redacted]	[redacted]	£32,734
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Ponatinib	[redacted]	[redacted]	£29,730
			Inotuzumab	[redacted]	[redacted]	£20,594
			FLAG-IDA	[redacted]	[redacted]	£36,310

Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Ponatinib	[redacted]	[redacted]	£63,146
			Inotuzumab	[redacted]	[redacted]	£51,892
			FLAG-IDA	[redacted]	[redacted]	£58,538
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Ponatinib	[redacted]	[redacted]	£28,621
			Inotuzumab	[redacted]	[redacted]	£18,098
			FLAG-IDA	[redacted]	[redacted]	£33,792
Parametric function adopted to model EFS and OS for ponatinib	Lognormal SPM is used to model EFS and OS	Log logistic SPM are used to model EFS and OS	Ponatinib	[redacted]	[redacted]	£28,098
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£18,125
Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£33,199
SCT as subsequent treatment option for KTE-X19 patients	Not included	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Ponatinib	[redacted]	[redacted]	£32,605
			Inotuzumab	[redacted]	[redacted]	£23,127
			FLAG-IDA	[redacted]	[redacted]	£37,088
Inclusion of chemotherapy costs with ponatinib	Included	Excluded	Ponatinib	[redacted]	[redacted]	£30,137

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model

B.3.8.4 Summary of sensitivity analyses results

The sensitivity analyses demonstrated that the KTE-X19 ICERs were in general robust to variations in the majority of parameters. As expected, altering the model time horizon and the proportion of patients cured (via alternative survival analyses methods) had substantial impact on the ICERs. The scenarios that increased the ICERs above £50,000 per QALY (use of MCM for survival and MAIC to model clinical efficacy) are not considered appropriate due to the limitations of these modelling methods (see sections B.2.9.4 and B.3.3.3). ICERs were also sensitive to the utility of the progressed disease state.

The probabilistic results were generally aligned with deterministic results. KTE-X19 had a greater than 85% probability of being cost-effective at a WTP of £50,000 against all comparators, indicating with high certainty that KTE-X19 is a highly cost-effective treatment for R/R ALL patients.

B.3.9 Subgroup analysis

Results for the Philadelphia chromosome subgroups have been presented in the previous sections for ease of comparison.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

To increase the face validity of the model as well as to make sure that the model is scientifically accurate, the validity of the model has been checked using the following steps:

- Modelling guidelines from NICE and ISPOR: Well-established cost-effectiveness guidelines from NICE and ISPOR have been adhered to throughout the modelling process (59, 60).

- Technical validation: A senior modeler has performed thorough checks to ensure that the model has been programmed appropriately and produces logical outcomes (e.g., to verify that the model is not biased towards one arm or the other). Extreme analyses have been conducted to make sure the model provides robust estimates.

- Numerous univariate sensitivity analyses have been conducted to ensure that input parameters have a logical impact on the outcomes. It should be noted that it was not possible to explore the impact of the survival extrapolation in the univariate sensitivity analyses, as the survival extrapolation is dependent on multiple parameters and the univariate sensitivity analyses only vary one parameter at a time.

- Expert validation: Interviews have been conducted by health economic experts (2 UK) and 2 clinical experts (1 UK, 2 United States) in December 2020 validating the clinical and technical assumptions as well as the preliminary model inputs. The clinical expert interviews covered treatment patterns, how KTE-X19 would fit in the treatment pathway, prognostic factors for the MAIC, how allo-SCT and other treatments would be used post-progression, and cure definition. The technical health economic interviews covered the economic modelling framework, indirect treatment comparison datasets, and how to analyse EFS and OS. Furthermore, an advisory board was performed with ex-payers across the United Kingdom, France, Netherlands, Germany, and Canada in June 2021. An additional UK advisory board which recruited two UK clinicians and two economists with NICE committee experience was conducted in July 2021 (35).The advisory boards further discussed the modelling approach, comparative effectiveness datasets, and survival extrapolations.

B.3.11 Interpretation and conclusions of economic evidence

KTE-X19 is cost-effective at the EoL WTP threshold of £50,000/QALY in all base-case comparisons, with all ICERs falling well beneath the threshold. While KTE-X19

is associated with additional costs, it is also associated with substantial discounted life years and QALYs gains. Uncertainty in the model is underpinned by a fairly limited number of parameters, mainly those driving the survival assumptions and subsequent treatment options applied in the model. None of the results obtained from the PSA and OWSAs increased the ICER above the EoL WTP threshold of £50,000 per QALY gained.

Strengths of the economic analysis

The analysis considered all relevant comparators and subgroups in the scope. Multiple analyses were undertaken in the model, both adjusting for different baseline characteristics as well as match-adjusted comparisons. A well-conducted historical control arm study was included for the comparison against blinatumomab, and extensive survival modelling approaches were explored. The model structure and assumptions were validated with several UK clinicians and health economists.

Limitations of the economic analysis

ZUMA-3 was a single-arm study and thus the results are subject to the standard limitations of unanchored ITCs. The ZUMA-3 data is immature and thus the survival extrapolations are associated with uncertainty. However, the growing body of evidence supporting the long-term efficacy of CAR T-cell therapies in haematological cancers support the assumptions regarding cure rates in this population. Furthermore, the most recent data-cut from ZUMA-3 confirms a curative potential for KTE-X19, independently of subsequent SCT (Figure 22).

In summary, in addition to providing substantial survival benefit in this population of high unmet need, KTE-X19 is cost-effective to the UK NHS at the EoL WTP threshold of £50,000, for which it meets the eligibility criteria.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adult [ID1494]

Clarification questions

December 2021

File name	Version	Contains confidential information	Date
ID1494 KTE-X19 Clarification Responses_2.0 [ACIC]	V2.0	Yes	20/01/2022

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. Priority: Will data from the latest data cut (July 2021) be incorporated into the clarification response?

Company response: Whilst key figures and tables for the latest data cut (July 2021) have been provided in the company evidence submission to support the long-term effectiveness of KTE-X19 in r/r adult ALL, the clinical study report (CSR) will not become available until technical engagement, at which time it will be submitted as new evidence in line with the appraisal process. The latest data cut will not be incorporated into the clarification response.

A2. Priority: Please clarify if censoring in ZUMA-3 due to commencement of SCT can be considered as non-informative censoring. In particular, please provide further information relating to the characteristics of the 14 patients who received allo-SCT after KTE-X19 treatment, and any documented reason for having the procedure. If possible, categorise patients into those in whom the intention was always for KTE-X19 to bridge to allo-SCT, and into those in whom the prognosis after KTE-X19 had declined and where an unplanned allo-SCT was performed. For patients falling into the second group, comment on the likelihood that the data supporting the statement in the CS that survival is independent of subsequent allo-SCT are confounded.

Company response: We consider that censoring due to allo-SCT is likely to be informative. As detailed below, in ZUMA-3 subsequent allo-SCT was almost exclusively given to patients in deep remission.

In total, 14 of 78 subjects treated at target dose went on to receive an allo-SCT during ZUMA-3 at the investigator's discretion. This includes 10 of 55 subjects treated with KTE-X19 in Phase 2, and 4 of 23 subjects treated with target dose at Phase 1. For the 10 subjects that went on to receive an allo-SCT in Phase 2, the median time from KTE-X19 infusion to allo-SCT was 98 days (range: [redacted] to [redacted] days). For Phase 1, median time from KTE-X19 infusion to allo-SCT was [redacted] days (range: [redacted] to [redacted] days).

Baseline characteristics for the patients who received subsequent allo-SCT are presented in Table 1.

Table 1: Selected Demographic and Baseline Characteristics for Subjects who Received Subsequent Allo-SCT (Phase 1 + 2 target dose)

Subject ID	Country	Age	Number of Prior Therapies	Prior Allogeneic SCT	Refractory Status [a]
[redacted]					

Clinical site responses to request for 'a short clarification why the subject proceeded to allo-SCT' for the 10 of 55 subjects who received subsequent allo-SCT at Phase 2 are presented in Table 2. [redacted]

Table 2: Reasons for Subsequent Allo-SCT in Subjects Treated With KTE-X19 (Phase 2)

Coded Reason[a]	Additional Context
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

Whilst documented reasons for the 4 of 23 patients treated at target dose in Phase 1 that went on to receive a subsequent SCT are not available, 3 of 4 patients had achieved CR/CRi per central assessment, including 2 patients with CR. It is likely that these patients received allo-SCT to consolidate KTE-X19 induced remission rather than due to a worsening of prognosis, although this cannot be confirmed. One further patient treated at Phase 1 - who had extramedullary disease at baseline - had achieved a best overall response of partial remission to KTE-X19 based on investigator assessment of disease response. Given the dismal outcomes associated with the presence of extramedullary disease in adult R/R ALL (1,2), it is possible that the investigator's intention for this patient was always to consolidate with allo-SCT in the event of a response, albeit without documented reasons this is only inferred.

In summary, 12 of 14 patients who went on to receive subsequent allo-SCT had achieved CR/CRi per central assessment, with a further patient achieving CRi per investigator assessment. An additional patient with a particularly dismal prognosis at baseline achieved partial remission per investigator assessment. The clinical site rationale for subsequent allo-SCT following KTE-X19 treatment during Phase 2 was to consolidate KTE-X19 induced remission, rather than in response to worsening prognosis. [redacted]

Documented reasons are not available for the 4 subjects that received subsequent allo-SCT at Phase 1. However, based on remission status and high-risk features we consider it likely that these patients received allo-SCT to consolidate remission as a pre-planned measure, rather than in response to worsening prognosis.

Although ZUMA-3 is not powered to analyse KTE-X19 versus KTE-X19 followed by allo-SCT, in a sensitivity analysis of median OS stratified by censoring at allo-SCT, survival in responders appeared to be independent of subsequent SCT at the most recent data analysis (July 2021) (Figure 1).

Figure 1: Kaplan-Meier plot of OS for OCR subjects using investigator review by subsequent allogeneic SCT group (Phase 1 + 2 target dose: data cut 23/07/21)

Data cutoff date = 23/07/21.
Key: CI, confidence interval; NE, not evaluable; NR, not reached; OCR, overall complete remission; SCT, stem cell transplant.
Source: (3).

In addition, we would like to re-iterate the anticipated positioning of KTE-X19 in clinical practice. Clinical expert feedback received as part of this submission was that KTE-X19 is likely to be used in adults with R/R B-cell ALL who:

- Have relapsed post-SCT;
- Are ineligible for SCT (on the basis of age, frailty, comorbidities or other criteria);
- Are unlikely to achieve SCT via existing bridging therapies (primary refractory, relapsed within 12 months, failed ≥2 lines of prior therapy).

Given this positioning, we consider it highly unlikely that KTE-X19 would be used as a bridge to allo-SCT, instead being considered as a standalone treatment option in UK clinical practice.

A3. Priority: Those patients who did not receive CAR T-cell infusion because of AEs were assumed to have the same prognosis as people receiving FLAG-IDA. Please clarify whether this assumption will be favourable to patients intended to receive KTE-X19, as the FLAG-IDA group is not constituted of people who all have AEs, and are likely to be a healthier

group. Please also provide analyses producing ICERs, using alternative assumptions to that in the base case.

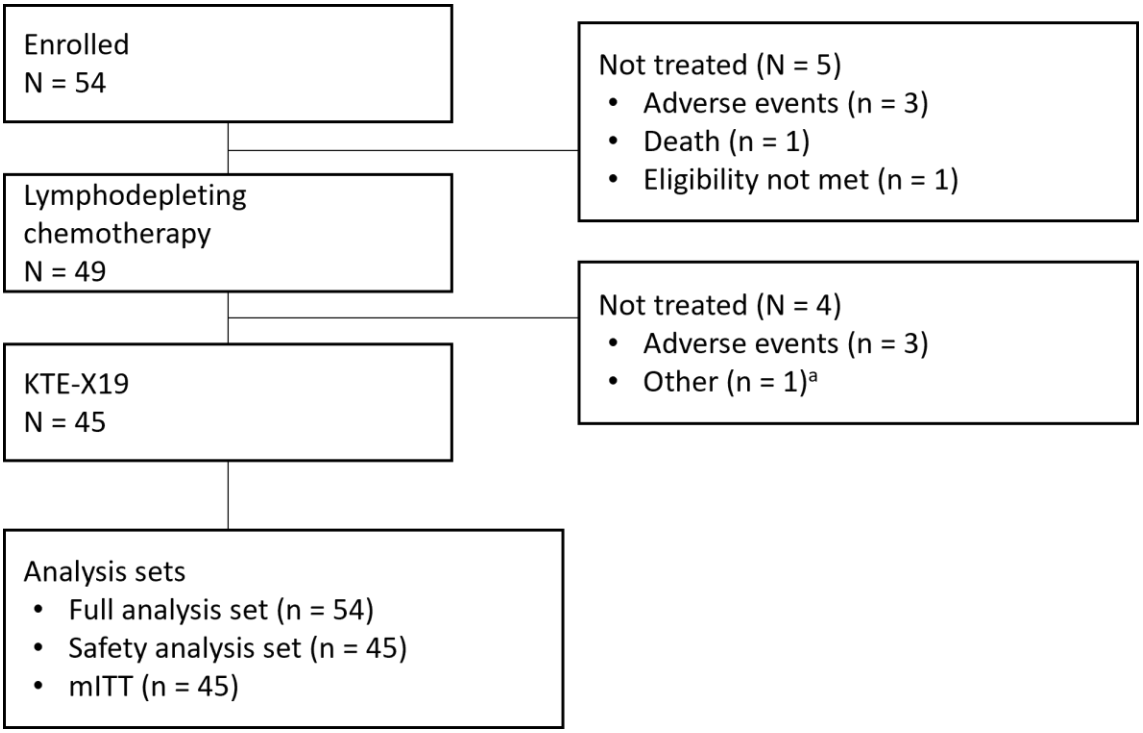
Company response: It is true that patients eligible to receive FLAG-IDA may be a healthier group than all those patients with AEs. However, long-term survival (the main driver of QALYs gain) is very poor with FLAG-IDA (cure fraction of 8% in our model) and the uninfused FLAG-IDA group only makes up 11% of the entire model cohort. Thus, FLAG-IDA contributes at most 0.88% (11% * 8%) of the long-term QALY gain. (There would also be upfront cost-reductions in the KTE-X19 arm that would offset the QALY loss if palliative care were assumed instead).

We have not conducted any additional scenario analysis as we have already demonstrated the model to be insensitive to assumptions relating to the uninfused patients in our submission: Two extreme scenario analyses were carried out in the model (1) All patients who fail to receive infusion are assumed to receive FLAG-IDA (2) All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA). These increased or decreased the ICER by less than £2,000 vs. inotuzumab, and less than £1,000 vs. FLAG-IDA, blinatumomab and ponatinib.

A4. P.45: B.2.3.3 and Figure 10 and P.49: B.2.4.1: Please clarify exactly the treatment status of the analysis populations (mITT from phase I and phase II) and how they are distinct from the ITT populations in the two phases (Fig. 61 also needs this information, to be comparable to Fig.62).

Company response: The Phase 1 and Phase 2 mITT population consisted of all patients enrolled and treated with KTE-X19. The ITT population was defined as all patients enrolled in ZUMA-3. During Phase 2, 71 subjects were enrolled (ITT), of which 55 subjects received treatment with KTE-X19 (mITT). During Phase 1, 54 subjects were enrolled, of which 45 received treatment with KTE-X19 (mITT). An objective of Phase 1 was to determine a target dose to take through to Phase 2, and as such only 23 of 45 treated subjects received KTE-X19 at the elected target dose of $1x10^6$ anti-CD19 CAR+ T-cells/kg. This target dose reflects the dosing of KTE-X19 expected in clinical practice, and that of the anticipated marketing authorisation. Combining the Phase 2 mITT (N = 55) and Phase 1 target dose mITT (N = 23) provides the largest analysis set at the anticipated dose of approval, with the longest follow-up. Figure 2 provides an updated subject disposition for Phase 1, so that it is comparable to that of Phase 2 (Figure 62 in our submission).

Figure 2: Disposition of Subjects (Phase 1, Full Analysis Set)



Key: AE, adverse event; mITT, modified intent-to-treat.

[a] One subject was not treated with KTE-X19 due to a study-wide pause in enrolment and treatment following the death of another subject in the study.

A5. P.47, Table 8: Please provide median age for phases 1+2 population.

Company response: The median age for the Phase 1 + 2 target dose population was [redacted] years (range: [redacted] to [redacted] years).

A6. P.80-81: Please provide the Quality-of-life data in a table (currently only in text narrative).

Company response:

Table 3: EQ-5D-5L evaluation summary by level and visit (Phase 2, mITT)

Dimension	Category, n (%)	Screening (N = 51)	Day 28 (N = 42)	Month 3 (N = 26)	Month 6 (N = 25)	Month 9 (N = 10)	Month 12 (N = 14)
Mobility	1: No problems walking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2: Slight problems walking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3: Moderate problems walking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4: Severe problems walking	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5: Unable to walk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Self-care	1: No problem washing/dressing myself	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2: Slight problem washing/dressing myself	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3: Moderate problem washing/dressing myself	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4: Severe problem washing/dressing myself	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5: Unable to wash or dress myself	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Usual activities	1: No problems doing usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2: Slight problems doing usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3: Moderate problems doing usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4: Severe problems doing usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5: Unable to do usual activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain / discomfort	1: No pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2: Slight pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3: Moderate pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4: Severe pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5: Extreme pain or discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety / depression	1: Not anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2: Slightly anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3: Moderately anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	4: Severely anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	5: Extremely anxious or depressed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cutoff date = 09/09/2020.
Key: EQ-5D-5L, European Quality of Life-5 Dimensions 5-level version.
Notes: Percentages are based on the number of subjects who completed EQ-5D-5L surveys at each time point.
Source: ZUMA-3 Clinical Study Report Table 80 dataset ADQS (4)

Table 4: EQ-5D-5L VAS score and change from baseline by visit (Phase 2, mITT)

Variable	Statistic / Category	Screening (N = 51)	Day 28 (N = 42)	Month 3 (N = 26)	Month 6 (N = 25)	Month 9 (N = 10)	Month 12 (N = 14)
VAS score	n	51	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (STDEV)	68.2 (21.8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (Q1, Q3)	70.0 (50.0, 85.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	5.0, 100.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	n	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (STDEV)	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (Q1, Q3)	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline by category[a]	Improved, n (%)	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Stable, n (%)	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Deteriorated, n (%)	NA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cutoff date = 09/09/2020
Key: EQ-5D-5L, European Quality of Life-5 Dimensions 5-level version; Max, maximum; Min, minimum; NA, not applicable; Q1, first quartile; Q3, third quartile;STDEV, standard deviation; VAS, visual analogue scale.
Notes: N represents the number of subjects who completed the 2-page EQ-5D-5L survey (with EQ-5D-5L and VAS elements). n represents the number of subjects who populateddata elements for the corresponding variables. The EQ-5D-5L VAS ranges from 0 to 100 with a higher score indicating a better health state. Percentages are based on the number of subjects who completed VAS surveys at each time point and at screening.
a Improvement or deterioration was defined as a change in VAS score of ≥ 7 points relative to the score at screening.
Source: ZUMA-3 Clinical Study Report Table 81 dataset ADQS (1).

A7. P.84 B.2.9. Please clarify why the search for comparator studies was not updated (last search November 2020).

Company response: Apologies for the confusion, this is a typographical error. The search for comparator studies was updated alongside the clinical evidence review search in September 2021. The wording should have been 'The SLR was conducted on June 12, 2019, and subsequently updated in November 2020 and September 2021, to ensure all relevant literature was captured.'

A8. P.97 Clarify whether the proportional hazards assumption is violated for EFS data for inotuzumab. It is explicitly mentioned for other data sets but not this one.

Company response: Based on the Grambsch and Therneau tests and visual inspection of the diagnostic figures (log-log survival plots and Schoenfeld residuals), no clear violation of

the proportional hazards assumption was suggested for KTE-X19 (Phase 1 + 2 combined analysis set) vs inotuzumab after matching for EFS.

A9. P.109 B.2.10.3: Please provide details of the Grade 5 adverse events.

Company response: As described on Page 109 of our submission, there were two deaths observed due to AEs that were considered related to KTE-X19. One subject died on Day 8 due to a neurologic AE of brain herniation that was deemed related to KTE-X19, and one subject died on Day 18 due to septic shock that was deemed related to lymphodepleting chemotherapy (with a positive culture of *Pseudomonas aeruginosa*) and KTE-X19.

A10. Please clarify if the clinical evidence review search and the ITC search are the same or different (Appendix p.53 states that the '*initial SLR was updated in September 2021*', but the ITC search only appears to have been updated up to November 2020: Doc B (p.84); the former search appears to produce 88 publications, the latter 68 publications. Are the 68 a subset of the 88?)

Company response: As described in A7, the search for comparator studies was updated alongside the clinical evidence review search in September 2021. The 68 publications identified in the ITC search are a subset of the 88 publications identified in the clinical evidence review search.

A11. Please provide the baseline characteristics for patients broken down by Ph expression subgroup.

Company response: Baseline characteristics broken down by Philadelphia chromosome expression are presented in Table 5.

Table 5: Baseline Characteristics by Philadelphia Chromosome Status (Phase 1 + 2 target dose)

	Phase 1 and Phase 2 (N = 78)	
	Philadelphia Chromosome (Yes) (N = [redacted])	Philadelphia Chromosome (No) (N = [redacted])
Height (cm)		
n	[redacted]	[redacted]
Mean (STDEV)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Weight (kg)		
n	[redacted]	[redacted]
Mean (STDEV)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

ECOG performance status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
Prior blinatumomab, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Blinatumomab as the last prior therapy, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior inotuzumab, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior allogeneic SCT, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Prior autologous SCT, n (%)		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

Data cutoff date = 09/09/2020

Abbreviations: CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; LVD, longest vertical dimension; MLL, mixed lineage leukemia; NR, no response; PD, progressive disease; PR, partial remission; SCT, stem cell transplant; SPD, sum of the products of diameters; STDEV, standard deviation.

Note: Excludes information collected after retreatment.

Baseline is defined as the last assessment prior to the start of conditioning chemotherapy.

a. Two subjects with relapsed or refractory disease to 2nd or greater lines of therapy were erroneously not marked in the eCRF as such.

b. One subject had prior autologous transplant but was erroneously marked in the eCRF as relapsed/refractory disease after allogeneic SCT.

c. As measured by the SPD of all target lesions at baseline.

A12. Please provide KM plots for EFS for the mITT group for Ph+ patients.

Company response: as requested, the KM plot for Ph+ patients in the mITT group is presented in Figure 3 and Table 6.

Figure 3: Kaplan-Meier Plot of Relapse-free Survival Using Independent Review for Ph+ Patients (Phase 2, mITT)

Data cutoff date: 09/09/2020
Key: CI, confidence interval; NE, not evaluable.

Table 6: Relapse-free Survival Using Independent Review for Ph+ Patients (Phase 2, mITT)

RFS	Phase 2 (N = 15)
Number of subjects, n	
Events, n (%)	
Censored, n (%)	
KM median (95% CI) RFS (months)	
Min, Max RFS (months)	
Events	
Relapse, n (%)	
Death, n (%)	
Subject's best overall response not CR or CRi, n (%)	
Censoring reason	
Ongoing remission, n (%)	
Allogeneic SCT, n (%)	
Started new anti-cancer therapy, n (%)	
Lost to follow-up, n (%)	
Withdrawal of consent, n (%)	
Event-free rates % (95% CI) by KM estimation at	
3 months	
6 months	
9 months	
12 months	
15 months	

Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 09/09/2020.
Abbreviations: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; mITT, modified intent-to-treat; RFS, relapse-free survival; SCT, stem cell transplant.
Note: Percentages are based on the number of subjects in mITT analysis set with Philadelphia chromosome - Yes.
Relapse-free survival is defined as the time from the enrolment date to the date of relapse or death from any cause. Subjects who received KTE-X19 but did not achieve CR or CRi as the best overall response, and subjects who are enrolled but not dosed are counted as events on enrolment date. '+' indicates censoring.

A13. Please clarify what evidence exists to support the hypothesis that functional cures after KTE-X19 treatment is equivalent to functional cures from allo-SCT.

Company response: As discussed in section B.3.3.3 of our submission, it may be considered an optimistic approach to assume that the proportion of patients experiencing long-term survivorship (i.e. the cure fraction) have survival equal to that of the age- and gender matched population. As such, a standardised mortality ratio (SMR) of 1.09 was applied to the background mortality. The SMR of 1.09 has been sourced from a study in DLBCL, Maurer et al., 2014 (5), which was used by the company in the most recent NICE appraisal for KTE-X19 in mantle cell lymphoma (TA677), was the ERG's preferred SMR in TA567 (Tisagenlecleucel in R/R DLBCL) and the preferred SMR in TA559 (Axicabtagene ciloleucel in R/R DLBCL and primary mediastinal large B-cell lymphoma) (6–8) As stated in our submission, although no long-term data are available that compare outcomes post allo-SCT in R/R DLBCL vs. those in R/R ALL, short-term outcomes (up to 2 years) on current SoC for DLBCL are very similar to those observed in the blinatumomab and inotuzumab R/R ALL clinical studies (9).

Precedent exists for a similar approach to functional cure in ALL, albeit not specific to KTE-X19. In NICE's exploratory analysis of a CAR-T for the treatment of ALL as part of the mock appraisal of regenerative therapies, the York group modelled patients still alive at year 5 to be effectively cured. A mortality risk after 5 years was applied based on general population age- and gender-adjusted all-cause risk of mortality adjusted for excess morbidity and mortality reported in long-term survivors of ALL (6). Prior to CAR-T, the only potentially curative option for the treatment of R/R ALL was allo-SCT. Therefore, the long-term ALL survivor population used to inform longer-term morbidity and mortality risk is likely to be representative of allo-SCT functional cure.

In the blinatumomab for previously treated Ph- ALL appraisal (TA450) it was stated that 'If patients are cured then there should be no difference in mortality by treatment group.'. Although there was some discussion in this appraisal as to the exact timepoint at which this assumption could be applied, the concept itself was fully accepted by the ERG. Whilst acknowledging that this precedent is not KTE-X19 specific, in the absence of longer-term data for KTE-X19 cured patients, a similar approach is considered plausible. Of course,

plausibility does not equate to certainty, and a CDF recommendation with further data collection may help to further support this hypothesis.

In addition, a scenario presented in the tisagenlecleucel r/r ALL appraisal (TA554) explored extrapolating only up to a certain timepoint, at which time patients who remained alive in the model were subject to only general population mortality, adjusted by a SMR for long-term ALL survivors (11). This reflected an assumption that any ALL patient who remained alive beyond a certain timepoint can be considered to be effectively 'cured'.

Longer-term data with CAR-T - albeit in lymphoma - have also demonstrated long-lasting remissions, with results suggesting that loss of CAR T cell presence may not be a frequent mechanism of resistance to the therapy (12).

A14. Appendix P.64 and 67: Screening conducted independently by two reviewers. Please clarify the intended and conducted process in the event of disagreements, and whether there were any disagreements.

Company response: As described in Appendix D1.1 of our submission, study screening was carried out in two phases, i.e., title and abstract screening and full-text screening. Both steps were conducted by two independent reviewers. Differing opinions of the reviewers were solved through discussion, with a senior team member casting a deciding vote on any discrepancies. No disagreements occurred during screening.

A15. Appendix P.64-65 and Figure 60. The final numbers add-up to 87 not 88, please correct.

Company response: Apologies for the discrepancy, the number of publications included was 57 rather than 56 (Figure 4). The text should read 'Hence, 267 full-text publications were assessed for inclusion for data extraction. Of these, 210 were excluded based on the pre-defined PICOS criteria and 57 publications were included. In addition, the searching of conference proceedings (a total of 4102 records were identified) resulted in the inclusion of 26 conference abstracts for data extraction. The review of five most recently published and relevant systematic reviews resulted in an additional three publications to be included, whereas additional hand searches resulted in an additional two articles. Hence, a total of 88 publications were eventually included for data extraction.'. The updated PRISMA is presented in Figure 4.

A16. Appendix P.65 and Figure 60: Is this a single PRISMA flowchart for the clinical evidence review and the ITC/MAIC?

Company response: Yes, this PRISMA covers both the clinical evidence review and the ITC/MAIC.

A17. Appendix, please clarify the numbers of actual included publications and studies and clarify (and specify) exactly how many of the 88 included publications are in each analysis (clinical evidence review; ITC; MAIC, if applicable), and update the final box of the PRISMA flowchart accordingly, so that the trail is auditable.

Company response: The clinical evidence review included 88 publications for data extraction including 19 RCT publications and 69 non-RCT publications, as presented in Figure 4. Of the 88 studies included, 8 non-RCT publications relate to ZUMA-3 (Table 7).

Table 7: Identified studies for KTE-X19 in r/r adult ALL

Author Names & Publication year	Title
ZUMA-3 (NCT02614066)	
Oluwole *et al.*, 2018 (13)	Outcomes of patients with relapsed/refractory acute lymphoblastic leukemia treated with prior blinatumomab in zuma-3, a study of kte-c19, an anti-cd19 chimeric antigen receptor (car) t-cell therapy
Shah *et al.*, 2019a (14)	End of phase I results of ZUMA-3, a phase 1/2 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL)
Shah *et al.*, 2019b (15)	KTE-X19, an anti-cd19 chimeric antigen receptor t-cell therapy, in adult patients with relapsed/refractory acute lymphoblastic leukemia: end of phase 1 results of zuma-3
Shah *et al.*, 2017a (16)	KTE-C19 chimeric antigen receptor (CAR) T-cell therapy in adults with high-burden relapsed/refractory acute lymphoblastic leukemia (R/R all): updated results from phase 1/2 of ZUMA-3
Shah *et al.*, 2017b (17)	Preliminary Results of Novel Safety Interventions in Adult Patients (Pts) With Relapsed/Refractory Acute Lymphoblastic Leukemia (R/R ALL) in the ZUMA-3 Trial
Shah *et al.*, (2021a) (18)	KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study
Shah *et al.*, (2021b) (19)	KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results
Shah *et al*, (2021c) (20)	HEALTH-RELATED QUALITY OF LIFE AMONG REFRACTORY/RELAPSED B-CELL PRECURSOR ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH KTE-X19: PHASE 2 RESULTS FROM ZUMA-3 TRIAL

For the MAIC, 12 studies identified in the clinical evidence review were evaluated for eligibility to be included in the MAIC. Details of these 12 studies are presented in Table 8.

Table 8: Summary of the studies evaluated for inclusion in the MAIC

Study	Study design	Treatment
TOWER (NCT0201316; Kantarjian et al. 2017) (21)	Phase 3 open-label RCT	Chemotherapy
		Blinatumomab
INO-VATE (NCT01564784; Kantarjian et al. 2019; Kantarjian et al. 2016)(18,19)	Phase 3 open-label RCT	Chemotherapy
		Inotuzumab ozogamizin
NCT01363297 (DeAngelo et al. 2017) (24)	Phase 1/2 single-arm	Inotuzumab ozogamizin
NCT02000427 (Martinelli et al. 2017) (25)	Phase 2 single-arm	Blinatumomab
Kiyoi et al. 2020 (26)	Phase 2 single-arm	Blinatumomab
Topp et al. 2020 (NCT01209286 & NCT01466179) (27)	Phase 2 single-arm	Blinatumomab
GIMEMA (Bassan et al. 2019)(28)	Phase 2 single-arm	Chemotherapy
Kadia et al. 2015 (29)	Phase 2 single-arm	Chemotherapy
Ottman et al. 2002 (30)	Phase 2 single-arm	TKI (imatinib)
Ottman et al. 2007 (31)	Phase 2 single-arm	TKI (dasatinib)
Lilly et al. 2010 (32)	Phase 3 open-label RCT	TKI (dasatinib)
		TKI (dasatinib)
PACE (Cortes et al. 2018) (33)	Phase 2 single-arm	TKI (ponatinib)

Key: RCT, randomized controlled trial; TKI, tyrosine kinase inhibitor.

Of the 12 studies evaluated for eligibility to be included in the MAIC, two studies were included in the final comparison: INO-VATE and TOWER, for which there were 19 publications identified (Table 9). The remaining 61 publications were excluded at the data extraction stage.

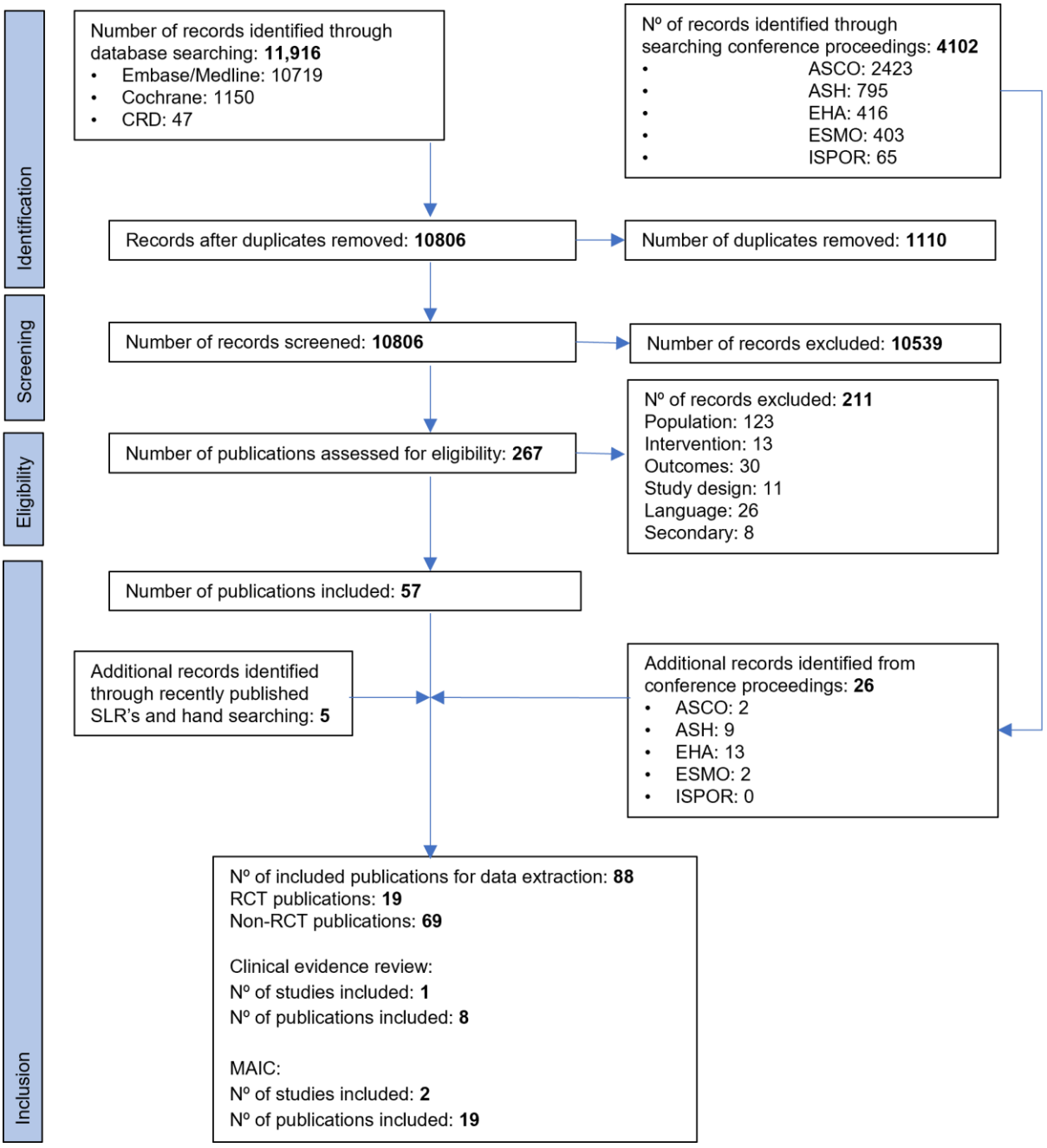
Table 9: Matching adjusted indirect comparison: included studies

Lead Author Name & Publication year	Title
TOWER (NCT02013167)	
Kantarjian, 2017a (original publication) (21)	Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia.
Dombret, 2019 (23)	Blinatumomab versus chemotherapy in first salvage or in later salvage for B-cell precursor acute lymphoblastic leukemia.
Stein, 2018a (24)	Exposure-adjusted adverse events comparing blinatumomab with chemotherapy in advanced acute lymphoblastic leukemia
Dombret, 2017 (25)	Blinatumomab vs SOC chemotherapy in first salvage compared with second or greater salvage in a phase 3 study.
Rambaldi, 2017 (26)	Maintenance Therapy with Blinatumomab in Adults with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ALL): Overall Survival in Adults Enrolled in a Phase 3 Open-Label Trial
Topp, 2016a (27)	Blinatumomab improved overall survival in patients with relapsed or refractory Philadelphia negative b-cell precursor acute lymphoblastic leukemia in a randomized, open-label phase 3 study (TOWER).
Topp, 2016b (28)	Health-Related Quality of Life (HRQoL) of Blinatumomab Versus Standard of Care (SOC) Chemotherapy in Patients with Relaspsed or Refractory Philadelphia Negative B-Cell Precursor

Lead Author Name & Publication year	Title
	Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER)
Rambaldi, 2020 (29)	Blinatumomab consolidation and maintenance therapy in adults with relapsed/refractory B-precursor acute lymphoblastic leukemia
INO-VATE (NCT01564784)	
Kantarjian, 2016 (original publication) (23)	Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia.
Jabbour, 2019 (30)	Efficacy and Safety of Inotuzumab Ozogamicin in Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia Treated in the INO-VATE Trial: Outcomes by Salvage-Treatment Phase.
Kantarjian, 2019a (22)	Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study.
Kantarjian, 2019b (31)	Inotuzumab ozogamicin (InO) treatment in patients with relapsed/refractory acute lymphoblastic leukemia (R/R ALL): Outcomes of patients treated in salvage one with a long duration of first remission.
Jabbour, 2018a (32)	Impact of minimal residual disease (MRD) status in clinical outcomes of patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) treated with inotuzumab ozogamicin (InO) in the phase 3 INO-VATE trial.
Jabbour, 2018b (33)	Efficacy and safety analysis by age cohort of inotuzumab ozogamicin in patients with relapsed or refractory acute lymphoblastic leukemia enrolled in INO-VATE.
Kantarjian 2017b (34)	Hepatic adverse event profile of inotuzumab ozogamicin in adult patients with relapsed or refractory acute lymphoblastic leukaemia: results from the open-label, randomised, phase 3 INO-VATE study
Ruiz-Garcia A. 2017, (35)	Quantitative Assessment of Inotuzumab Ozogamicin (InO) Response Relative to Investigator's Choice of Chemotherapy (ICC) in Adults With Relapsed or Refractory (R/R) CD22+ B-Cell Acute Lymphoblastic Leukemia (ALL).
DeAngelo, 2016 (36)	Inotuzumab ozogamicin (InO) for relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) in the phase III INO-VATE trial: Efficacy and safety by prior therapy.
Jabbour, 2016 (37)	Efficacy and safety of inotuzumab ozogamicin (InO) in older patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) enrolled in the phase 3 INO-VATE trial.
Kantarjian, 2021 (38)	Inotuzumab ozogamicin for relapsed/refractory acute lymphoblastic leukemia in the INO-VATE trial: CD22 pharmacodynamics, efficacy, and safety by baseline CD22

In summary, 8 publications included related to the pivotal trial of KTE-X19 (ZUMA-3), 19 publications relating to the pivotal trials of blinatumomab (TOWER) and inotuzumab ozogamicin (INO-VATE) were included in the MAIC, and the remaining 61 publications were excluded at the data extraction stage. The updated PRISMA is presented in Figure 4.

Figure 4: Clinical SLR PRISMA flow chart



A18. Appendix P.67: Details of ITC included studies - should this be Table 97 or Table 95?

Company response: Yes, thank you for highlighting this. The correct cross-reference should be to Table 97.

Section B: Clarification on statistical analyses and cost-effectiveness data

B1. Priority: Please provide an updated executable model that incorporates the functionality to explore the changes made within the clarification process

Company response: We have adapted the original economic model to incorporate the functionality to explore the changes made within the clarification process.

B2. Priority: Please provide an updated base case (deterministic and probabilistic) that incorporates all changes that are made following the clarification process. Provide supplementary analyses as you see fit.

Company response: We have updated our base-case and attached the updated results (deterministic and all sensitivity analyses) in the appendices. The base-case incremental cost-effectiveness results are also reported in the tables below.

Table 10: Updated base-case results (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	[redacted]	2.200	[redacted]	-	-	-	-	-
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	2.157	[redacted]	£70,783	£70,783
KTE-X19	[redacted]	8.411	[redacted]	[redacted]	4.053	[redacted]	£34,378	£17,203
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 11: Updated base-case results (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	[redacted]	2.200	[redacted]				-	-
Blinatumomab	[redacted]	3.541	[redacted]	[redacted]	1.341	[redacted]	£41,457	£41,457
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	0.816	[redacted]	£70,783	£139,048
KTE-X19	[redacted]	7.925	[redacted]	[redacted]	3.568	[redacted]	£36,380	£18,108
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Table 12: Updated base-case results (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	[redacted]	2.200	[redacted]	-	-	-	-	-
Ponatinib	[redacted]	3.374	[redacted]	[redacted]	1.17	[redacted]	£56,813	£56,813
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	0.983	[redacted]	£70,783	£85,085
KTE-X19	[redacted]	8.361	[redacted]	[redacted]	4.004	[redacted]	£33,972	£16,396

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

B3. Priority: Please confirm if Table 1 correctly represents the company's base case modelling choices.

Table 13: Naïve comparison survival models: datasets and comparisons

ID	Treatment	Dataset for model fitting	N	EFS/ PFS model	OS model	Comparisons used for
1	KTE-X19	ZUMA-3 Phase 1+2 mITT	78	Lognormal	Lognormal	Inotuzumab, for overall and Ph+ subgroup
						FLAG-IDA, for overall and Ph+ subgroup
						Ponatinib, for Ph+ subgroup
2	KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph- subgroup	61	Lognormal	Lognormal	Inotuzumab, for Ph- subgroup
						FLAG-IDA, for Ph- subgroup
						Blinatumomab, for Ph- subgroup
3	Inotuzumab	AD from INO-VATE ITT intervention arm	164	1-knot hazard spline	2-knot normal spline	KTE-X19, for overall and Ph+, Ph- subgroups
4	FLAG-IDA	AD from pooled INO-VATE and TOWER ITT comparator arms	162+134	Generalised gamma	Generalised gamma	KTE-X19, for overall and Ph+, Ph- subgroups
5	Blinatumomab	SCHOLAR-3 SCA-3	53	1-knot hazard spline	Lognormal	KTE-X19, for Ph- subgroup
6	Ponatinib	AD from PACE	32	Lognormal	Lognormal	KTE-X19, for Ph+ subgroup

Company response: We confirm that Table 12 correctly represents the company's base case modelling choices.

B4. Priority: Please ensure that the economic model is able to select the survival models as shown in Table 2. Produce ICERs for these survival models comparing each to the base case survival models for other interventions.

Table 2: Requested Analyses (1) - 14 scenarios with a single change of model in each, reporting each comparison where each respective model is applied.

Treatment	Dataset for model fitting	Outcome	Model
KTE-X19	ZUMA-3 Phase 1+2 mITT	EFS	Weibull
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Weibull
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Exponential
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Gompertz
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph- subgroup	EFS	Weibull
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph- subgroup	EFS	Exponential
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph- subgroup	OS	Weibull
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph- subgroup	OS	Gompertz
FLAG-IDA	AD from pooled INO-VATE and TOWER ITT comparator arms	OS	1-knot normal spline
Blinatumomab	SCHOLAR-3 SCA-3	EFS	Weibull MCM
Blinatumomab	SCHOLAR-3 SCA-3	EFS	Log logistic
Blinatumomab	SCHOLAR-3 SCA-3	OS	Weibull MCM
Ponatinib	AD from PACE	OS	MCM Weibull
Ponatinib	AD from PACE	OS	Gompertz

Company response: We confirm that the economic model is able to select the survival models shown in Table 2. The results for these scenarios are reported in Table 13 below.

Table 14: Results of requested scenarios for B4

Treatment	Dataset for model fitting	Outcome	Model	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
KTE-X19	ZUMA-3 Phase 1+2 mITT	EFS	Weibull	Inotuzumab	[redacted]	[redacted]	£17,459
				FLAG-IDA	[redacted]	[redacted]	£34,561
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Weibull	Inotuzumab	[redacted]	[redacted]	£20,543
				FLAG-IDA	[redacted]	[redacted]	£38,668
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Exponential	Inotuzumab	[redacted]	[redacted]	£24,857
				FLAG-IDA	[redacted]	[redacted]	£43,509
KTE-X19	ZUMA-3 Phase 1+2 mITT	OS	Gompertz	Inotuzumab	[redacted]	[redacted]	£17,813
				FLAG-IDA	[redacted]	[redacted]	£35,204
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph-subgroup	EFS	Weibull	Blinatumomab	[redacted]	[redacted]	£31,932
				Inotuzumab			£18,502
				FLAG-IDA			£36,721
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph-subgroup	EFS	Exponential	Blinatumomab			£31,649
				Inotuzumab			£18,155
				FLAG-IDA			£36,480
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph-subgroup	OS	Weibull	Blinatumomab			£35,488
				Inotuzumab			£21,094
				FLAG-IDA			£40,109
KTE-X19	ZUMA-3 Phase 1+2 mITT, Ph-subgroup	OS	Gompertz	Blinatumomab			£30,446
				Inotuzumab			£17,297
				FLAG-IDA			£35,307
FLAG-IDA	AD from pooled INO-VATE and TOWER ITT comparator arms	OS	1-knot normal spline	Inotuzumab			£17,306
				FLAG-IDA	[redacted]		£28,099
Blinatumomab	SCHOLAR-3 SCA-3	EFS		Blinatumomab	[redacted]	[redacted]	£31,376

			Weibull MCM	Inotuzumab	[redacted]	[redacted]	£18,177
				FLAG-IDA	[redacted]	[redacted]	£36,499
Blinatumomab	SCHOLAR-3 SCA-3	EFS	Log logistic	Blinatumomab	[redacted]	[redacted]	£31,415
				Inotuzumab	[redacted]	[redacted]	£18,228
				FLAG-IDA	[redacted]	[redacted]	£36,534
Blinatumomab	SCHOLAR-3 SCA-3	OS	Weibull MCM	Blinatumomab	[redacted]	[redacted]	£43,832
				Inotuzumab	[redacted]	[redacted]	£17,867
				FLAG-IDA	[redacted]	[redacted]	£36,071
Ponatinib	AD from PACE	OS =1	MCM Weibull	Ponatinib	[redacted]	[redacted]	£27,631
				Inotuzumab	[redacted]	[redacted]	£16,468
				FLAG-IDA	[redacted]	[redacted]	£34,076
Ponatinib	AD from PACE	OS	Gompertz	Ponatinib	[redacted]	[redacted]	£30,457
				Inotuzumab	[redacted]	[redacted]	£16,363
				FLAG-IDA	[redacted]	[redacted]	£33,926

B5. Priority: Please provide ICERs for the scenarios described in Table 3.

Table 3: Requested Analyses (2) - 3 analyses with two changes of model in each leaving other parameters as in the company's base case.

Outcome	KTE-X19 model	Comparator model
EFS	Weibull (Phase 1+2 mITT Ph-)	blinatumomab Weibull MCM
OS	Weibull (Phase 1+2 mITT)	FLAG-IDA 1-knot normal spline
OS	Weibull (Phase 1+2 mITT)	Ponatinib MCM Weibull

Company response: The results for the requested scenarios are reported in Table 14 below.

Table 15: Cost-effectiveness results for scenarios requested in B5

Outcome	KTE-X19 model	Comparator model	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
EFS	Weibull (Phase 1+2 mITT Ph-)	Blinatumomab Weibull MCM	Blinatumomab	[redacted]	[redacted]	£31,614
			Inotuzumab	[redacted]	[redacted]	£18,477
			FLAG-IDA	[redacted]	[redacted]	£36,704
OS	Weibull (Phase 1+2 mITT)	FLAG-IDA 1-knot normal spline	Inotuzumab	[redacted]	[redacted]	£20,719
			FLAG-IDA	[redacted]	[redacted]	£30,727
OS	Weibull (Phase 1+2 mITT)	Ponatinib MCM Weibull	Ponatinib	[redacted]	[redacted]	£31,570
			Inotuzumab	[redacted]	[redacted]	£19,728
			FLAG-IDA	[redacted]	[redacted]	£38,382

B6. Priority: Please supply the EFS and OS survival model choices, goodness of fit statistics and comparisons to KM data for the three MAIC adjusted KTE-X19 analyses. Please clarify also which of the two categorisations of salvage status was preferred in these analyses in the final MAIC analyses.

Company response: The requested survival models and goodness of fit statistics are provided in Appendix B6. 3 Salvage was used as ultimately it had a minimal impact on the effective sample size (ESS) while providing more stratification of the type of salvage.

B7. Priority: CS section B.2.9, ITC. Phillippo *et al*. (DOI: 10.1002/sim.8759) have raised serious concerns about MAIC and found simulated treatment comparison (STC) to be more robust to possible violations of assumptions. In the light of this and the significant ESS reductions arising in the MAIC analysis, please repeat the ITC using STC and present the resulting survival analysis and scenario analyses from the economic model.

Company response: Unfortunately, we have not been able to carry out an STC within the clarification timeline. However, the approach used is consistent with previous CAR-T appraisals and existing NICE guidance. In general, the use of MAIC approaches have been more widely used by NICE compared to STC. Other simulation studies have also concluded the opposite, for example Ramiro-Azocar et al., who concluded that MAIC should be used for survival outcomes (46). Furthermore, as already explained for the MAIC, it is the ZUMA-3 population that is generalisable to use of KTE-X19 in UK clinical practice and not that of either INO-VATE or TOWER. Therefore, we consider the naive comparisons to be the appropriate ones for inotuzumab and FLAG-IDA and the SCHOLAR-3 SCA-3 analysis for blinatumomab.

B8. Priority: CS section B.3.3.3, survival inputs and assumptions. Please supply smoothed plots of the observed hazard functions for each survival dataset used as model inputs. Please also include the hazard function of plausible survival distributions for comparison. Please also state any expectations and assumptions made concerning how the hazard is expected to evolve with time in each case.

Company response: The requested smooth plots have been provided in the appendix document B8. For comparator therapies, one would expect the hazard of progression to be at its highest in the first year and to decrease over time, plateauing by around 2-3 years, with death following a similar pattern. For those patients who receive an allo-SCT, there is generally a higher death rate during the first two years post-SCT which rapidly reduces thereafter (hence why we chose a timepoint of 3 years for our cure assumption). With a CAR-T the hazard rate for both progression and death appear to be much lower from the start, increasing up to 2 years with OS then reducing rapidly.

B9. Priority: CS section B.3.3.3, page 153. It is stated that *"Whether the predicted cure fractions for the comparators were in line with the proportion of patients reported to have survived following receipt of an allo-SCT*" and *"Clinical plausibility of long-term extrapolations beyond the trial period based on clinical experts' opinion and relevant published external data where possible"* were both included as criteria for survival function selection. However, sections B.3.3.3.2 – B3.3.3.4 only reference AIC, BIC and visual assessment of fit in the decisions. Please clarify if external evidence was used other than in the decision to apply a cure assumption. In particular, since models with AIC, BIC values up to 3-5 greater than the minima are considered to be plausible, please clarify why, for instance, the Weibull model was not considered for the base case or at least a scenario analyses for EFS and OS in the naïve KTE-X19 data for the overall population.

Company response: As stated in our submission, and in line with the available evidence, only patients who receive allo-SCT are assumed to be cured with comparator treatments. While our base case assumed a cure timepoint, it is the cured fraction at that timepoint that is a critical determinant of QALY gain. For the comparators, an important face validity exercise involved querying the INO-VATE, TOWER and SCA-3 datasets to establish 1) the proportion of patients who received an allo-SCT and 2) the proportion of patients reported to still be alive following their allo-SCT at the end of follow-up. These proportions could provide an indication of a feasible cure fraction from the comparator clinical studies for comparison with the cure fraction in the model (those alive at 3 years). It can be seen from the comparison in Table 15 below that the fractions are very similar.

Table 16: Comparison between model cure rates and proportions surviving post-SCT in comparator studies

Comparator	% receiving allo-SCT	Reported as died post-SCT	Maximum cured based on clinical data[1]	Model % alive at 3 years and assumed cured	Difference (model minus reported)
Inotuzumab overall population (INO-VATE)	48.2%	67.1% (53 of 79 with SCT)	15.9%	[redacted]	[redacted]
FLAG-IDA overall population (TOWER and INO-VATE pooled)	22.9%	58.3% (25 + 3 of 36 + 12 with SCT)	9.6%	[redacted]	[redacted]

Blinatumomab (SCHOLAR-3 SCA-3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ponatinib (PACE)	46.9%	NR	NR	[redacted]	NR

Key: NR, not-reported; SCT, stem-cell transplant;.
[1] % of SCT patients who survived multiplied by the proportion who received-SCT
[2] Not available from SCA-3, therefore TOWER data are used for this value

As long-term cure in R/R ALL is determined by the proportion transplanted, registry data on long-term survival post-SCT are the most relevant source, which we have already used in the model to adjust for long-term mortality of cured patients. Both blinatumomab and inotuzumab have only been routinely commissioned within the NHS within the last 4 years, which limits the possibility to elicit clinical opinion regarding long-term extrapolation. A study has been published with longer-term follow-up of blinatumomab (23), but 30% of patients received SCT in that study vs. [redacted] in the matched SCA-3 cohort. Similarly, longer-term follow-up of the INO-VATE study (22) showed a plateau somewhere between 15 and 20% after 3 years (thus in line with our model cure fraction of [redacted]), but INO-VATE notably required patients to have received no more than one prior salvage therapy.

With respect to KTE-X19, clinical expert opinion was elicited regarding the feasibility of the plateau in the model, but this was related to earlier data cuts. This exercise has not been repeated with the most recent data cut. When selecting the most appropriate model for KTE-X19, given that the statistical goodness of fit as measured by the AIC/BIC were similar across parametric models, the clinical plausibility of fits along with the best visual fit was used as a guide. The biggest driver of value in the model is the survival fraction at the 3-year timepoint, therefore similarity to the reported survival at 3 years is critical to model validity. Table 16 presents the cure fraction predicted by the different parametric model specifications. The latest data cut (Phase 1+2 mITT) reports a 3-year OS of [redacted] and it can be seen from Table 16 that the Weibull model predicts 3-year survival well below this value, hence why this was not selected for a scenario analysis.

For EFS, cure faction is far less critical as the model assumes that all patients alive at the cure timepoint are functionally cured and have general population utility. However, it can be seen from Table 17 that our lognormal base case is not the most favourable curve in terms of longer-term EFS. Furthermore, the model is insensitive to the EFS curve selected, with ICERs varying by less than £500 from the original company base case for all curves, including the Weibull distribution.

Table 17: KTE-X19 3-year OS estimates from parametric models

Lognormal (base case)	Exponential	Weibull	Loglogistic	Gompertz	Generalized gamma
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 18: KTE-X19 3-year EFS estimates from parametric models

Lognormal (base case)	Exponential	Weibull	Loglogistic	Gompertz	Generalized gamma
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B10. Priority: CS Table 91. Please give details of which MCM models were used in the scenario "*Survival functions adopted to model EFS and OS of KTE-X19 and comparators*". Please justify the choice of Weibull model as a scenario analysis for FLAG-IDA OS given the high BIC statistic. Please also clarify whether the MCM models used an SMR for general population mortality.

Company response: As explained in the submission, we do not consider the MCMs to be valid for the survival analysis. There were insufficient data from KTE-X19 for an MCM and having selected a hybrid (cure timepoint) approach for KTE-X19 we felt that use of the same approach for the comparators, where there is the potential for cure at a similar timepoint, would be less biased. The scenario analysis using the MCMs can be considered purely exploratory in order to establish the impact on the ICER of assuming negligible cure fractions. In all populations and both EFS and OS, the log-normal MCM was the model used for KTE-X19, inotuzumab, blinatumomab and ponatinib, and the generalised gamma was the model used for FLAG-IDA. Note that these were not necessarily the best fitting MCM models according to AIC and BIC criteria.

In the FLAG-IDA OS parametric and mixture cure models, only the exponential, Weibull and generalised gamma converged. Log-normal, log-logistic and Gompertz did not result in clinically plausible extrapolations. The generalized gamma had been chosen as the base case, leaving exponential and Weibull models as alternatives. Both had similarly poor visual fit and AIC/BIC, therefore the Weibull was selected in the sensitivity analysis. The difference in the ICER between the exponential and Weibull is very small, less than £1,000.

We confirm that the MCMs also applied an SMR for general population mortality in the cured fraction.

B11. Priority: CS page 237. Please clarify why scenario analyses weren't included for the MAIC analyses other than for inotuzumab and FLAG-IDA in the overall population. Please perform these extra analyses.

Company response: As explained in the submission, no Ph subgroup data were available for FLAG-IDA and inotuzumab; neither the Kaplan-Meier curves nor the patient baseline characteristics for Ph subgroups were presented in the INO-VATE publication (all patients from TOWER were Ph-). It was therefore only possible to adjust the ZUMA-3 data to the INO-VATE overall population and not the Ph subgroups.

If the overall population MAIC were to be used for the subgroup analysis, the only aspect of the MAIC analysis that would change in the subgroups would be the costs and QALYs of the patients not infused with KTE-X19, to which we know the model is not sensitive, and the costs of subsequent therapies: On page 237 of our submission, scenario "Distribution of patients in the KTE-X19 arm that fail to receive infusion", the two scenarios selected change the ICER against inotuzumab by approximately £2,000 and that against FLAG-IDA by approximately £1,000.

B12. Priority: Please present the results of all tests for proportional hazards between the MAIC adjusted ZUMA-3 and comparator populations. Please present ICERs for scenarios in which a hazard ratio obtained from each adjusted comparison is applied to the EFS and OS survival functions from the appropriate ZUMA-3 dataset. Present these results also for the STC analysis.

Company response: Results of the requested tests are presented in the B12 Appendices. It can be seen from the tests that no comparisons conclusively satisfy the assumption of proportional hazards. Furthermore, our preferred base case survival curves for KTE-X19 were lognormal, which are incompatible with a proportional hazards modelling approach. Only the OS Gompertz model leads to a similar but lower plateau to that observed in the latest data cut. However, we have included the option to select a proportional hazards modelling approach in the updated model Controls sheet (under the comparator drop-down boxes labelled "Survival modelling approach"). The hazard ratios implemented for these can be found in the sheet "HR_calculations".

B13. Priority: Provide sensitivity analyses where new anticancer therapies are taken as an event rather than as censored. Clarify for what reasons new anticancer therapies were provided.

Company response: We have not been able to incorporate this sensitivity analysis into our model, but the reason for subsequent therapy and the Kaplan-Meier plots of the sensitivity

analysis are provided below. Only [redacted] were censored for having received subsequent anti-cancer therapies other than allo-SCT. The reasons and treatments received are as follows:

- [redacted]
- [redacted]
- [redacted]

Therefore, the [redacted] did not experience an event as per the protocol and thus censoring was appropriate. For [redacted]

which is a clinician decision and usually seen as high-risk feature for progression.
It can be seen below that the EFS rate at 12 months is only [redacted] than that provided in submission Table 17. The impact of subsequent therapies is modelled in term of cost and OS, as those patients were not censored for OS, therefore a modelling scenario employing this sensitivity analysis is unlikely to make a material difference to the cost-effectiveness results.

Table 19: Relapse-free Survival Using Investigator Review - Sensitivity Analysis with Subsequent Anti-Cancer Therapies Considered as Events (Not Including Subsequent Allo-SCT)

RFS	Phase 1 and Phase 2 (N = 78)
Number of subjects, n	78
Events, n (%)	[redacted]
Censored, n (%)	[redacted]
KM median (95% CI) RFS (months)	[redacted]
Min, Max RFS (months)	[redacted]
Events	[redacted]
Relapse, n (%)	[redacted]
Death, n (%)	[redacted]
Subject's best overall response not CR or CRi, n (%)	[redacted]
Started new anti-cancer therapy, n (%)	
Censoring reason	[redacted]
Ongoing remission, n (%)	[redacted]
Allogeneic SCT, n (%)	[redacted]
Lost to follow-up, n (%)	[redacted]
Withdrawal of consent, n (%)	
Event-free rates % (95% CI) by KM estimation at	[redacted]
3 months	[redacted]
6 months	[redacted]

9 months	

RFS	Phase 1 and Phase 2 (N = 78)
12 months	[redacted]
15 months	
18 months	
24 months	
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 09/09/2020
Key: CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; KM, Kaplan-Meier; RFS, relapse-free survival; SCT, stem cell transplant.
Note: Percentages are based on the number of all dosed subjects.

Figure 5: Relapse-free Survival Using Investigator Review - Sensitivity Analysis with Subsequent Anti-Cancer Therapies Considered as Events (Not Including Subsequent Allo-SCT) (Phase 1, 1e6 Dose Level and Phase 2, All Dosed Subjects)

[redacted]

Data cutoff date: 09/09/2020.

B14. Priority: Please clarify where median values were used in the model in preference to means. For example, the median duration of hospitalisation during KTE-X19 infusion was [redacted] days, although the range shows that this data is skewed and that the mean is likely to be higher than the median. Where possible, use means in the model if this isn't already the case.

Company response: Median values were not typically used in preference to means in the model. For instance, in the example provided above for duration of hospitalisation, the model does not use the median value of [redacted] days, but instead the mean duration of

hospitalisation, which is [redacted] days from the Phase 1 and Phase 2 ZUMA-3 combined data, as stated in Table 53 of our submission.

B15. Priority: Please clarify why it is assumed that having previously treated B-precursor ALL is not associated with a reduction in utility compared to the general population, although the risk of death is assumed to be greater. Please explore the impact on the ICER of assuming that people in disease-free survival have a lower utility than an age- and sex-matched population, and also assuming that the utility decrement of patients with progressed disease is constant.

Company response: For clarity, in our model, all patients alive at the cure timepoint, regardless of whether in EFS or progressed disease (PD), assume the utility of the general population. This is the approach that was preferred in TA567 and TA677 (39,40) (in the latter case, an approach proposed by the ERG).

In all appraisals of CAR-T therapies considered by NICE (TA554, TA559, TA567, TA667) (39–42) while a higher risk of death was generally preferred by committee, we can only find two examples where long-term survivors were assumed to have lower utility than the general population:

- In TA567 (Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies), long-term survivors were assumed to have the utility of the PFS health state

- In TA677 (Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma), while general population utility was incorporated into the ERG base case for long-term survivors, the ERG also explored the impact of a 10% and 20% reduction in utility vs. the general population.

First, we consider the approach in TA567, using the utility of the EFS health state. The general population utility at the model baseline age of 43 is 0.889, whereas the EFS health state in our model has been allocated a utility value of 0.822, thus 0.067 less than that of the general population. If we apply this decrement to the cured patients over the model time horizon, assuming the difference in utility of 0.067 vs. general population utility is maintained, the ICERs in the overall population increase by ~£2,500 for inotuzumab, ~£1,200 for FLAG-IDA and ~£2,400 for blinatumomab (see Table 19). Note that, as PD utility is only applied up to the cure timepoint of 3 years, we have not removed the age-decrement from PD utility in this scenario given that it reaches a maximum of only -0.01 after 3 years, so will have minimum impact on results.

Table 20: B15 cure utility scenario analysis

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
Inotuzumab	[redacted]	4.053	[redacted]	£18,416	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£36,914	£34,378
Blinatumomab	[redacted]	4.825	[redacted]	£34,111	£31,690

Note: Inotuzumab and FLAG-IDA results are in the overall population, blinatumomab in the Ph-

Secondly, we now consider the approach in TA677, applying a % reduction to the general population utility. The general population utility at the model baseline age of 43 is 0.889 and reducing this utility by 10% leads to a utility for cured patients of 0.800, lower than the baseline EFS of 0.822. This clearly lacks face validity over the longer term, given that recently-treated patients in EFS are likely to have poorer quality of life than those who have had years to recover from their ALL treatment. Although some of this is accounted for via utility decrements from adverse events, these tend to be acute, shorter term decrements affecting a selection of patients rather than representative of the day-to-day impact of treatment on quality of life, including mental health and on daily living activities.

In summary, the first approach of using the EFS health state utility is the more valid approach of the two, but as stated above, is likely to underestimate the utility of cured patients who have had a chance to recover from their treatment. We therefore maintain that the base case, applying utility of the general population to cured patients, remains the most valid approach.

B16. Priority: Clarify whether the efficacy data for the overall population are used in the Ph+ population (as shown in Table 41). If yes, please clarify why the results are different for KTE-X19 in Tables 76 and 78; if no, please clarify what data were used.

Company response: The KTE-X19 efficacy data informing the Ph+ subgroup analysis is the same as the overall population. The difference in results for the KTE-X19 arm for the overall population vs. Ph+ population is driven by the different assumptions regarding treatment allocation for non-infused patients. Patients in the KTE-X19 arm who do not qualify to receive the CAR-T infusion, for non-AE related reasons, receive a mix of the comparator treatments in the model. In the overall population, this is a mix of inotuzumab, blinatumomab, and salvage chemotherapy. In the Ph+ population, ponatinib is also included, which leads to different outcomes. The KTE-X19 efficacy data are not changed in either

scenario, but the assumptions around which treatments non-infused patients receive are modified.

B17. Priority: Clarify that the intention regarding subsequent treatments post-progression was that all initial regimens would have the same percentage of patients receiving subsequent treatments. Clarify on what basis this assumption was made. Additionally, it appears that the numbers in Table 65 are incorrect. Within the model, the sums of the percentages are 37.18% for KTE-X19 and FLAG-IDA, 37.68% for blinatumomab, 32.05% for inotuzumab, and 38.70% for ponatinib. Please amend these values if the intention was equal proportions.

Company response: As stated in our submission, distribution of subsequent treatments was based on the ZUMA-3 trial (Phase 1 and Phase 2 combined). However, patients were assumed to not be re-treated with their initial therapy and therefore the distribution was re-weighted to remove the re-treatment therapy in the case of blinatumomab, inotuzumab and ponatinib. However, patients who received salvage chemotherapy initially were assumed to receive the same frequency of subsequent treatment as KTE-X19. The proportions reported in Table 65 of the submission are identical to those in the corresponding sheet of the model ('Subsequent Tx').

B18. Priority: For many analyses, full incremental analyses can be performed. For example where there are solely naive comparisons, and presumably this has been undertaken to provide the results in Table 87. Please provide results stating the efficiency frontier where appropriate.

Company response: Full incremental analyses have been performed and are reported for the model base-case results in our response to question B2.

B19. CS Appendix N. To aid visual inspection of goodness of fit, please supply versions of all Figures for all models with extrapolation to 5 years and confidence intervals on the KM functions.

Company response: The requested figures are provided in appendix B19.

B20. CS Table 25 suggests that a survival model was fitted to the mITT phase 1+2 Ph+ population (N=17) for comparison with the ponatinib data from PACE. However, Tables 39 and 41 state that the overall ZUMA-3 population was used. Please clarify this

discrepancy. If a model was fitted to the PH+ data please provide details of the model selection process.

Company response: The ITC against ponatinib compared ZUMA-3 Ph+ phase 1+2 patient data (N = 17) to PACE patient data. However, we would like to draw the ERG's attention to the text in Table 25 at the top of page 90 of our submission: "*Note: the economic model utilizes the ZUMA-3 mITT phase 1+2 overall population for the comparison*". The cost effectiveness section correctly refers to use of the overall ZUMA-3 population dataset for the modelling, as the sample size of Ph+ subgroup was considered too small to inform KTE-X19 EFS and OS survival modelling.

B21. Please clarify why Table 25 states that the analysis population for the comparison with blinatumomab is using mITT phase 2 data only, yet the economic model uses both phase 1 and phase 2 mITT data.

Company response: The SCHOLAR-3 SCA-3 analysis did indeed use the ZUMA-3 phase 2 mITT dataset [redacted] patients from the ZUMA-3 dataset could not be matched), as this was the pivotal dataset underpinning the regulatory filing. The phase 1+2 mITT dataset was larger, with longer follow-up times, and was therefore in principle preferred as a basis for economic modelling, though it is worth noting that the 95% CI of the Kaplan-Meier plots of the two datasets overlap. Furthermore, using the phase 2 mITT dataset for blinatumomab would have diverged from the approach used for the other comparators and would have generated different costs and QALYs in the KTE-X19 comparison vs. blinatumomab compared with those generated from the other comparisons within the same population.

However, we would like to draw the ERG's attention to a scenario analysis vs. blinatumomab in our submission, whereby the survival curves derived from the ZUMA-3 phase 2 mITT dataset replaced those from the phase 1+2 mITT dataset, in line with the SCHOLAR-3 SCA-3 matched comparison.(see Table 92, second of the two scenarios entitled "Source of patients' baseline characteristics and KTE-X19 EFS and OS"). This scenario had only a minor impact on results, reducing the ICER from £29,317 in the base case to £27,790.

B22. Please clarify why 1:1 matching was undertaken for SCHOLAR-3 in preference to 1:many.

Company response: 1:1 matching was used due to a design decision that prioritised the minimisation of heterogeneity between matched cohorts over statistical efficiency.

B23. Please supply the EFS and OS survival model choices, goodness of fit statistics and comparisons to KM data for the ZUMA-3 mITT phase 1+2 Ph- (N=61) and TOWER ITT (n=271) analyses for the alternative blinatumomab analysis.

Company response: The requested survival data and analyses are provided in Appendix B23.

B24. CS page 102 and Table 28. Please clarify how the SCA-3 population was larger than SCA-1 given the definitions provided in which the criteria for SCA-3 appear to be more restrictive than for SCA-1.

Company response: In the SCA-1 cohort only patients from ZUMA-3 who were previously naïve to blinatumomab or inotuzumab therapy ([redacted] patients of the 55 patients in the ZUMA-3 phase 2 mITT dataset) were matched 1:1 to patients from historical clinical trials who had previously been naïve to blinatumomab or inotuzumab therapy. Of the original [redacted] blinatumomab or inotuzumab-naïve ZUMA-3 patients only [redacted] could be matched.

In the SCA-3 cohort all patients from ZUMA-3, irrespective if they had previously been pre-treated with blinatumomab or inotuzumab therapy, were matched 1:1 to patients from historical clinical trials who had previously been naïve to blinatumomab or inotuzumab therapy. Of the original 55 ZUMA-3 patients only [redacted] could be matched.

B25. CS Table 25 page 88. Please clarify why both N=164 and N=162 for the INO-VATE dataset.

Company response: The N=164 refers to the inotuzumab arm of INO-VATE whereas the N=162 refers to the chemotherapy arm.

B26. Please provide a KM plot for ZUMA-3 versus SCA-2 as were provided for SCA-1 and SCA-3 (Figures 31 and 32). Please clarify if there was a reason for omitting this data.

Company response: As a number of patients in SCA-2 were excluded post matching due to protocol deviations (as noted in the CSR); the pre-specified balancing threshold was no longer met and univariate methods were no longer appropriate. Instead, adjusted Cox regressions were used for comparative analysis.

B27. MAIC report section 3.6.2.1 page 55. Please clarify if and how patient characteristics were appropriately centred before estimating the logistic regression weights.

Company response: The method of moments approach outlined by Signorovitch et al. 2010 (55), which involved centring of the patient characteristics, was used to estimate the logistic regression weights given the lack of individual level data from the external trials. To implement this approach, we used the example R code provided in Appendix of NICE TSD

18 (available through this link: http://nicedsu.org.uk/technical-support-documents/population-adjusted-indirect-comparisons-maic-and-stc/).

B28. Supplement Table 137 with the actual distribution used rather than only the CIs. Clarify why variables that would normally be considered fixed, such as the drug cost for fludarabine have been included in the PSA - remove any variables that should not be in the PSA.

Company response: Please excuse this oversight. We agree with the ERG that fixed variables such as unit costs should not be included in the PSA and these have been removed in the updated post-clarification model.

B29. Clarify how the currencies were chosen for the costs of adverse events. For example, for sepsis the currency WH07D (Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1) was selected, at a cost of £1503, however there are many other candidate currencies. For example, WJ06B to WJ06J, all of which have the word sepsis in the title, and with costs ranging from £1531 to £10,038. Please review all costs, as the clinical input received to date suggested that these often appeared low.

Company response: The currencies for adverse event costs were aligned with prior NICE TAs where possible. In cases where this was not possible, the currencies were chosen based upon their names. The table below summarises the rationale behind the costs and currencies chosen for AEs in the model.

Table 21: Source and rationale for how AE costs were selected in the economic model

AE	Rationale
Abdominal pain	In line with TA567 using NEL instead of DC
Acute kidney injury	In line with TA567
Alanine aminotransferase increased	In line with TA554
Anaemia	In line with TA567
Bacteraemia	The same currency is used as for sepsis - In line with TA554
Bacterial infectious disorders	Chosen based upon currency names
Constipation	Assume same as diarrhoea
CRS	In line with TA554
Decrease in appetite	Chosen based upon currency names
Device related infection	Chosen based upon currency names
Diarrhea	In line with TA567
Encephalopathy	In line with TA554 only using NEL & NES instead of DC
Febrile neutropenia	In line with TA451
Fluid overload	Chosen based upon currency names containing "fluid disorders"

Fungal infectious disorders	Chosen based upon currency names containing "infections"
Fungal pneumonia	Assume same as pneumonia
Hyperglycaemia	Chosen based upon currency names containing "Other haematological or Splenic disorders"
Hypertension	In line with TA554
Hypertransaminasemia	Assumed same as ALT increase
Hypokalaemia	In line with TA567 only using NES instead of DC
Hypophosphatemia	In line with TA567 and TA554
Hypotension	Assumed same as Hyperglycaemia
Hypoxia	In line with TA554
Increase in blood bilirubin	Chosen based upon currency names containing "NES Toxic Effect of Other Substance with CC Score 1-2+"
Infection pathogen unspecified	Chosen based upon currency names containing "infections"
Leukopenia	In line with TA541
Lipase increase	In line with TA451
Lymphocyte count decreased	In line with TA554
Neutropenia	In line with TA567
Neutropenic sepsis	Assumed same as sepsis
Neutrophil count decreased	Assumed to be the same as Neutropenia
Platelet count decreased	Assumed same as thrombocytopenia
Pneumonia	Used currency names containing pneumonia
Pulmonary edema	In line with TA554
Pyrexia	In line with TA567
Rash	Used currency names containing Skin Disorders
Respiratory failure	In line with TA554
Sepsis	DC Infections or Other Complications of Procedures, with Single Intervention as weighted average of day case currency names containing sepsis would result in a cost of £292 which is too low
Septic shock	Assumed the same as sepsis
Subdural hematoma	Used currency names containing Muscular, Balance, Cranial or Peripheral Nerve Disorders, Epilepsy or Head Injury
Thrombocytopenia	In line with TA567 and TA554
Viral infectious disorders	Chosen based upon currency names containing "infections"
VOD	In line with TA541
White blood cell count decreased	In line with TA567

B30. P 185. Clarify why the weighted average of NHS ref codes for Peripheral Blood Stem Cell Harvest and Bone Marrow Harvest are preferred as an estimate for leukapheresis than the NHS ref code for Leucopheresis.

Company response: The costing of leukapheresis was based on the approach taken in NICE TA559 (8) where a weighted average was taken of all healthcare resource groups (HRGs) codes for stem cell and bone marrow harvest in the NHS reference costs. In TA559, the company explained that this was also the approach taken by the authors of the NICE regenerative medicines report (56). As this was not an issue raised by the ERG or committee in TA559, we felt it was appropriate to follow the same methodology. We would also like to highlight that the source of costs for leukapheresis has a very minimal impact upon the results. To illustrate this, scenario results for the overall population where the NHS reference cost code for Leucopheresis is selected in the updated base-case model are presented below.

Table 22: Scenario analysis results, alternative NHS reference costs for leukaphereis overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£17,604	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£34,651	£34,378

Table 23: Scenario analysis results, alternative NHS reference costs for leukaphereis, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£32,043	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£36,811	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£18,656	£18,108

Table 24: Scenario analysis results, alternative NHS reference costs for leukaphereis, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£29,837	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£34,247	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£16,802	£16,396

B31. P.136 Clarify the assumptions used, if any, to prevent patients "*in the PD health state being alive for a long time which is not compatible with the pathology*"

Company response: This statement refers to our assumption that following the cure timepoint all patients, regardless of whether they were in the EFS or PD health state, were assumed to be cured. Clearly this is at odds with what is known about survival in heavily pre-treated R/R ALL on comparator therapies (and one reason why KTE-X19 qualifies as an End of Life therapy). In the following paragraph of the submission, we go on to explain why the assumption of cure, regardless of health state occupancy, is valid:

"This is because the way RFS KM are derived does not allow for robustly informative extrapolation:

- *The curves start from lower probability of survival (excluding the non-responders, looking at RFS curves for only CR/CRi patients the RFS at 2-3 year is more aligned to the plateau seen for OS (~35-40%)*
- *There is also a high level of censoring 40% consisting mainly of patients in ongoing remission (15%) and patients who received a subsequent allo-SCT (18%),*

representing a proportion without progression of 33% again much more aligned with the OS plateau ~40%.

This assumption is applied for both intervention and comparators as it is not a ZUMA-3 specific issue but is seen also in other studies:

- *The INO-VATE modelled OS curve plateau around 16% at 3 years, while the EFS modelled curve plateau around 8% at 3 years*
- *The SCHOLAR-3 SCA-3 modelled OS curve plateau at 11% at 3 years, while the EFS modelled curve plateau at 0% at 3 years."*

This issue was also raised in TA559 (Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies) (42). Clinical experts explained that patients receiving axicabtagene ciloleucel would need to have high fitness criteria and that they may have salvage chemotherapy if their disease relapses after having axicabtagene ciloleucel and that it is clinically plausible that a small proportion of patients could have long-term survival after disease relapse with axicabtagene ciloleucel. This would be equally true with KTE-X19, particularly as the model assumes that patients may receive subsequent therapies more effective than salvage chemotherapy.

B32. P.143 Clarify the source for the information relating to '*in line with UK clinical practice*'.

Company response: In the NICE submission for blinatumomab (TA450) administration and dosing of FLAG- IDA was based on the FLAG-IDA protocol from the Royal Surrey NHS Foundation Trust. 4 cycles were considered, which is based on exposure data for the SOC chemotherapy arm in the TOWER FAS (Section 5.5.3.2, TA450) (57).

B33. Please provide a sensitivity analysis where the actual costs of tocilizumab observed in the ZUMA-3 study are included.

Company response: The results for this scenario conducted in the updated post-clarification model are presented in the tables below.

Table 25: Scenario analysis results, tocilizumab costs from ZUMA-3, overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£18,076	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£34,972	£34,378

Table 26: Scenario analysis results, tocilizumab costs from ZUMA-3, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£32,516	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£37,158	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£19,188	£18,108

Table 27: Scenario analysis results, tocilizumab costs from ZUMA-3, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£30,223	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£34,570	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£17,280	£16,396

B34. Please provide a sensitivity analysis where the AEs included in the model have been continuity corrected for all interventions (by adding half an event to the observed data, and one event to the total number of observations) where there were less than 5 events observed.

Company response: The results for the requested scenario analysis are presented below.

Table 28: Scenario analysis results, AEs continuity corrected, overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£17,209	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£34,328	£34,378

Table 29: Scenario analysis results, AEs continuity corrected, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£31,699	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£36,461	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£18,209	£18,108

Table 30: Scenario analysis results, AEs continuity corrected, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£29,496	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£33,923	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£16,404	£16,396

B35. Clarify why a 5% threshold was applied for AEs in relation to KTE-X19 treatment, but 2% was used for INO-VATE. Provide sensitivity analyses using 2% as the threshold for KTE-X19.

Company response: The INO-VATE trial publication defined serious treatment-emergent AEs as those with an incidence ≥2% and reported AE incidence accordingly. The AE rates included in the model are based on incidence thresholds defined in the key clinical studies. We would like to highlight to the ERG that AE rates within the model have a very minimal impact upon the results. To illustrate this, we provide the scenario below where we have removed AEs by setting the incidence of all treatment-related AEs is set to 0. It can be seen that the model is not very sensitive to the inclusion of AEs and we therefore have not

provided the requested scenario using a 2% threshold for KTE-X19 as this would have a very minimal effect upon the results.

Table 31: Scenario analysis results, AEs removed from the model, overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£20,490	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£33,755	£34,378

Table 32: Scenario analysis results, AEs removed from the model, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£30,671	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£36,010	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£22,189	£18,108

Table 33: Scenario analysis results, AEs removed from the model, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£28,502	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£33,508	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£19,966	£16,396

B36. Clarify why no dose reductions for ponatinib were considered. In Cortes *et al.* (2018), dose reductions to 30 mg or 15 mg once daily were applied to manage adverse events or implemented proactively following recommendations from the sponsor in October 2013. The authors state that unless benefit-risk analysis justified treatment with a higher dose, the following dose reductions were recommended: 15 mg once daily for CP-CML patients with

McyR, and 30 mg once daily for CP-CML patients without McyR, AP-CML patients, and BP-CML patients.

Company response (Note: updated from response on 13th): Based on ponatinib's SmPC (58) ponatinib should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity (45mg once daily). Dose reduction is only considered for CP-CML. The relevant excerpt from the posology section 4.2 of the SmPC is provided below. As a result, we have not amended the economic model to assume ponatinib dose reductions.

"*The risk of arterial occlusive events is likely to be dose-related. Reducing the dose of Iclusig to 15 mg should be considered for CP-CML patients who have achieved a major cytogenetic response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to cytogenetic response, and BCR-ABL transcript levels (see sections 4.4 and 5.1).*"

B37. Provide a sensitivity analysis where the costs of chemotherapy are not included for ponatinib.

Company response: This scenario was previously provided in the last row of CS Table 93. The ICER vs. ponatinib changed from a base case value of £28,001 to £30,137.

B38. Please clarify the likelihood of informative censoring in the post-relapse EQ-5D data shown in Table 43. Clarify how many patients did not fill in EQ-5D post-progression.

Company response: Unfortunately, we have not been able to obtain this information from our biostatistics provider. We will attempt to obtain this information in time for technical engagement.

B39. Please provide a sensitivity analysis where the terminal care costs are not applied to functionally cured patients

Company response: The results for this scenario are presented in the tables below. It can be seen that the model is not very sensitive to this scenario, as terminal care costs comprise less than 10% of the total costs for each modelled treatment.

Table 34: Scenario analysis results, terminal care costs removed for cured patients, overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£17,070	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£34,240	£34,378

Table 35: Scenario analysis results, terminal care costs removed for cured patients, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£31,546	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£36,377	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£18,070	£18,108

Table 36: Scenario analysis results, terminal care costs removed for cured patients, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£29,372	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£33,834	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£16,263	£16,396

B40. Clarify the source informing the setting where conditioning chemotherapy was performed (65% of patients receiving this in hospital and 35% receiving this in an outpatient setting).

Company response: The source for this assumption is the NICE submission for tisagenlecleucel, TA554 (11). Although the proportions of patients that had received conditioning chemotherapy in the inpatient and outpatient setting respectively was redacted in the company submission, we were able to back-calculate this from table 46 (page 238 of committee papers) of the submission. Dividing the total cost of pre-treatment (£7,101.38) by the average daily cost of hospitalisation (£772.11) results in a proportion of 65.79% of

patients who would receive pre-treatment hospitalisation. We note that technically this should have been rounded to 66%, resulting in a corresponding proportion of 34% of patients having outpatient chemotherapy, however we consider this to be negligible given the very minimal impact upon the results. We have updated the proportions in the updated post-clarification model which we will share on the 20th of January.

B41. Clarify what is meant on page 219 where it is stated that 'Conversely, unadjusted patient data from the overall ZUMA-3 population are used'.

Company response: Please disregard this sentence, which was left over from a legacy version of the submission.

B42. Clarify the likelihood that in the PSA that ranking of utility states become unintuitive, for instance that the utility for progressed disease is higher than for event-free survival.

Company response: In 1000 probabilistic sensitivity analysis (PSA) simulations, there was a 6.2% chance that the utility values become unintuitive.

B43. Clarify whether a systematic literature review was undertaken to identify evidence related to both the SMR and the utility associated with functionally cured patients.

Company response: A targeted literature review of NICE TA guidance and associated grey literature e.g., ERG reports, Company submissions etc. was conducted (rather than a systematic literature review) to source these values. The search was specifically designed to identify evidence from previous NICE technology appraisals and to identify assumptions and data that had been accepted by the committees within these appraisals.

B46. Clarify why only oral administration costs were assumed for dexamethasone although this can be given intravenously. Further, clarify why oral chemotherapy costs were assumed for dexamethasone, which is not a chemotherapy. Clarify why cyclophosphamide is indicated as an intravenous drug but the administration costs included are for an oral intervention. Please check the accuracy in this respect for remaining interventions.

Company response: The ZUMA-3 CSR did not specify whether patients received oral or intravenous (IV) dexamethasone and this data was not easily accessible at the time of the submission. Given that these costs comprise such a small proportion of overall costs in the KTE-X19 arm, we assumed that all patients would receive oral dexamethasone. The model

is not sensitive to the choice of dexamethasone formulation, as ICERs only increase by a very small amount when IV administration costs are applied as shown in the tables below.

Table 37: Scenario analysis results, IV admin costs applied for dexamethasone, overall population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Inotuzumab	[redacted]	4.053	[redacted]	£17,437	£17,203
FLAG-IDA	[redacted]	6.210	[redacted]	£34,555	£34,378

Table 38: Scenario analysis results, IV admin costs applied for dexamethasone, Ph- population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Blinatumomab	[redacted]	4.825	[redacted]	£31,907	£34,753
FLAG-IDA	[redacted]	5.702	[redacted]	£36,707	£36,380
Inotuzumab	[redacted]	3.545	[redacted]	£18,466	£18,108

Table 39: Scenario analysis results, IV admin costs applied for dexamethasone, Ph+ population

Technologies	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)	New Base case ICER
KTE-X19	-	-	-	-	-
Ponatinib	[redacted]	4.987	[redacted]	£29,703	£29,508
FLAG-IDA	[redacted]	6.161	[redacted]	£34,150	£33,972
Inotuzumab	[redacted]	4.004	[redacted]	£16,633	£16,396

Oral chemotherapy costs were assumed for dexamethasone because although this is not a chemotherapy, the drug was administered as part of the bridging chemotherapy regimen, thus it was felt that these administration costs were applicable.

Thank you to the ERG for pointing out the error in the administration costs for cyclophosphamide. These costs have now been updated to reflect IV costs in the post-clarification model.

B47. Clarify the approach towards calculation of administration costs for each drug form. For example, why for dexamethasone the number of administrations is indicated as 6, but the total administration costs are equal £211 (one unit cost for oral chemotherapy administration).

Company response: The model assumes that for intravenous drugs, an administration cost would be incurred for each instance where these drugs was taken. For oral drugs, it was deemed that applying an administration cost for each time a tablet was taken would lead to large overestimates costs and that the administration costs for these drugs would only be incurred once per dosing cycle. The model contains 6 administrations of dexamethasone but the cost stated equates to one administration cost. This is similar to Hydroxyurea, which has 10 administrations and only one administration cost. For Hydroxyurea, administration cost is derived based upon a formula to derive total number of packs used per administration (assuming wastage) so assuming the administration cost is applied per pack this is correct. The formula is given below.

Round up (Daily dose * Number of doses over 14 days / (Pack size * Concentration))

The model has been modified so the administration costs for all oral treatments are derived using the above formula.

B48. Clarify whether table B76:D79 in Sheet: Drug and Admin cost introduces errors into the results. Cell D77 appears to refer to monthly and not weekly costs as is stated.

Company response: Apologies, the heading weekly cost in cell D76 is misleading, however the calculations have been implemented correctly. The ERG is correct that the cost in cell D77 is a monthly cost, not weekly, however this is accounted for within the Markov trace sheet 'PF-BLIN'. In cells P28:P3162, the formulae ensures that these administration costs are applied every 6 weeks only, rather than every weekly cycle. This is in line with the blinatumomab dosing schedule described in section B.3.5.1 within Document B, specifically, that blinatumomab is administered as a continuous IV infusion over 4 weeks and between each treatment cycle there is a treatment-free interval of 2 weeks.

B49. Please separate the administration costs for blinatumomab for the first and the subsequent cycles, since in-hospital treatment should be considered for the 1st cycle only (Sheet: Drug and Admin cost, B71:D73).

Company response: Apologies if this is unclear in the model, however the administration costs for blinatumomab for the first and the subsequent cycles have already been separated. The table in sheet 'Drug and Admin cost', B71:D73 presents the administration costs (in-hospital costs) that are applied in the 1st cycle only (see sheet 'PF-BLIN', cells P28:P3162),

whilst the table in cells B77:D80 present administration costs for subsequent cycles. Headings have been added to the updated model to clarify this.

B50. Please include vial wastage within the model. When vial wastage is considered, consider using weight distributions in order to more accurately reflect the costs of weight-based dosages.

Company response: The model has been amended to account for vial wastage. The original submitted model did use weight distributions for treatments such as inotuzumab and FLAG-IDA however only used mean BSA for the CAR-T pre-treatment costs. In the updated model, weight distributions have been used to calculate treatment costs for the CAR-T pre-treatment costs.

B51. Please explain the choice of the selected products when multiple products are available on the market, for example for filgrastim. For instance, was the lowest price chosen, or a weighted price based on market share?

Company response: For generic drugs where multiple products were available on the market, the lowest priced product was selected.

B52. Sheet: Adverse Event costs, Cell J24:25. The costs for tocilizumab appear to have been included for 1 day only. Clarify the intended duration of tocilizumab treatment and amend the formulae if appropriate.

Company response: Total costs for tocilizumab in cell J25 are calculated as the sum of the acquisition and administration costs multiplied by the mean duration of CRS (4.3 days). The intended duration of tocilizumab treatment is 4.3 days and this has been accounted for thus we do not believe there is an error in the formulae.

B53. P 142 For blinatumomab, some data are sourced from Von Stackelberg *et al.* (2016) which recruited a paediatric population. Please clarify the reasons for the choice and how it may influence the results of the model.

Company response: The costs of blinatumomab will to some extent be a function of the proportion of patient who respond and then are consolidated and transplanted. Von Stackelberg is a conservative estimate of blinatumomab costs as the population, being younger, will have had more eligible for transplant. The model includes an option (not presented in the scenario analyses) to use the number of cycles from Rambaldi et al (59). (median age 53; 3.1. cycles vs. 1.5 cycles for Von Stackelberg). When Rambaldi is selected as the basis for costs in the original submitted model then KTE-X19 dominates blinatumomab.

B54. P 143 Please clarify the reference/source for the statement "*maximum of 4 28-day cycle, in line with UK clinical practice*".

Company response: Please see the response for question B32.

B55. Table 46, p 176 Clarify the rationale behind assuming that respiratory failure has the same duration and disutility as pneumonia.

Company response: The durations of these disutilities are derived from ZUMA-3 and they are not assumed equal. Disutility for pneumonia has a duration of 11.3 days whilst respiratory failure has a duration of 1.6 days. It is only the disutility value itself that is assumed equal for these two AEs. The disutility of -0.22 is assumed to be the same for respiratory failure and pneumonia, sourced a paper written by Stein et al (2018) (60). This is the utility stated as a serious infection and had the highest decline in utility reported in the study. We did not identify any specific sources for respiratory failure disutility in the literature. Given the lack of data on respiratory failure, we equated the utilities for respiratory failure and pneumonia.

B56. P 178 Clarify any possible reasons for the large difference in utilities for progressed patients in blinatumomab SMC submission and in the ZUMA-3 study. Does this suggest a difference in the populations?

Company response: The blinatumomab SMC submission Detailed Advice Document (61) does not describe the method used to obtain the utility of progressed patients in detail. It simply states "*Utility value for the post-relapse state was derived using indirect comparison and mapping techniques*.". On the other hand, the EQ-5D-5L was prospectively measured in the ZUMA-3 study. There are therefore differences in methodology that are likely to have led to differences in progressed utility value between the two studies. The method used to measure utility in the ZUMA-3 study adheres more closely to the NICE reference case and has been mapped to the EQ-5D-3L using NICE's recommended algorithm.

B57. p. 190. On page 142 it is said that the inotuzumab dosing reflected in the model was in line with INO-VATE study. However, the referenced publication (reference 26, Kantarjian et al (2016)) states the following: "*Once a patient achieved complete remission or complete remission with incomplete hematologic recovery, the dose that was administered on day 1 of each cycle was reduced to 0.5 mg for the duration of the trial.*" Please clarify why dose reduction for inotuzumab from 0.8 mg/m^2 to 0.5 mg/m^2 was not considered.

Company response: This was indeed an oversight. We have implemented the dose reduction in the updated economic model in line with Table 1 of the inotuzumab SmPC (62).

B58. Clarify whether the mean age of the population considered in the company base case is 43 years as used in the model.

Company response: We confirm that the mean age of the population considered in the company base case is 43 years as used in the model and summarised in table 38 of Document B.

B59. Clarify the assumptions used to differentiate between columns F, G, H, and I in the Sheet: Survival calculations for KTE-X19 OS and the intention of these calculations. This clarification request applies to all other treatments and for EFS.

Company response: The assumptions are summarised in Table 39.

Table 40: Description of survival assumptions applied within the economic model

SURVIVAL	TREATMENT	COLUMN TITLE	EXCEL COLUMN	DESCRIPTION
Overall Survival	**KTE-X19**	KTE-X19 OS curve	**F**	• Based on modeling approach (spline vs parametric / mixture cure) and model selection, retrieve appropriate extrapolation • In case of mixture cure model, adjust the extrapolations for the cure fractions
		KTE-X19 OS adjusted with Gen pop	**G**	• Adjust for general population mortality
		KTE-X19 added	**H**	• For spline and parametric survival model, adjust for cure assumption (time of cure or cure proportion)
		KTE-X19 OS	**I**	• Reweight OS curve based on X19 for those infused and comparators for those who did not get KTE-X19 infusion (based on treatment failure distribution)
	Comparators (BLIN, INO, PONA, CHEMO)	<Comp> OS curve	**J, N, R, V**	• Based on modeling approach (spline vs parametric / mixture cure) and model selection, retrieve appropriate extrapolation • In case of mixture cure model, adjust the extrapolations for the cure fractions
		<*Comp*> OS adjusted with Gen pop	**K, O, S, W**	• Adjust for general population mortality
		<*Comp*> OS - Active	**L, P, T, X**	• For spline and parametric survival model, adjust for cure assumption (time of cure or cure proportion)
		<*Comp*> OS Hazard of death	**M, Q, U, Y**	• Calculate the hazard of death
Event Free Survival	**KTE-X19**	KTE-X19 EFS curve	**AA**	• Based on modeling approach (spline vs parametric / mixture cure) and model selection, retrieve appropriate extrapolation • Normalize EFS extrapolation based on response rate • In case of mixture cure model, adjust the extrapolations for the cure fractions

		KTE-X19 EFS cure added	**AB**	• For spline and parametric survival model, adjust for cure assumption (time of cure or cure proportion)
		KTE-X19 EFS adjusted	**AC**	• Reweight EFS curve based on X19 for those infused and comparators for those who did not get KTE-X19 infusion (based on treatment failure distribution)
		KTE-X19 EFS Active	**AD**	• Compare KTE-X19 EFS and OS curves, and select minimum (ensuring EFS < OS)
		KTE-X19 EFS Hazard of death	**AE**	• Calculate the hazard of death
	Comparators (BLIN, INO, PONA, CHEMO)	<Comp> EFS curve	**AF, AJ, AN, AR**	• Based on modeling approach (spline vs parametric / mixture cure) and model selection, retrieve appropriate extrapolation • In case of mixture cure model, adjust the extrapolations for the cure fractions
		<*Comp*> EFS cure adjusted	**AG, AK, AO, AS**	• For spline and parametric survival model, adjust for cure assumption (time of cure or cure proportion)
		<*Comp*> EFS - Active	**AH, AL, AP, AT**	• Compare comparators EFS and OS curves, and select minimum (ensuring EFS < OS)
		<*Comp*> EFS Hazard of death	**AI, AM, AQ, AU**	• Calculate the hazard of death

Key: BLIN, blinatumomab; CHEMO, salvage chemotherapy; EFS, event free survival; INO, inotuzumab; OS, overall survival; PONA, ponatinib.

B60. SMR is applied to the cycle-specific death transition probabilities (calculated at 'Life Tables' column O). Please correct the model by converting the probabilities to rates before applying the SMR then estimating probabilities from the adjusted rate. Note: this would avoid the need to use the MIN function in column U.

Company response: We thank the ERG for pointing this out and have corrected the error in the updated economic model.

B61. CS Table 30. Some of the KTE-X19 related AEs Worst Grade 3 or higher occurring in >5% are not considered in the model (e.g., tachycardia, aphasia, hypocalcaemia) despite the stated intention. Please amend the model to account for these.

Company response: Please note that Table 30 in the CS presents AE incidence for the Phase 2 ZUMA-3 population only. The model is however based on the combined Phase 1 and Phase 2 mITT ZUMA-3 population. Thus, whilst some AEs occur in >5% of the Phase 2 population, the incidence of these AEs is <5% for the combined population used in the model. Therefore, they have not been incorporated into the model.

B62. CS page 115. For those whose CRS was resolved, the median duration of CRS was 7.5 days, however the model uses 4.3 days. Please clarify the discrepancy and amend the model if necessary. Note means are preferred to medians if available.

Company response: Please note that the median duration referred to on page 115 is for the Phase 2 dataset only, whereas the model is comprised of the combined Phase 1 and Phase 2 mITT ZUMA-3 dataset, hence the discrepancy in values.

B63. CS page 116. For those whose neurologic AEs were resolved, the median duration of neurologic AEs was 7.0 days, however the model uses 5.86 days. Please clarify the discrepancy and amend the model if necessary. Note means are preferred to medians if available.

Company response: As above, the discrepancy is due to the data on page 116 being from the ZUMA-3 Phase 2 dataset, whilst the value in the model is representative of the combined Phase 1 and Phase 2 mITT ZUMA-3 dataset.

B64. CS page 116. There appears to be some discrepancies between some of the KTE-X19 related AE rates. For example, 44% had worst Grade 3 or higher thrombocytopenia, however only 23.1% were included in the model (CS Table 42). Please clarify all discrepancies between both CS sections and amend the model if necessary.

Company response: The AE rates on page 116 are those observed in Phase 2 of ZUMA-3. The model relies on data from the modified intent-to-treat population from combined Phase 1

and Phase 2 ZUMA-3 data, hence the discrepancies in some of the AE rates reported in the clinical sections of the submission and the model. No changes to the model have been made.

B65. CS Table 42. Some of the KTE-X19 related AE rates are reported as NR (not reported), however CS Table 30 reports these values. For example, the AE rate for diarrhoea was reported for 2 subjects out of the 55 patients. Please clarify all discrepancies between both sections and amend the model if necessary.

Company response: The incidence of adverse events for KTE-X19 patients were included in the model if ≥5% of the population experienced a grade 3 or 4 event.

Constipation, diarrhoea, decreased appetite and rashes were included in the model as these adverse events were experienced in the clinical trials for comparators, however, since less than 5% of KTE-X19 patients experienced grade 3 or 4 of these events (), they were not included in the model.

Following the ERG comment, the Phase 2 and Phase 1/2 incidence for these adverse events have been added to the model for KTE-X19 using Table 2 from Shah, et al 2021 (19) to inform the Phase 1 adverse event incidence and Table 40 below to inform Phase 2.

Table 41: Company submission Table 30 – phase 2 AEs

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
Diarrhoea	12 (22)	7 (13)	3 (5)	2 (4)	0 (0)	0 (0)
Constipation	8 (15)	6 (11)	2 (4)	0 (0)	0 (0)	0 (0)
Decreased appetite	8 (15)	6 (11)	2 (4)	0 (0)	0 (0)	0 (0)
Rash	6 (11)	4 (7)	2 (4)	0 (0)	0 (0)	0 (0)

Source: page 110 of company submission

B66. CS Table 42. There appears to be some discrepancies between some of the inotuzumab related AE rates mentioned there and the INO-VATE referenced publication (Kantarjian 2016 Supplementary Appendix Table S1). For example, CS Table 42 mentions that 11.6% had VOD, however Table S1 states it is 9% of patients who had VOD Grade 3 or higher. Please clarify all discrepancies between both sources and amend the model if necessary.

Company response: The Grade 3 and higher adverse events for inotuzumab were sourced from Kantarjian 2019 (22) from either table 4 (which presents the incidence of serious adverse events) and supplementary table 3 (which presents the incidence of all adverse events). Both tables have been compared with the adverse event rates in the model and the

rates in the model are consistent (see screenshots below with relevant entries highlighted). Therefore, no changes needed to be made to the model.

TABLE 4. Incidence of Treatment-Emergent Serious Adverse Events

Serious Adverse Event	InO (n = 164), No. (%)					SoC (n = 143), No. (%)				
	Any Grade	Grade ≥3	Grade 3	Grade 4	Grade 5	Any Grade	Grade ≥3	Grade 3	Grade 4	Grade 5
Any	85 (51.8)	80 (48.8)	37 (22.6)	17 (10.4)	26 (15.9)	72 (50.3)	71 (49.7)	34 (23.8)	21 (14.7)	16 (11.2)
Febrile neutropenia	19 (11.6)	19 (11.6)	16 (9.8)	3 (1.8)	0 (0)	27 (18.9)	27 (18.9)	20 (14.0)	7 (4.9)	0 (0)
Veno-occlusive liver disease	23 (14.0)	19 (11.6)	8 (4.9)	6 (3.7)	5 (3.0)	3 (2.1)[a]	3 (2.1)	3 (2.1)	0 (0)	0 (0)
Sepsis	4 (2.4)	4 (2.4)	0 (0)	2 (1.2)	2 (1.2)	10 (7.0)	10 (7.0)	1 (0.7)	7 (4.9)	2 (1.4)
Disease progression	8 (4.9)	8 (4.9)	0 (0)	0 (0)	8 (4.9)	5 (3.5)	5 (3.5)	0 (0)	0 (0)	5 (3.5)
Pneumonia	10 (6.1)	9 (5.5)	5 (3.0)	1 (0.6)	3 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory failure	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)	0 (0)	6 (4.2)	6 (4.2)	0 (0)	3 (2.1)	3 (2.1)
Pyrexia	5 (3.0)	2 (1.2)	2 (1.2)	0 (0)	0 (0)	3 (2.1)	1 (0.7)	0 (0)	1 (0.7)	0 (0)
Neutropenic sepsis	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.6)	4 (2.8)	4 (2.8)	1 (0.7)	3 (2.1)	0 (0)
Septic shock	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.6)	3 (2.1)	3 (2.1)	1 (0.7)	1 (0.7)	1 (0.7)
Fungal pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	3 (2.1)	0 (0)	0 (0)
Hyperbilirubinemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0 (0)
Subdural hematoma	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	3 (2.1)	2 (1.4)	1 (0.7)	0 (0)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2.1)	2 (1.4)	0 (0)	2 (1.4)	0 (0)

Abbreviations: InO, inotuzumab ozogamicin; SoC, standard of care (intensive chemotherapy).
The data represent the safety population from the January 4, 2017, data cutoff. Serious adverse events with an incidence ≥2% in either of the treatment arms are shown. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).
[a]A clinical site visit conducted in July 2017 (after the clinical database had been locked) confirmed that a fourth case of veno-occlusive liver disease/sinusoidal obstruction syndrome had occurred in a patient in the SoC arm. This case occurred in March 2013 (~3 months after the patient received the last dose of the study drug treatment), was not entered onto the case report form, and, therefore, is not included.

Supporting Table 3. All-cause and treatment-related treatment-emergent adverse events

	InO (n=164)				SoC (n=143)			
	All-cause		Treatment-related		All-cause		Treatment-related	
Adverse event†	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Any	163 (99.4)	149 (90.9)	144 (87.8)	115 (70.1)	143 (100)	138 (96.5)	130 (90.9)	114 (79.7)
Thrombocytopenia	81 (49.4)	67 (40.9)	55 (33.5)	40 (24.4)	87 (60.8)	85 (59.4)	71 (49.7)	70 (40.9)
Neutropenia	80 (48.8)	77 (47.0)	62 (37.8)	59 (36.0)	66 (46.2)	63 (44.1)	57 (39.9)	54 (37.8)
Anemia	55 (33.5)	37 (22.6)	33 (20.1)	20 (12.2)	79 (55.2)	63 (44.1)	60 (42.0)	50 (35.0)
Nausea	53 (32.3)	3 (1.8)	26 (15.9)	0 (0)	68 (47.6)	0 (0)	50 (35.0)	0 (0)
Febrile neutropenia	44 (26.8)	44 (26.8)	23 (14.0)	23 (14.0)	77 (53.8)	77 (53.8)	65 (45.5)	65 (45.5)
Pyrexia	52 (31.7)	5 (3.0)	23 (14.0)	3 (1.8)	60 (40.2)	8 (5.6)	34 (23.8)	4 (2.8)
Leukopenia	47 (28.7)	44 (26.8)	31 (18.9)	29 (17.7)	54 (37.8)	53 (37.1)	37 (25.9)	36 (25.2)
Diarrhea	30 (18.3)	1 (0.6)	10 (6.1)	0 (0)	56 (39.2)	1 (0.7)	31 (21.7)	1 (0.7)
Headache	45 (27.4)	4 (2.4)	13 (7.9)	2 (1.2)	38 (26.6)	1 (0.7)	13 (9.1)	0 (0)
Lymphopenia	31 (18.9)	27 (16.5)	21 (12.8)	19 (11.6)	36 (25.2)	36 (25.2)	24 (16.8)	24 (16.8)
Fatigue	42 (25.6)	4 (2.4)	22 (13.4)	2 (1.2)	24 (16.8)	3 (2.1)	15 (10.5)	1 (0.7)
Constipation	28 (17.1)	0 (0)	8 (4.9)	0 (0)	34 (23.8)	0 (0)	10 (7.0)	0 (0)
Vomiting	26 (15.9)	2 (1.2)	11 (6.7)	1 (0.6)	35 (24.5)	0 (0)	25 (17.5)	0 (0)
Hyperbilirubinemia	35 (21.3)	10 (6.1)	17 (10.4)	6 (3.7)	24 (16.8)	9 (6.3)	12 (8.4)	4 (2.8)
Hypokalemia	25 (15.2)	11 (6.7)	8 (4.9)	2 (1.2)	33 (23.1)	13 (9.1)	15 (10.5)	5 (3.5)
AST increased	37 (22.6)	7 (4.3)	17 (10.4)	1 (0.6)	16 (11.2)	5 (3.5)	8 (5.6)	1 (0.7)
Abdominal pain	21 (12.8)	3 (1.8)	6 (3.7)	1 (0.6)	27 (18.9)	2 (1.4)	11 (7.7)	1 (0.7)
GGT increased	35 (21.3)	18 (11.0)	21 (12.8)	8 (4.9)	12 (8.4)	7 (4.9)	2 (1.4)	2 (1.4)
Insomnia	24 (14.6)	0 (0)	6 (3.7)	0 (0)	22 (15.4)	0 (0)	3 (2.1)	0 (0)
Cough	22 (13.4)	0 (0)	2 (1.2)	0 (0)	23 (16.1)	1 (0.7)	6 (4.2)	0 (0)
ALT increased	25 (15.2)	6 (3.7)	14 (8.5)	2 (1.2)	18 (12.6)	7 (4.9)	8 (5.6)	1 (0.7)
Rash	14 (8.5)	0 (0)	4 (2.4)	0 (0)	27 (18.9)	0 (0)	16 (11.2)	0 (0)
Epistaxis	24 (14.6)	2 (1.2)	6 (3.7)	1 (0.6)	13 (9.1)	2 (1.4)	3 (2.1)	0 (0)
Decreased appetite	19 (11.6)	2 (1.2)	11 (6.7)	2 (1.2)	18 (12.6)	3 (2.1)	12 (8.4)	2 (1.4)
Hypotension	12 (7.3)	1 (0.6)	3 (1.8)	0 (0)	24 (16.8)	6 (4.2)	4 (2.8)	1 (0.7)
Chills	18 (11.0)	0 (0)	6 (3.7)	0 (0)	17 (11.9)	0 (0)	10 (7.0)	0 (0)
Blood AP increased	21 (12.8)	3 (1.8)	9 (5.5)	0 (0)	10 (7.0)	0 (0)	5 (3.5)	0 (0)
Pain in extremity	13 (7.9)	0 (0)	0 (0)	0 (0)	16 (11.2)	1 (0.7)	5 (3.5)	1 (0.7)
Back pain	18 (11.0)	5 (3.0)	2 (1.2)	0 (0)	10 (7.0)	1 (0.7)	0 (0)	0 (0)
Dyspnea	10 (6.1)	2 (1.2)	2 (1.2)	0 (0)	18 (12.6)	3 (2.1)	4 (2.8)	0 (0)
Dizziness	12 (7.3)	0 (0)	2 (1.2)	0 (0)	16 (11.2)	0 (0)	4 (2.8)	0 (0)
Veno-occlusive liver disease	23 (14.0)	19 (11.6)	21 (12.8)	17 (10.4)	3 (2.1)‡	3 (2.1)	0 (0)	0 (0)
Mucosal inflammation	6 (3.7)	1 (0.6)	2 (1.2)	1 (0.6)	20 (14.0)	3 (2.1)	16 (11.2)	2 (1.4)
Hypocalcemia	11 (6.7)	3 (1.8)	2 (1.2)	1 (0.6)	15 (10.5)	5 (3.5)	4 (2.8)	1 (0.7)
Tachycardia	6 (3.7)	0 (0)	2 (1.2)	0 (0)	16 (11.2)	1 (0.7)	2 (1.4)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; InO, inotuzumab ozogamicin; SoC, standard of care (intensive chemotherapy).

†Data are n (%) and represent the safety population (data cutoff: January 4 2017). All-cause adverse events with an incidence ≥10% in either of the two treatment arms are shown. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0.

B67. CS Table 42. There appears to be some discrepancies between some of the blinatumomab related AE rates mentioned there and the TOWER referenced publication (Kantarjian 2017 Supplementary Appendix Tables S4, S5, and S6). For example, CS Table 42 mentions that 17.6% had thrombocytopenia of Grade 3 or higher, however Table S4 states this proportion for all grades, and Table S6 never mentions it as a Grade 3. Please clarify all discrepancies between both sources and amend the model if necessary.

Company response: The Grade 3 and higher adverse events for Blinatumomab were sourced from Stein, et al. (63) from table 5. As indicated in the screenshots below, the tables have been compared to the adverse event rates in the model and the rates in the model are consistent. Therefore, no changes needed to be made to the model.

Table 5 Any-grade adverse reactions occurring in ≥ 10% or grade ≥ 3 occurring in ≥ 5% of the blinatumomab-treated adults in first cycle of therapy (TOWER)

Adverse reaction	Blinatumomab ($N=267$)		Standard-of-care chemotherapy ($N=109$)	
	Any grade, *n* (%)	Grade ≥ 3, *n* (%)	Any grade, *n* (%)	Grade ≥ 3, *n* (%)
Blood and lymphatic system disorders				
Neutropenia[a]	84 (31)	76 (28)	67 (61)	61 (56)
Anemia[b]	68 (25)	52 (19)	45 (41)	37 (34)
Thrombocytopenia[c]	57 (21)	47 (18)	42 (39)	40 (37)
Leukopenia[d]	21 (8)	18 (7)	9 (8)	9 (8)
Cardiac disorders				
Arrhythmia[e]	37 (14)	5 (2)	18 (17)	0 (0)
General disorders and administration-site conditions				
Pyrexia	147 (55)	15 (6)	43 (39)	4 (4)
Edema[f]	48 (18)	3 (1)	20 (18)	1 (1)
Immune system disorders				
Cytokine release syndrome[g]	37 (14)	8 (3)	0 (0)	0 (0)
Infections				
Infections—pathogen unspecified	74 (28)	40 (15)	50 (46)	35 (32)
Bacterial infectious disorders	38 (14)	19 (7)	35 (32)	21 (19)
Viral infectious disorders	30 (11)	4 (1)	14 (13)	0 (0)
Fungal infectious disorders	27 (10)	13 (5)	15 (14)	9 (8)
Injury, poisoning, and procedural complications				
Infusion-related reaction[h]	79 (30)	9 (3)	9 (8)	1 (1)
Investigations				
Hypertransaminasemia[i]	40 (15)	22 (8)	13 (12)	7 (6)
Nervous system disorders				
Headache	61 (23)	1 (< 1)	30 (28)	3 (3)
Skin and subcutaneous tissue disorders				
Rash[j]	31 (12)	2 (1)	21 (19)	0 (0)

B68. CS Table 42. There appears to be some discrepancies between some of the ponatinib-related AE rates mentioned there and the PACE referenced publication (Cortes 2018 Table 2). For example, CS Table 42 mentions that 6.3% had rash of Grade 3 or higher, however Table 2 from PACE states it is 3% of patients who had rash Grade 3 or higher. Please clarify all discrepancies between both sources and amend the model if necessary.

Company response: This was indeed an oversight. The model has been corrected to capture rash for 1/32 patients (3%).

B69. Please explain why the QALY loss due to KTE-X19 related AEs was 0.012 whereas this was 0.0713 for mantle cell lymphoma [ID1313]. In addition, provide a scenario analysis where AEs due to conditioning therapy are accounted for in terms of cost and QALY impact.

Company response: QALY loss due to KTE-X19 related AEs was 0.0713 in the mantle cell lymphoma [ID1313] submission compared to 0.012 in the model.

One of the reasons for this change is the average duration and the average utility decrement for adverse events is higher in the mantle cell lymphoma [ID1313] submission than the ZUMA-3 model. In the mantle cell lymphoma submission, the averages are 25.6 days and 0.164 respectively, while the averages for the ZUMA-3 model are 8.8 days and 0.144 respectively for all adverse events (see Table 41 and Table 42 below).

One reason why the mantle cell lymphoma submission durations were higher is that if data weren't available, it was assumed the durations were equal to the average of the other durations (26 days), whereas all durations in the ZUMA-3 model were derived from the patient-level data. For example, Hypokalaemia and Hypocalcaemia have been assigned 26 days in the MCL submission, while ZUMA-3 data outputted 1 day for these events.

Furthermore, the total number of AEs in the mantle cell lymphoma submission is higher than those applied in the ZUMA-3 model (35 compared to 20). The ZUMA-3 model excluded the adverse events which fewer than 5% of patients experienced, whereas the mantle cell lymphoma submission has included all available adverse events.

When the adverse event decrements durations and percentages in the ZUMA-3 model were aligned with the submission, the QALY decrement for the AE's increased to -0.063 (when AEs in the ZUMA-3 not in the submission had the rate for that AE set to 0) and -0.071 (when AEs in the ZUMA-3 not in the submission had the rate for that AE set to be equal to the rate in the ZUMA-3 model).

A small correction was also made in the model as the order of adverse events in the "Adverse event cost" tab did not exactly match the order on the "Parameters" sheet. This had a slight impact in the "Sumproduct" formula for the one-off AE disutility for KTE-X19, but this had no significant impact on results.

The model has also been modified to include the option of a one-off disutility of -0.039 for the adverse events of conditioning therapy. The value was derived from the adverse event rates observed in the mantle cell lymphoma [ID1313] submission. This utility decrement is included in the updated model base-case.

Table 42: Mantle cell lymphoma adverse events table

AE	Decrement	Duration	Total % with AE
Acute kidney injury	-0.15	26	4%
Alanine aminotransferase increased	-0.15	26	15%
Anaemia	-0.15	14	74%
Aphasia	-0.15	12	4%
Aspartate aminotransferase increased	-0.15	26	16%
Asthenia	-0.15	26	3%
Confusional state	-0.15	12	12%
CRS	-0.78	11	15%
Diarrhoea	-0.15	26	6%
Dizziness	-0.15	26	3%
Dyspnoea	-0.15	16	1%

Encephalopathy	-0.15	12	24%
Fatigue	-0.15	26	3%
Headache	-0.15	26	1%
Hypertension	-0.15	5	18%
Hypocalcaemia	-0.15	26	6%
Hypogammaglobulinaemia	0	26	1%
Hypokalaemia	-0.15	26	4%
Hyponatraemia	-0.15	26	10%
Hypophosphataemia	-0.15	16	32%
Hypotension	-0.15	26	29%
Hypoxia	-0.15	26	22%
Leukopenia	-0.15	21	12%
Lymphocyte count decreased	-0.15	64	12%
Muscular weakness	-0.15	26	3%
Nausea	-0.15	26	1%
Neutropenia	-0.15	47	50%
Neutrophil count decreased	-0.15	17	75%
Platelet count decreased	-0.15	50	47%
Pleural effusion	-0.15	26	1%
Pyrexia	-0.15	2	16%
Somnolence	-0.15	26	3%
Thrombocytopenia	-0.15	63	16%
Upper respiratory tract infection	-0.15	26	1%
White blood cell count decreased	-0.15	40	72%

Total QALY decrement for AEs	-0.07

Table 43: ZUMA-3 adverse events table

AE	Decrement	Duration	Total % with AE
Abdominal pain	-0.05	7	
Acute kidney injury	-0.11	15	
Alanine aminotransferase increased	0.00	20	15.40%
Anaemia	-0.15	15	44.90%
Bacteraemia	-0.20	15	
Bacterial infectious disorders	-0.22	15	
Constipation	-0.05	7	
CRS	[redacted]	4	25.60%
Decrease in appetite	0.00	0	
Device related infection	-0.05	4	0.00%
Diarrhoea	-0.05	7	
Encephalopathy	-0.22	6	12.80%
Febrile neutropenia	-0.09	6	21.80%
Fungal infectious disorders	-0.22	15	
Fungal pneumonia	-0.22	11	

Hyperglycaemia	-0.06	8	9.00%
Hypertension	-0.07	4	7.70%
Hypertransaminasemia	0.00	20	
Hypocalcaemia	-0.20	1	
Hypokalaemia	-0.20	1	6.40%
Hypophosphatemia	-0.07	3	26.90%
Hypotension	-0.07	2	34.60%
Hypoxia	-0.22	2	21.80%
Increase in blood bilirubin	0.00	0	
Infection pathogen unspecified	-0.22	15	
Leukopenia	-0.09	12	
Lipase increase	0.00	20	
Lymphocyte count decreased	-0.07	19	11.50%
Neutropenia	-0.09	13	33.30%
Neutropenic sepsis	-0.20	15	
Neutrophil count decreased	0.00	10	34.60%
Platelet count decreased	-0.05	12	32.10%
Pneumonia	-0.22	11	7.70%
Pulmonary edema	-0.01	11	
Pyrexia	-0.11	1	39.70%
Rash	-0.06	7	
Respiratory failure	-0.22	2	6.40%
Sepsis	-0.20	15	
Septic shock	-0.20	6	
Subdural hematoma	-0.22	6	
Thrombocytopenia	-0.09	20	23.10%
Viral infectious disorders	-0.22	15	
VOD	-0.21	28	
White blood cell count decreased	-0.05	17	23.10%

Total QALY decrement for AEs	-0.01

B70. CS Table 46. Please clarify the references used for durations of AEs. Note means are preferred to medians if available.

Company response: The duration of adverse events used in the model were the mean number of days for each adverse event. They were derived from the ZUMA 3 ADaM files.

The patient level duration was derived by subtracting the day a patient started an adverse event and subtracting the day the patient recovered. The means over each adverse event were then found.

B71. CS page 192. Regarding blinatumomab costs, please clarify the following discrepancies and amend the model if necessary:

a) The bag was assumed to change every 3 days, however in the blinatumomab TA450 (committee papers p230) it was changed every 4 days.

Company response: We based our costing on the assumptions in TA554 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 year) (11), as by this time blinatumomab was routinely commissioned within the NHS and resource use assumptions were stated to include "*advice from clinical experts experienced in the treatment of patients aged up to 25 with r/r B-cell ALL in the UK*." Although the assumptions regarding frequency of bag change are not explicitly stated in TA554, they are implicit within Table 50 of the Tisa-cel submission (drug costs for the adult dose) in that 7 vials per week are assumed for the infusion. As the vial size is 38.5µg/day and the maximum daily dose is 28µg day, 3 vials could be used to make 4 days' worth of infusions, yet this was not the assumption presented in Tisa-cel Table 50 and it does not appear that the assumption of one vial per day has been challenged anywhere in that appraisal. Note that the maximum stability of blinatumomab, once reconstituted, is 4 days at room temperature (55).

Conversely, in the blinatumomab submission it is stated "It was assumed that all subsequent cycles would be received" and there is no reference to UK clinical input "*It was assumed that all subsequent cycles would be received on an outpatient basis with IV bag changes every 4 days in an outpatient infusion centre*." However, we note that on page 161 of the submission it is stated that only 28µg of the vial is usable, which implies no vial splitting: "*The acquisition cost of blinatumomab was based on its list price to the NHS (£2017.00 per 38.5 µg vial [28 µg of useable contents*])."

b) The IV cost of changing the pump (CS Table 57) was assumed to be that of NHS currency code SB13Z (Deliver more complex parenteral chemotherapy at first attendance), however in the blinatumomab STA450 (committee papers p231) the code used was SB15Z (Deliver subsequent elements of a chemotherapy cycle).

Company response: We agree that this currency should be subsequent elements and have updated the model accordingly**.**

c) The pump cost per day (Excel model 'Drug and drug admin costs' cell C77) uses £3.89, however in the blinatumomab STA450 (committee papers p231) the cost is £3.84.

Company response: £3.89 is the cost used in TA554 (Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 year), stated to be the cost used in TA450 inflated from 2014–2015 to 2016–2017. The two figures therefore relate to the same unit cost.

B72. CS Table 59. Regarding filgrastrim costs (Excel model 'Drug and drug admin costs' row 117), please clarify whether the day cost is that of one syringe or a pack of five syringes. Amend the model if necessary.

Company response: Thank you to the ERG for pointing out this error. The unit cost of £250.75 refers to a pack of five syringes. We have now amended this in the model.

B73. CS page 201. Regarding subsequent treatment costs, please clarify the following discrepancies and amend the model if necessary:

a) For inotuzumab administration costs (Excel model 'Subsequent Tx' cell H62), the administration costs for cycle 1 were used for the subsequent two cycles.

Company response: Thank you to the ERG for pointing out this error. We have now amended the formulae such that the administration costs for subsequent cycles of inotozumab are applied to these respective cycles.

b) For blinatumomab costs (Excel model 'Subsequent Tx' cell F40), it appears administration and pump costs are double counted.

Company response: Thank you to the ERG for pointing out this error. We have now amended the formulae to remove the double counting of administration and pump costs.

Section C: Textual clarification

C1. On p151 it is stated that the SCA-3 cohort is blinatumomab-naive. Should this read blinatumomab and inotuzumab naive?

Company response: That is correct, apologies for the discrepancy, the SCA-3 cohort is comprised of blinatumomab and inotuzumab naïve patients.

C2. On page 16 of the document A, in Table 4, should it be “survival rate” and not “survival free rate”?

Company response: Thanks for pointing this out, the text should read “survival rate”.

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B.1.1 Base-case results

Incremental cost-effectiveness results are presented for each comparison below. Clinical outcomes and disaggregated results from the model are presented in Appendix J.

B.1.1.1 Overall population

FLAG-IDA is the least costly treatment and is thus the baseline comparator in the incremental analysis. It can be seen in Table 1 that although KTE-X19 is associated with higher costs it is also associated with substantial life-year and QALY gains.

In the comparison versus inotuzumab (using a naïve comparison), it can be seen in Table 1 that although KTE-X19 is associated with higher costs it is also associated with substantial life-year and QALY gains, with an incremental gain of 4.053 LYs and [redacted] QALYs. The ICER of £17,203 per QALY lies considerably below the willingness to pay (WTP) threshold of £50,000/QALY for end-of-life (EoL) therapies.

In the comparison versus FLAG-IDA (using a naïve comparison) it can be seen in Table 1 that although KTE-X19 is associated with higher costs it is also associated with substantial life-year and QALY gains, with an incremental gain of 6.211 LYs and [redacted] QALYs. As FLAG-IDA is largely comprised of generic drugs, the cost increase is substantial when compared with the comparisons versus novel agents, but as expected the QALY gains are substantially greater with the novel agents. The ICER of £34,378 per QALY lies below the WTP threshold of £50,000/QALY for EoL therapies. These results should, however, be considered alongside clinician feedback that few patients are offered this option given both its poor effectiveness and poor toxicity profile. The latter is of particular importance in the expected positioning of KTE-X19, as many patients will have already been through a burdensome SCT and/or relapsed following multiple lines of therapy.

Table 1: Base-case results (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	[redacted]	2.200	[redacted]	-	-	-	-	-
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	2.157	[redacted]	£70,783	£70,783
KTE-X19	[redacted]	8.411	[redacted]	[redacted]	4.053	[redacted]	£34,378	£17,203
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Figure 1: Cost-efficiency frontier, overall population

B.1.1.2 Ph- population

The base-case cost-effectiveness results for the Ph- population are presented in Table 2. FLAG-IDA is again the least costly treatment and is thus the baseline comparator in the incremental analysis.

In the base-case comparison versus blinatumomab, individual blinatumomab-naïve patients in the SCHOLAR-3 SCA-3 cohort, were matched to ZUMA-3 patients, regardless of whether they were blinatumomab naïve or experienced. Despite the inherent bias against KTE-X19 in this comparison, it can be seen in Table 2 that KTE-X19 is more costly (incremental costs of [redacted]) but also more effective against blinatumomab. KTE-X19 is associated with an incremental QALY gain of [redacted] QALYs and 3.635 LYs vs. blinatumomab. The ICER for KTE-X19 vs. blinatumomab is £234,753 per QALY.

The pairwise results in this population for KTE-X19 vs. FLAG-IDA and inotuzumab follow a similar pattern, as KTE-X19 is again both more costly but also more effective against these comparators. Compared to FLAG-IDA, KTE-X19 is associated with an incremental cost of [redacted] in the Ph- population and incremental QALY gain of [redacted] QALYs and 5.725 LYs. The ICER for KTE-X19 vs. FLAG-IDA is £36,380. The incremental costs for KTE-X19 vs. inotuzumab are [redacted], with an incremental gain of [redacted] QALYs and 3.568 LYs. The subsequent ICER is £18,108 per QALY for KTE-X19 vs. inotuzumab.

The cost-effectiveness results for KTE-X19 in this population indicate that KTE-X19 is likely to be considered cost-effective against all comparators given that all of the ICERs lie below the WTP threshold of £50,000/QALY for EoL therapies.

Table 2: Base-case results (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	£87,038	2.200	1.601				-	-
Blinatumomab	£135,326	3.541	2.766	[redacted]	1.341	[redacted]	£41,457	£41,457
Inotuzumab	£204,901	4.357	3.266	[redacted]	0.816	[redacted]	£70,783	£139,048
KTE-X19	£261,673	7.925	6.401	[redacted]	3.568	[redacted]	£36,380	£18,108
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.								

Figure 2: Cost-efficiency frontier, Ph- population

B.1.1.3 Ph+ population

The cost-effectiveness results for KTE-X19 in the Ph+ population are presented in Table 3. FLAG-IDA is again the least costly treatment and is thus the baseline comparator in the incremental analysis.

In the comparison against ponatinib, a naïve comparison was carried out between the ZUMA-3 overall population and patients recruited to the PACE trial. It can be seen in Table 3 that although KTE-X19 is associated with higher costs (incremental costs of [redacted]) it is also associated with substantially higher LYs (incremental gain of 4.987 LYs) and QALYs (incremental gain of [redacted] QALYs). These gains are substantial within the context of Ph+ patients, who have a particularly poor prognosis with few treatment options at this point in the treatment pathway. The ICER of £29,508 lies below the WTP threshold of £50,000/QALY for EoL therapies.

Consistent with the results in the overall population, KTE-X19 is more costly but also more effective against inotuzumab and FLAG-IDA, resulting in ICERs of £16,396 per QALY vs. inotuzumab and £33,972 per QALY vs. FLAG-IDA. The ICERs for inotuzumab and FLAG-IDA in the Ph+ population are however slightly lower than those observed in the overall population (£17,203 and £34,378 per QALY for inotuzumab and FLAG-IDA respectively). No INO-VATE or TOWER subgroup data were used for these analyses hence the total costs and QALYs for inotuzumab and FLAG-IDA remain as per the overall population comparison. Conversely, unadjusted patient data from the overall ZUMA-3 population are used which leads to lower incremental costs but higher incremental life years and QALYs for KTE-19 in the Ph+ comparisons compared with those for the overall population.

Table 3: Base-case results (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
FLAG-IDA	[redacted]	2.200	[redacted]	-	-	-	-	-
Ponatinib	[redacted]	3.374	[redacted]	[redacted]	1.17	[redacted]	£56,813	£56,813
Inotuzumab	[redacted]	4.357	[redacted]	[redacted]	0.983	[redacted]	£70,783	£85,085
KTE-X19	[redacted]	8.361	[redacted]	[redacted]	4.004	[redacted]	£33,972	£16,396

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 3: Cost-efficiency frontier, Ph- population

[redacted]

B.1.2 Sensitivity analyses

B.1.2.1 Deterministic sensitivity analysis

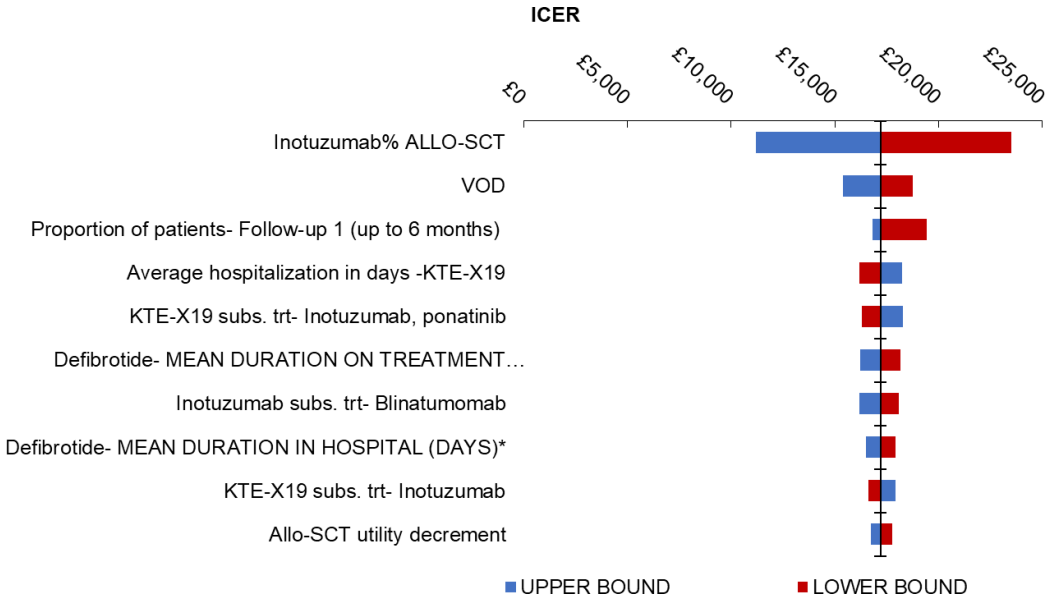
One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. Only parameters which could be varied independently were varied in one-way sensitivity analyses (OWSA). The OWSA thus excluded survival modelling parameters but included utility values derived from the ZUMA-3 EQ-5D regression analyses. The lower and upper bounds for the latter were determined by the upper and lower confidence intervals of the regression coefficients in combinations with the associated variance-covariance matrix. Uncertainty estimates have been provided in Appendix M, the majority of which were underpinned by an assumption of a standard error of the mean of 20%. The OWSA results are presented in tornado diagrams (Figure 4 to Figure 11) where each parameter (y axis) is ranked (highest to lowest) by its impact on the model result. Only the 10 parameters that had the largest impact on the results are included in the tornado diagrams.

The most influential parameter across all the comparisons was the proportion of patients receiving an SCT in the comparator arm. When varied between its upper and lower bounds, this parameter led to differences in the ICERs ranging from £3,345 to £14,697 per QALY. Other influential parameters include the number of inpatient days for KTE-X19 patients, the incidence of VOD (in the KTE-X19 vs. inotuzumab comparisons) and the proportion of blinatumomab patients allocated to inotuzumab and ponatinib as subsequent treatments.

Table 4: OWSA results, overall population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	30%	67%	£23,485	£11,205	£12,280
VOD incidence	7%	16%	£18,751	£15,370	£3,381
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£19,426	£16,816	£2,610
Average hospitalization in days -KTE-X19	13	30	£16,163	£18,243	£2,079
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£16,309	£18,265	£1,956
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£18,173	£16,232	£1,941
Inotuzumab subs. trt- Blinatumomab	8%	18%	£18,067	£16,182	£1,885
Defibrotide- MEAN DURATION IN HOSPITAL (DAYS)*	17	40	£17,904	£16,501	£1,403
KTE-X19 subs. trt- Inotuzumab	5%	11%	£16,606	£17,916	£1,310
Allo-SCT utility decrement	-0.34	-0.78	£17,755	£16,717	£1,051

Figure 4: OWSA results, overall population, inotuzumab

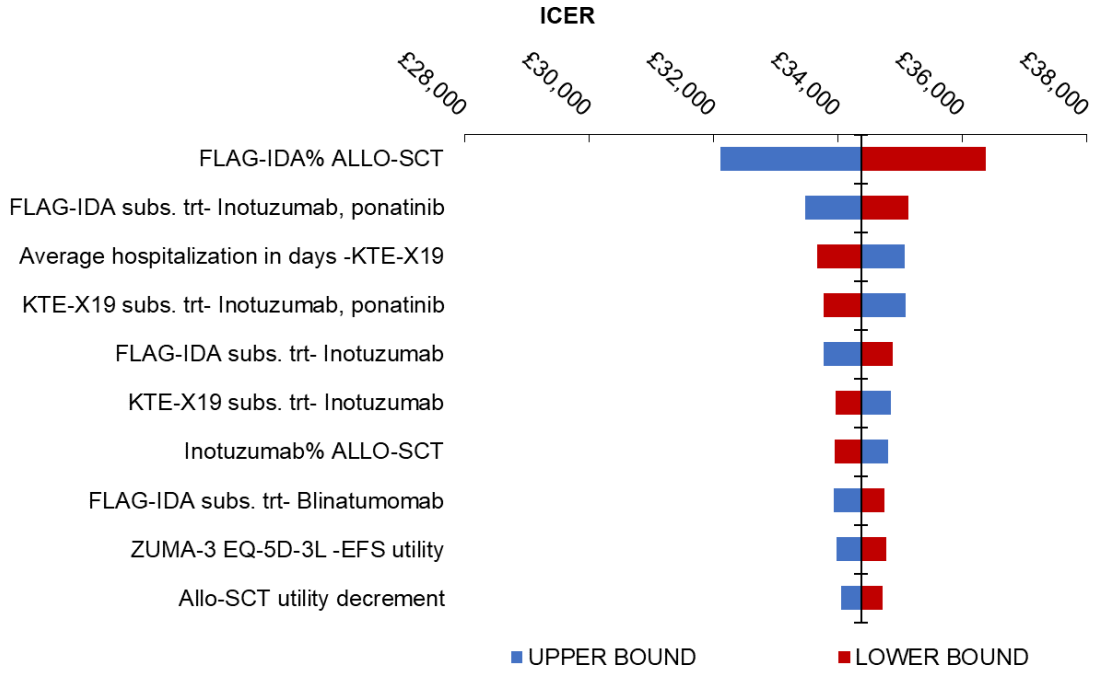


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant

Table 5: OWSA results, overall population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£36,390	£32,114	£4,276
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£35,134	£33,481	£1,653
Average hospitalization in days -KTE-X19	13	30	£33,672	£35,085	£1,413
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£33,771	£35,100	£1,329
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£34,883	£33,775	£1,107
KTE-X19 subs. trt- Inotuzumab	5%	11%	£33,973	£34,863	£890
Inotuzumab% ALLO-SCT	30%	67%	£33,953	£34,810	£858
FLAG-IDA subs. trt- Blinatumomab	7%	16%	£34,752	£33,932	£820
ZUMA-3 EQ-5D-3L - EFS utility	0.74	0.91	£34,785	£33,981	£804
Allo-SCT utility decrement	-0.34	-0.78	£34,728	£34,058	£678

Figure 5: OWSA results, overall population, FLAG-IDA

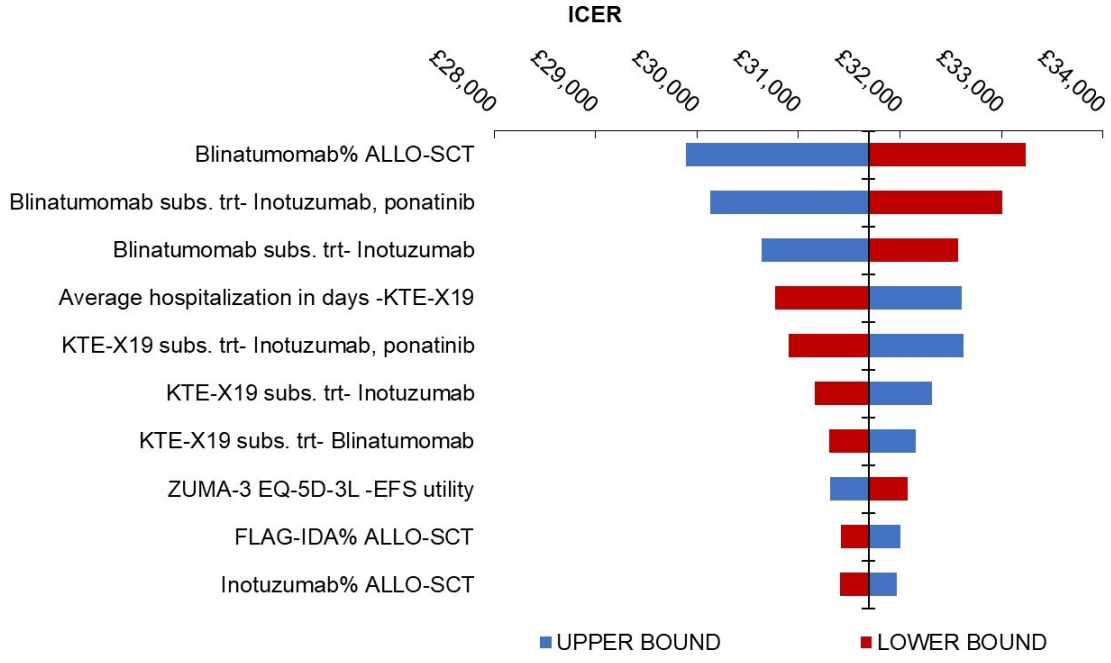


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant

Table 6: OWSA results, Ph- population, blinatumomab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Blinatumomab% ALLO-SCT	8%	19%	£33,236	£29,891	£3,345
Blinatumomab subs. trt- Inotuzumab, ponatinib	8%	19%	£33,012	£30,128	£2,884
Blinatumomab subs. trt- Inotuzumab	6%	14%	£32,572	£30,640	£1,931
Average hospitalization in days -KTE-X19	13	30	£30,772	£32,607	£1,835
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£30,901	£32,627	£1,725
KTE-X19 subs. trt- Inotuzumab	5%	11%	£31,163	£32,319	£1,156
KTE-X19 subs. trt- Blinatumomab	5%	11%	£31,300	£32,155	£856
ZUMA-3 EQ-5D-3L - EFS utility	0.74	0.91	£32,077	£31,312	£765
FLAG-IDA% ALLO-SCT	15%	32%	£31,417	£32,002	£585
Inotuzumab% ALLO-SCT	30%	67%	£31,413	£31,970	£557

Figure 6: OWSA results, Ph- population, blinatumomab

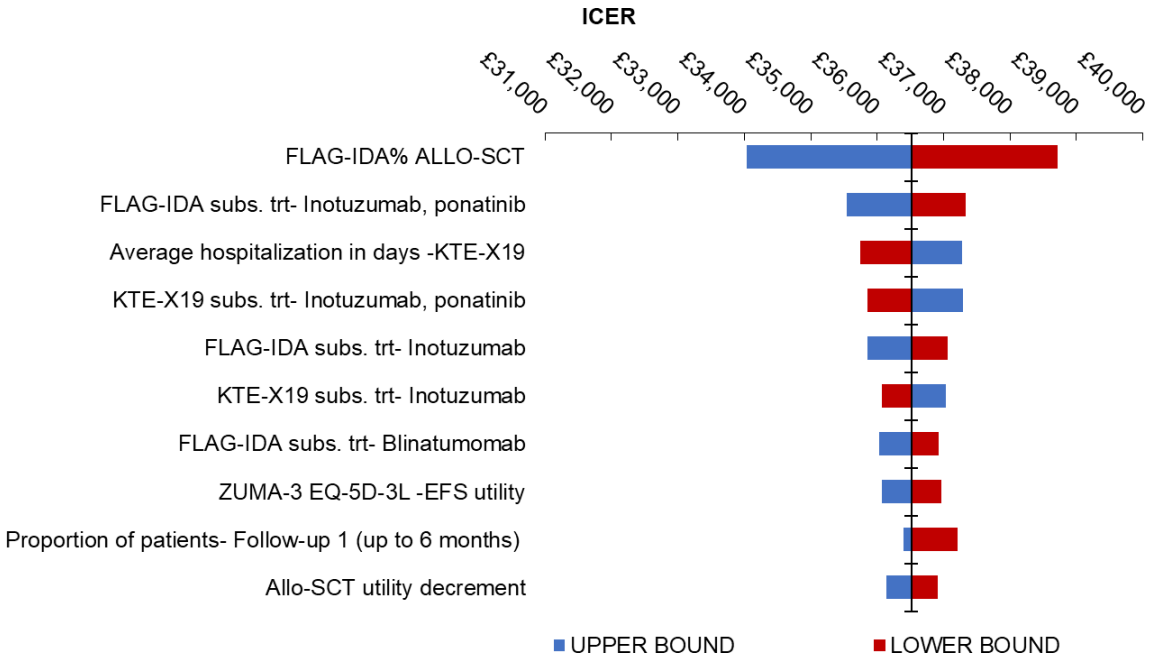


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 7: OWSA results, Ph- population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£38,724	£34,033	£4,691
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£37,336	£35,540	£1,796
Average hospitalization in days -KTE-X19	13	30	£35,748	£37,283	£1,535
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£35,856	£37,299	£1,444
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£37,063	£35,860	£1,203
KTE-X19 subs. trt- Inotuzumab	5%	11%	£36,075	£37,042	£967
FLAG-IDA subs. trt- Blinatumomab	7%	16%	£36,921	£36,030	£891
ZUMA-3 EQ-5D-3L - EFS utility	0.74	0.91	£36,965	£36,077	£888
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£37,211	£36,394	£816
Allo-SCT utility decrement	-0.34	-0.78	£36,919	£36,146	£783

Figure 7: OWSA results, Ph- population, FLAG-IDA

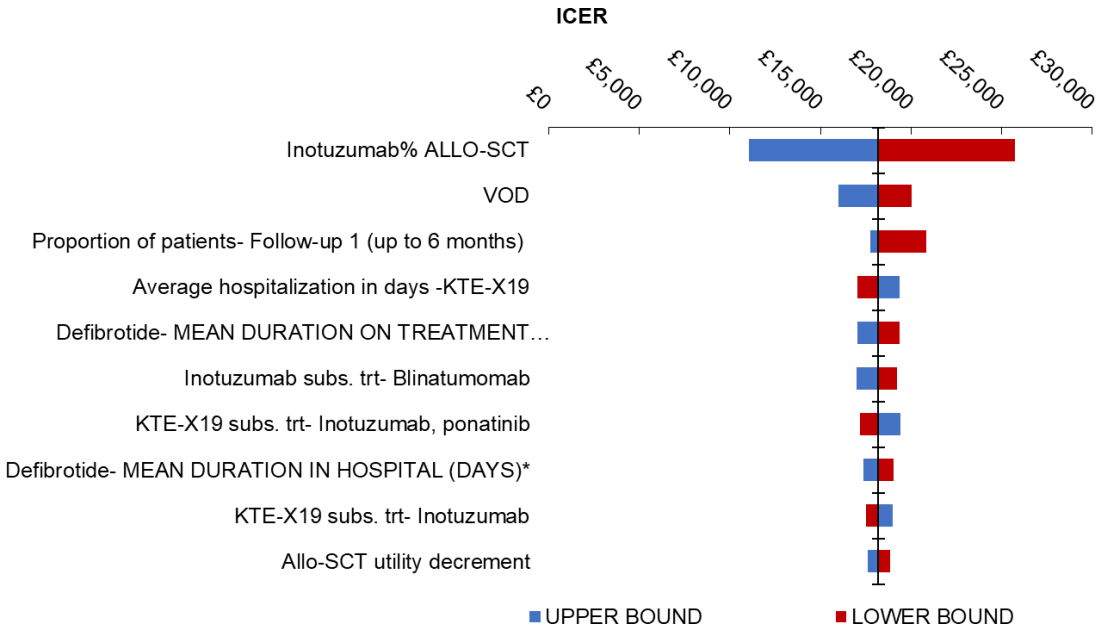


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 8: OWSA results, Ph- population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	30%	67%	£25,751	£11,053	£14,697
VOD incidence	7%	16%	£20,054	£16,009	£4,045
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£20,829	£17,745	£3,085
Average hospitalization in days -KTE-X19	13	30	£17,024	£19,380	£2,356
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£19,364	£17,040	£2,324
Inotuzumab subs. trt- Blinatumomab	8%	18%	£19,236	£16,981	£2,255
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£17,190	£19,405	£2,215
Defibrotide- MEAN DURATION IN HOSPITAL (DAYS)*	17	40	£19,042	£17,362	£1,680
KTE-X19 subs. trt- Inotuzumab	5%	11%	£17,526	£19,010	£1,484
Allo-SCT utility decrement	-0.34	-0.78	£18,867	£17,621	£1,260

Figure 8: OWSA results, Ph- population, inotuzumab

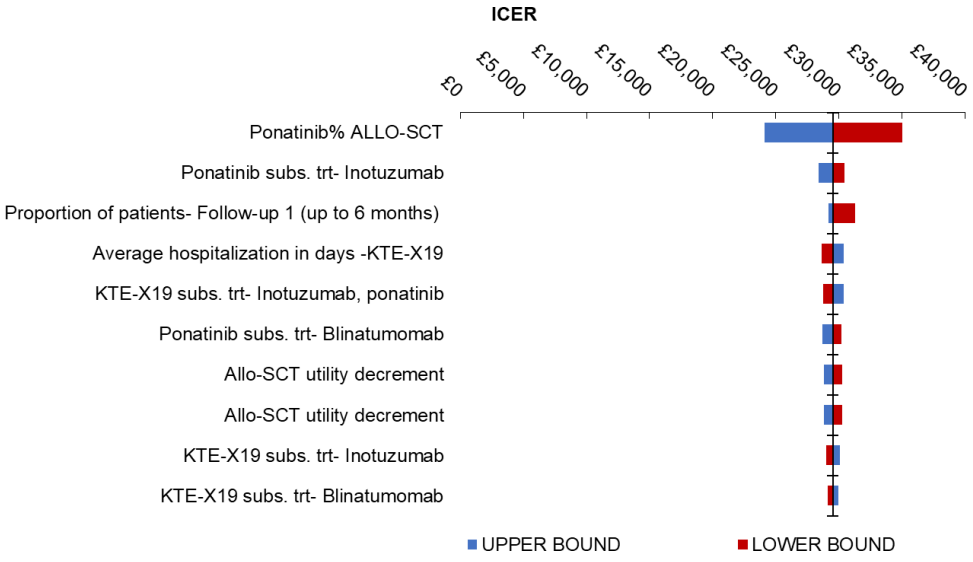


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant; VOD, veno-occlusive disease.

Table 9: OWSA results, Ph+ population, ponatinib

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Ponatinib% ALLO-SCT	29%	65%	£35,012	£24,137	£10,875
Ponatinib subs. trt- Inotuzumab	7%	16%	£30,458	£28,382	£2,075
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£31,273	£29,201	£2,071
Average hospitalization in days -KTE-X19	13	30	£28,657	£30,360	£1,703
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£28,773	£30,382	£1,609
Ponatinib subs. trt- Blinatumomab	8%	18%	£30,211	£28,675	£1,536
Allo-SCT utility decrement	-0.34	-0.78	£30,258	£28,840	£1,435
Allo-SCT utility decrement	-0.34	-0.78	£30,258	£28,840	£1,418
KTE-X19 subs. trt- Inotuzumab	5%	11%	£29,017	£30,095	£1,078
KTE-X19 subs. trt- Blinatumomab	5%	11%	£29,145	£29,943	£798

Figure 9: OWSA results, Ph+ population, ponatinib

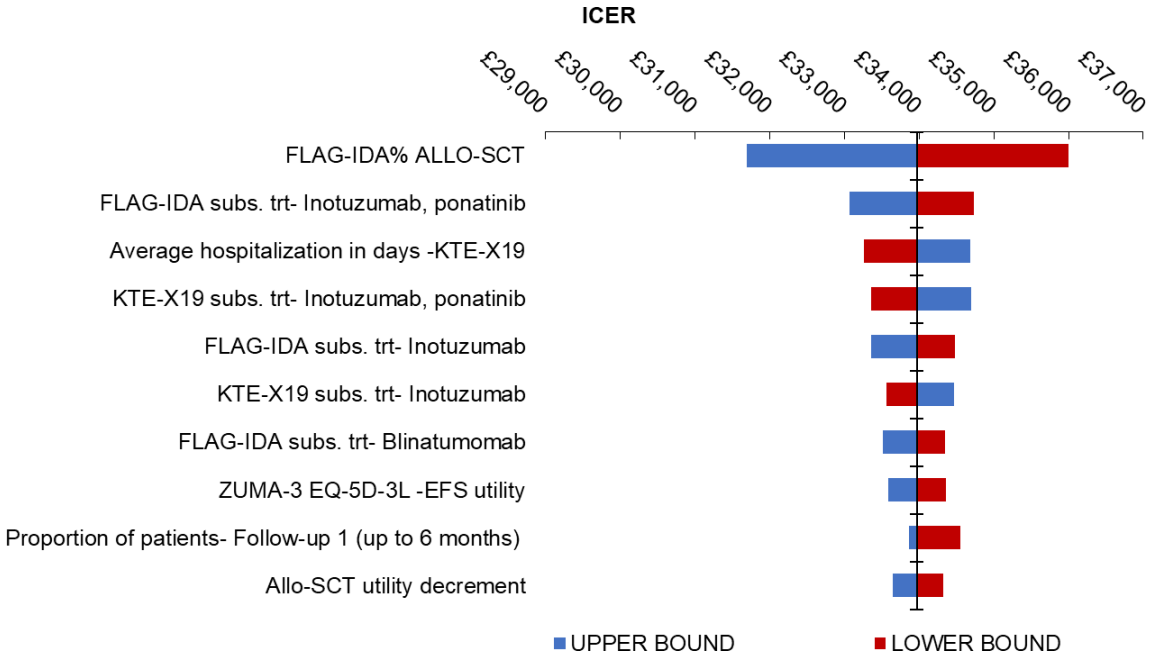


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 10: OWSA results, Ph+ population, FLAG-IDA

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	15%	32%	£35,996	£31,694	£4,302
FLAG-IDA subs. trt- Inotuzumab, ponatinib	7%	15%	£34,734	£33,067	£1,667
Average hospitalization in days -KTE-X19	13	30	£33,260	£34,684	£1,424
KTE-X19 subs. trt- Inotuzumab, ponatinib	7%	15%	£33,357	£34,703	£1,346
FLAG-IDA subs. trt- Inotuzumab	5%	11%	£34,481	£33,364	£1,116
KTE-X19 subs. trt- Inotuzumab	5%	11%	£33,562	£34,463	£902
FLAG-IDA subs. trt- Blinatumomab	5%	11%	£34,349	£33,522	£826
ZUMA-3 EQ-5D-3L - EFS utility	0.74	0.91	£34,365	£33,588	£778
Proportion of patients- Follow-up 1 (up to 6 months)	33%	100%	£34,554	£33,871	£683
Allo-SCT utility decrement	-0.34	-0.78	£34,320	£33,653	£676

Figure 10: OWSA results, Ph+ population, FLAG-IDA

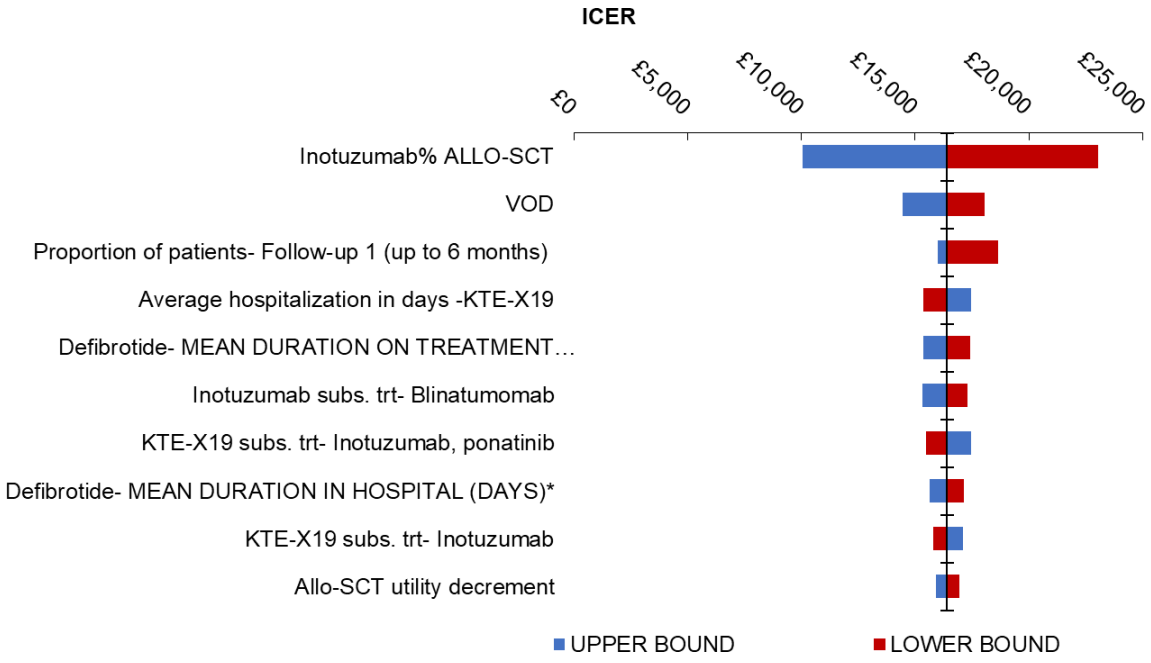


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

Table 11: OWSA results, Ph+ population, inotuzumab

Parameter	Lower bound	Upper bound	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	30%	67%	£23,059	£10,041	£13,018
VOD incidence	7%	16%	£18,051	£14,437	£3,613
Proportion of patients-Follow-up 1 (up to 6 months)	33%	100%	£18,650	£16,004	£2,646
Average hospitalization in days -KTE-X19	13	30	£15,344	£17,449	£2,104
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	14	32	£17,434	£15,358	£2,076
Inotuzumab subs. trt-Blinatumomab	8%	18%	£17,320	£15,305	£2,014
KTE-X19 subs. trt-Inotuzumab, ponatinib	7%	15%	£15,488	£17,476	£1,989
Defibrotide- MEAN DURATION IN HOSPITAL (DAYS)*	17	40	£17,147	£15,646	£1,501
KTE-X19 subs. trt-Inotuzumab	5%	11%	£15,790	£17,122	£1,332
Allo-SCT utility decrement	-0.34	-0.78	£16,929	£15,927	£1,014

Figure 11: OWSA results, Ph+ population, inotuzumab



Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant

B.1.2.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values and a distribution was assigned to these parameters. These uncertainty estimates are provided in section **Error! Reference source not found.**, the majority of which were underpinned by an assumption of a standard error of the mean of 20% for the upper and lower bound values. Exceptions to this include parameters obtained from survival and the ZUMA-3 EQ-5D regressions, which were covaried in the PSA as constrained by their respective variance-covariance matrices. 1,000 simulations were run for the probabilistic sensitivity analysis (PSA), by which time the ICERs had converged to a stable mean, represented by the probabilistic ICERs.

The probabilistic cost-effectiveness results are reported in Table 13 to Table 15. The probabilistic results are closely aligned with the deterministic results, as the ICERs across all subgroups and comparators rise only slightly. The highest probabilistic ICER obtained for KTE-X19 is in the analysis vs. FLAG-IDA for the Ph- population. At £37,955 per QALY, this value lies closely to the corresponding base-case ICER

which is £36,515 per QALY. None of the probabilistic ICERs thus exceed the £50,000/QALY threshold for EoL therapies.

Output from the PSA iterations is presented as scatter points on the cost-effectiveness planes in Figure 12 to Figure 14. All points lie in the northeast quadrants of the plane, indicating that KTE-X19 is more costly and more effective compared to the comparator technologies. Cost-effectiveness acceptability curves (CEACs) are presented in Figure 15 to Figure 17. The CEACs show that the probability of KTE-X19 increases in line with the WTP threshold. Conversely, the CEAC for FLAG-IDA decreases at increased WTP thresholds, across all 3 sub-groups, whilst remaining considerably low for blinatumomab and inotuzumab. The probability that KTE-X19 was the most cost-effective treatment at a WTP threshold of £50,000/QALY was above 90% in all sub-groups other than the Ph- population (Table 12). However, the probability of cost-effectiveness for this sub-group remained high at 83%.

Table 12: Probability that KTE-X19 is the most cost-effective treatment

		Probability that KTE-X19 is the most cost-effective comparator at a WTP of:	
Population	**Comparators**	**£40,000/QALY**	**£50,000/QALY**
Overall	Inotuzumab FLAG-IDA	74%	94%
Philadelphia -	Blinatumomab FLAG-IDA Inotuzumab	54%	83%
Philadelphia +	Ponatinib FLAG-IDA Inotuzumab	66%	90%

Key: QALY, quality-adjusted life years; WTP, willingness to pay

Table 13: Probabilistic results - overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.407	[redacted]	-	-	-	-
Inotuzumab	[redacted]	4.401	[redacted]	[redacted]	4.006	[redacted]	£18,942
FLAG-IDA	[redacted]	2.235	[redacted]	[redacted]	6.172	[redacted]	£35,635

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 14: Probabilistic results - Ph- population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	7.895	[redacted]	-	-	-	-
Blinatumomab	[redacted]	3.137	[redacted]	[redacted]	4.759	[redacted]	£33,753
FLAG-IDA	[redacted]	2.238	[redacted]	[redacted]	5.657	[redacted]	£37,955
Inotuzumab	[redacted]	4.348	[redacted]	[redacted]	3.548	[redacted]	£20,060

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 15: Probabilistic results - Ph+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	8.310	[redacted]	-	-	-	-
Ponatinib	[redacted]	3.465	[redacted]	[redacted]	4.845	[redacted]	£31,465
FLAG-IDA	[redacted]	2.250	[redacted]	[redacted]	6.060	[redacted]	£35,528
Inotuzumab	[redacted]	4.375	[redacted]	[redacted]	3.935	[redacted]	£18,036

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 12:Scatter plot, overall population

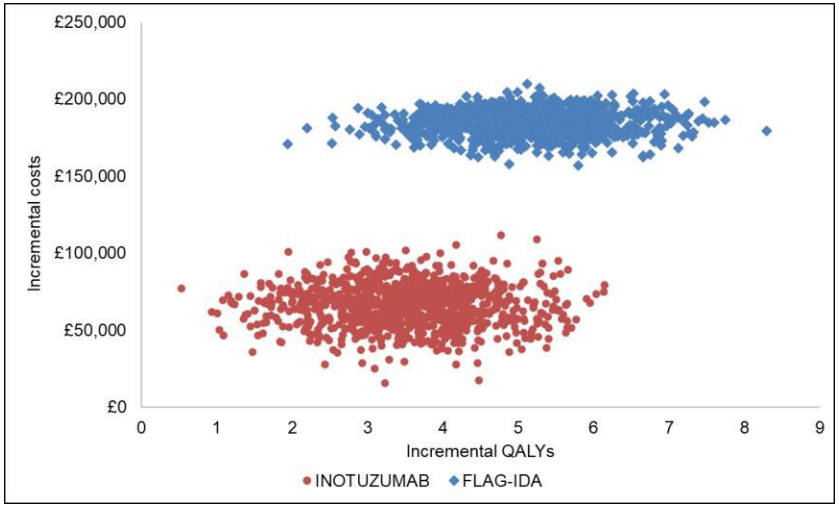


Figure 13: Scatter plot, Ph- population

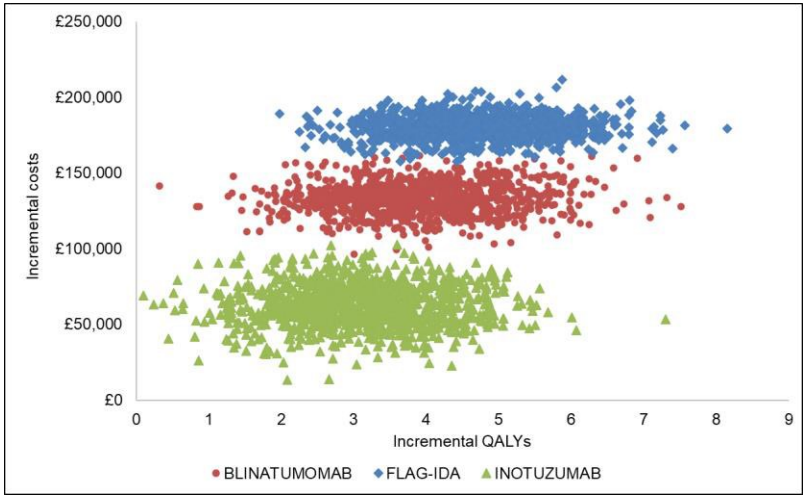


Figure 14: Scatter plot, Ph+ population

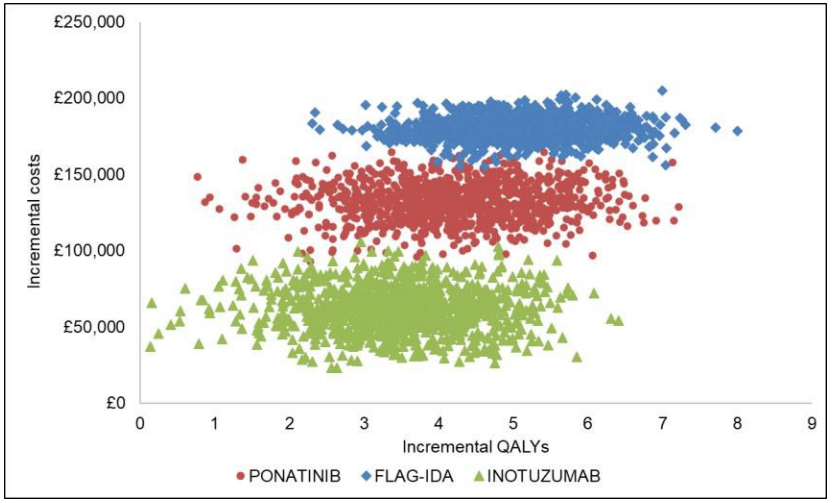


Figure 15: CEAC, overall population

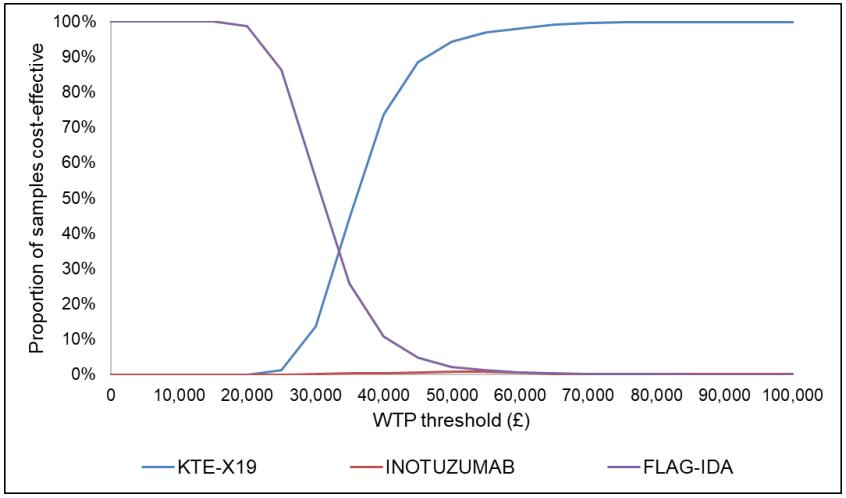


Figure 16: CEAC, Ph- population

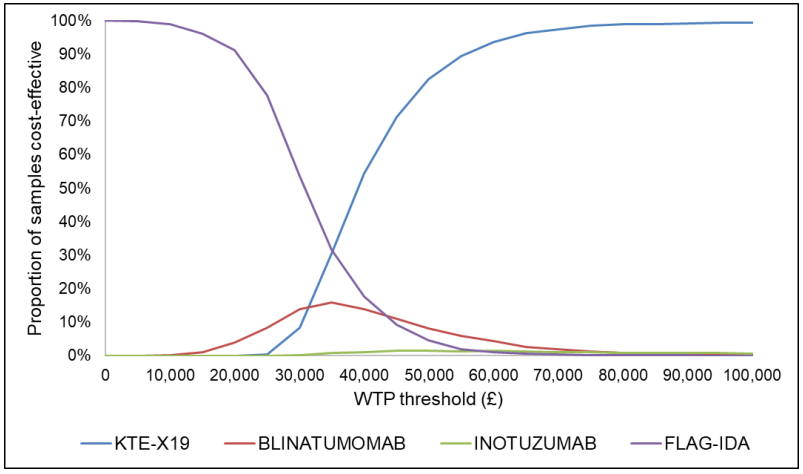
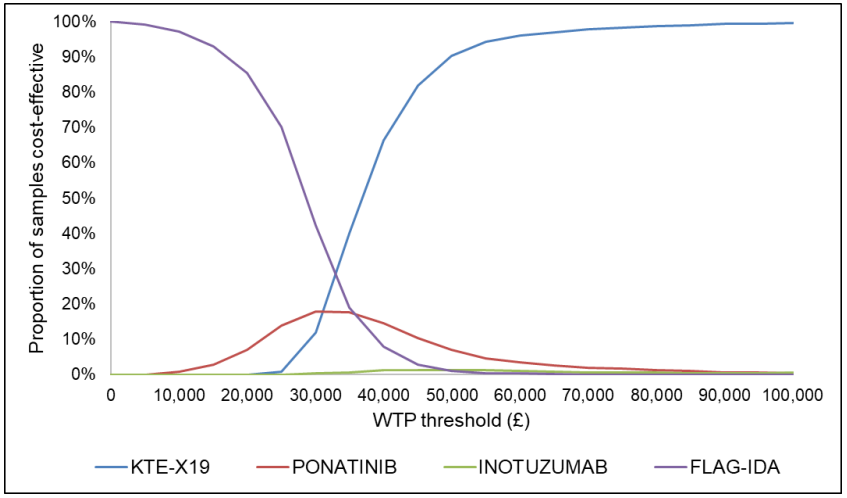


Figure 17: CEAC, Ph+ population



B.1.2.3 Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters underpinning the model base-case was examined through several scenario analyses. The scenarios analyses results are presented in Table 16 to Table 18. The scenarios were explored for each of the 3 populations for which the cost-effectiveness of KTE-X19 has been examined (overall population, Ph- and Ph+). In general, it is notable that very few scenarios led to ICERs above the EoL WTP threshold of £50,000/QALY.

For the analysis considering the overall population, the scenarios that had the largest impact upon the ICER were the selection of a mixture-cure model (MCM) to model EFS and OS for all treatments, using the MAIC to model relative clinical efficacy and when the time horizon was reduced to 20 years. When the best-fitting MCM was selected as opposed to the spline and SPM models as in the base-case, the incremental QALYs for KTE-X19 reduced considerably (from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA). This reduction in incremental QALYs increased the ICERs for KTE-X19 vs. inotuzumab and FLAG-IDA to £50,296 and £60,732 compared to £17,203 and £34,378 in the base-case. These results are unsurprising as they decrease the cure advantage of KTE-X19 versus the comparators. It should be borne in mind that the MCMs were not selected for our base case because the cure fractions varied widely, which strongly suggested lack of enough data to inform this type of survival model (see section B.3.3.3). A similar pattern was observed with the MAIC was selected, as the incremental QALYs reduced from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA. This led to increased ICERs of £27,097 and £52,380 per QALY for KTE-X19 vs. inotuzumab and FLAG-IDA respectively. Again, the MAICs were not deemed to provide the most suitable basis for comparison, as discussed in section B.2.9. Reducing the time horizon from a life-time horizon to 20 years had a similar impact as the incremental costs did not change by much whilst the incremental QALYs reduced from [redacted] to [redacted] vs. inotuzumab and from [redacted] to [redacted] vs. FLAG-IDA. This led to increased ICERs of £23,316 and £47,912 for KTE-X19 vs. inotuzumab and FLAG-IDA respectively, compared to £17,203 and £34,378 in the base-case.

In the analysis of the Ph- subgroup, the scenarios that had the largest impact upon the ICER were the reduction of the time horizon to 20 years and the selection of a log normal SPM function to model EFS and a Weibull function to model OS in the blinatumomab arm. Once again, reducing the time horizon to 20 years reduced the QALY gains associated with KTE-X19, leading to higher ICERs ranging from £24,595 per QALY to £50,866 against the comparators. Opting for alternative parametric functions to model EFS and OS for blinatumomab as opposed to a generalised gamma SPM for both EFS and OS, as in the base-case, reduced the QALY gains considerably in the blinatumomab arm, from [redacted] to [redacted], thus increasing the ICER from £29,317 to £54,945 per QALY.

The scenario analysis results for the Ph+ subgroup were in line with those obtained for the overall population, as the scenarios that had the largest impact upon the ICER were the selection of a MCM for EFS and OS for all treatments and a 20 year when the time horizon for the analysis. In the scenario where the alternative survival functions were adopted for EFS and OS, the ICERs ranged from £48,836 to £67,122 per QALY for KTE-X19 vs. the comparators. This was a considerable increase from the base-case range of £16,396 to £33,972 per QALY. When the time horizon was reduced to 20 years, the ICERs ranged from £22,202 to £47,338 per QALY.

Table 16: Results of scenario analysis – overall population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Inotuzumab**	[redacted]	[redacted]	**£17,203**
			FLAG-IDA	[redacted]	[redacted]	**£34,378**
Time horizon	57 years	20 years	Inotuzumab	[redacted]	[redacted]	£23,316
			FLAG-IDA	[redacted]	[redacted]	£47,912
Discount rate for costs and outcomes (QALYs)	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Inotuzumab	[redacted]	[redacted]	£13,213
			FLAG-IDA	[redacted]	[redacted]	£25,753
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Inotuzumab	[redacted]	[redacted]	£18,813
			FLAG-IDA	[redacted]	[redacted]	£36,068
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Inotuzumab	[redacted]	[redacted]	£15,775
			FLAG-IDA	[redacted]	[redacted]	£31,577
Modelling of clinical efficacy between treatment arms	Naïve comparison	MAIC	Inotuzumab	[redacted]	[redacted]	£27,097
			FLAG-IDA	[redacted]	[redacted]	£52,380
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Inotuzumab	[redacted]	[redacted]	£19,069
			FLAG-IDA	[redacted]	[redacted]	£38,245
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Inotuzumab	[redacted]	[redacted]	£17,672
			FLAG-IDA	[redacted]	[redacted]	£35,357

	General population utility	TA541	Inotuzumab	[redacted]	[redacted]	£19,503
			FLAG-IDA	[redacted]	[redacted]	£39,198
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Inotuzumab	[redacted]	[redacted]	£14,900
			FLAG-IDA	[redacted]	[redacted]	£33,456
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Inotuzumab	[redacted]	[redacted]	£19,387
			FLAG-IDA	[redacted]	[redacted]	£35,257
PD utility source	ZUMA-3	Blinatumomab SMC submission	Inotuzumab	[redacted]	[redacted]	£17,873
			FLAG-IDA	[redacted]	[redacted]	£34,654
		Tisagenlecleucel SMC submission	Inotuzumab	[redacted]	[redacted]	£17,205
			FLAG-IDA	[redacted]	[redacted]	£34,379
KTE-X19 AE disutility source	Literature	ZUMA-3	Inotuzumab	[redacted]	[redacted]	£17,514
			FLAG-IDA	[redacted]	[redacted]	£34,798
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Inotuzumab	[redacted]	[redacted]	£17,194
			FLAG-IDA	[redacted]	[redacted]	£34,366
AE related costs	Included	Excluded	Inotuzumab	[redacted]	[redacted]	£20,536
			FLAG-IDA	[redacted]	[redacted]	£33,788
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Inotuzumab	[redacted]	[redacted]	£19,913
			FLAG-IDA	[redacted]	[redacted]	£37,555

Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Inotuzumab	[redacted]	[redacted]	£50,296
			FLAG-IDA	[redacted]	[redacted]	£60,732
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£17,567
			FLAG-IDA	[redacted]	[redacted]	£35,064
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£16,054
Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£30,776
SCT as subsequent treatment option for KTE-X19 patients	No SCT	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Inotuzumab	[redacted]	[redacted]	£22,575
			FLAG-IDA	[redacted]	[redacted]	£38,339

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model

Table 17: Results of scenario analysis – Ph- population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Blinatumomab**	[redacted]	[redacted]	**£31,690**
			Inotuzumab	[redacted]	[redacted]	**£18,202**
			FLAG-IDA	[redacted]	[redacted]	**£36,515**
Time horizon	57 years	20 years	Blinatumomab	[redacted]	[redacted]	£44,704

			Inotuzumab	[redacted]	[redacted]	£24,595
			FLAG-IDA	[redacted]	[redacted]	£50,866
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Blinatumomab	[redacted]	[redacted]	£23,577
			Inotuzumab	[redacted]	[redacted]	£14,005
			FLAG-IDA	[redacted]	[redacted]	£27,355
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Blinatumomab	[redacted]	[redacted]	£35,483
			Inotuzumab	[redacted]	[redacted]	£21,603
			FLAG-IDA	[redacted]	[redacted]	£40,228
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Blinatumomab	[redacted]	[redacted]	£29,856
			Inotuzumab	[redacted]	[redacted]	£17,416
			FLAG-IDA	[redacted]	[redacted]	£34,743
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Blinatumomab	[redacted]	[redacted]	£35,386
			Inotuzumab	[redacted]	[redacted]	£20,162
			FLAG-IDA	[redacted]	[redacted]	£40,615
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Blinatumomab	[redacted]	[redacted]	£32,622
			Inotuzumab	[redacted]	[redacted]	£18,694
			FLAG-IDA	[redacted]	[redacted]	£37,552
		TA541	Blinatumomab	[redacted]	[redacted]	£36,299
			Inotuzumab	[redacted]	[redacted]	£20,611

			FLAG-IDA	[redacted]	[redacted]	£41,622
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Blinatumomab	[redacted]	[redacted]	£30,835
			Inotuzumab	[redacted]	[redacted]	£16,526
			FLAG-IDA	[redacted]	[redacted]	£35,934
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Blinatumomab	[redacted]	[redacted]	£32,517
			Inotuzumab	[redacted]	[redacted]	£19,828
			FLAG-IDA	[redacted]	[redacted]	£37,075
PD utility source	ZUMA-3	Blinatumomab SMC submission	Blinatumomab	[redacted]	[redacted]	£31,586
			Inotuzumab	[redacted]	[redacted]	£18,909
			FLAG-IDA	[redacted]	[redacted]	£36,712
		Tisagenlecleucel SMC submission	Blinatumomab	[redacted]	[redacted]	£31,689
			Inotuzumab	[redacted]	[redacted]	£18,204
			FLAG-IDA	[redacted]	[redacted]	£36,516
KTE-X19 AE disutility source	Literature	ZUMA-3	Blinatumomab	[redacted]	[redacted]	£32,194
			Inotuzumab	[redacted]	[redacted]	£18,575
			FLAG-IDA	[redacted]	[redacted]	£37,000
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Blinatumomab	[redacted]	[redacted]	£31,675
			Inotuzumab	[redacted]	[redacted]	£18,191
			FLAG-IDA	[redacted]	[redacted]	£36,502

AE related costs	Included	Excluded	Blinatumomab	[redacted]	[redacted]	£30,711
			Inotuzumab	[redacted]	[redacted]	£22,245
			FLAG-IDA	[redacted]	[redacted]	£36,048
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Blinatumomab	[redacted]	[redacted]	£33,560
			Inotuzumab	[redacted]	[redacted]	£21,233
			FLAG-IDA	[redacted]	[redacted]	£39,911
Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Blinatumomab	[redacted]	[redacted]	£63,320
			Inotuzumab	[redacted]	[redacted]	£40,420
			FLAG-IDA	[redacted]	[redacted]	£55,555
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£30,731
			Inotuzumab	[redacted]	[redacted]	£17,517
			FLAG-IDA	[redacted]	[redacted]	£35,583
Parametric function adopted to model EFS and OS for blinatumomab	1-knot spline hazard is used to model EFS, lognormal SPM is used to model OS	Lognormal SPM is used to model EFS, generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£59,877
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£16,762
	Not included		Blinatumomab	[redacted]	[redacted]	£36,793

SCT as subsequent treatment option for KTE-X19 patients		Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Inotuzumab	[redacted]	[redacted]	£24,346
			FLAG-IDA	[redacted]	[redacted]	£40,873

Table 18: Results of scenario analysis – Ph+ population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Ponatinib**	[redacted]	[redacted]	**£29,508**
			Inotuzumab	[redacted]	[redacted]	**£16,396**
			FLAG-IDA	[redacted]	[redacted]	**£33,972**
Time horizon	57 years	20 years	Ponatinib	[redacted]	[redacted]	£40,702
			Inotuzumab	[redacted]	[redacted]	£22,202
			FLAG-IDA	[redacted]	[redacted]	£47,338
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Ponatinib	[redacted]	[redacted]	£22,292
			Inotuzumab	[redacted]	[redacted]	£12,605
			FLAG-IDA	[redacted]	[redacted]	£25,450
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Ponatinib	[redacted]	[redacted]	£30,729
			Inotuzumab	[redacted]	[redacted]	£17,735
			FLAG-IDA	[redacted]	[redacted]	£35,349
			Ponatinib	[redacted]	[redacted]	£27,071

Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Inotuzumab	[redacted]	[redacted]	£14,949
			FLAG-IDA	[redacted]	[redacted]	£31,143
Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Ponatinib	[redacted]	[redacted]	£32,783
			Inotuzumab	[redacted]	[redacted]	£18,170
			FLAG-IDA	[redacted]	[redacted]	£37,788
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Ponatinib	[redacted]	[redacted]	£30,333
			Inotuzumab	[redacted]	[redacted]	£16,843
			FLAG-IDA	[redacted]	[redacted]	£34,938
		TA541	Ponatinib	[redacted]	[redacted]	£33,562
			Inotuzumab	[redacted]	[redacted]	£18,585
			FLAG-IDA	[redacted]	[redacted]	£38,731
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Ponatinib	[redacted]	[redacted]	£28,741
			Inotuzumab	[redacted]	[redacted]	£14,900
			FLAG-IDA	[redacted]	[redacted]	£33,456
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Ponatinib	[redacted]	[redacted]	£30,280
			Inotuzumab	[redacted]	[redacted]	£17,889
			FLAG-IDA	[redacted]	[redacted]	£34,493
PD utility source	ZUMA-3	Blinatumomab SMC submission	Ponatinib	[redacted]	[redacted]	£29,478
			Inotuzumab	[redacted]	[redacted]	£17,080

			FLAG-IDA	[redacted]	[redacted]	£34,296
		Tisagenlecleucel SMC submission	Ponatinib	[redacted]	[redacted]	£29,508
			Inotuzumab	[redacted]	[redacted]	£16,398
			FLAG-IDA	[redacted]	[redacted]	£33,973
KTE-X19 AE disutility source	Literature	ZUMA-3	Ponatinib	[redacted]	[redacted]	£29,943
			Inotuzumab	[redacted]	[redacted]	£16,696
			FLAG-IDA	[redacted]	[redacted]	£34,390
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Ponatinib	[redacted]	[redacted]	£29,496
			Inotuzumab	[redacted]	[redacted]	£16,388
			FLAG-IDA	[redacted]	[redacted]	£33,960
AE related costs	Included	Excluded	Ponatinib	[redacted]	[redacted]	£28,554
			Inotuzumab	[redacted]	[redacted]	£20,011
			FLAG-IDA	[redacted]	[redacted]	£33,541
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Ponatinib	[redacted]	[redacted]	£31,325
			Inotuzumab	[redacted]	[redacted]	£19,096
			FLAG-IDA	[redacted]	[redacted]	£37,229
Survival functions adopted to model EFS and OS of KTE-X19 and comparators	SPM and spline models are used (see Table 41)	MCM are used	Ponatinib	[redacted]	[redacted]	£67,122
			Inotuzumab	[redacted]	[redacted]	£48,836
			FLAG-IDA	[redacted]	[redacted]	£60,269

Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Ponatinib	[redacted]	[redacted]	£30,189
			Inotuzumab	[redacted]	[redacted]	£34,655
			FLAG-IDA	[redacted]	[redacted]	£16,736
Parametric function adopted to model EFS and OS for ponatinib	Lognormal SPM is used to model EFS and OS	Log logistic SPM are used to model EFS and OS	Ponatinib	[redacted]	[redacted]	£28,350
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£15,218
Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£30,387
SCT as subsequent treatment option for KTE-X19 patients	Not included	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Ponatinib	[redacted]	[redacted]	£34,183
			Inotuzumab	[redacted]	[redacted]	£21,811
			FLAG-IDA	[redacted]	[redacted]	£37,958
Inclusion of chemotherapy costs with ponatinib	Included	Excluded	Ponatinib	[redacted]	[redacted]	£30,686

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model

B.1.2.4 Summary of sensitivity analyses results

The sensitivity analyses demonstrated that the KTE-X19 ICERs were in general robust to variations in the majority of parameters. As expected, altering the model time horizon and the proportion of patients cured (via alternative survival analyses methods) had substantial impact on the ICERs. The scenarios that increased the ICERs above £50,000 per QALY (use of MCM for survival and MAIC to model clinical efficacy) are not considered appropriate due to the limitations of these modelling methods (see sections B.2.9.4 and B.3.3.3). ICERs were also sensitive to the utility of the progressed disease state.

The probabilistic results were generally aligned with deterministic results. KTE-X19 had a greater than 83% probability of being cost-effective at a WTP of £50,000 against all comparators, indicating with high certainty that KTE-X19 is a highly cost-effective treatment for R/R ALL patients.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults [ID1494]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Leukaemia Care
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Leukaemia Care** is a national blood cancer charity, founded in 1969. We are dedicated to ensuring that anyone affected by blood cancer receives the right information, advice and support. Approximately 85-90% of our income comes from fundraising activities – such as legacies, community events, marathons etc. Leukaemia Care also receives funding from a wide range of pharmaceutical companies, but in total those funds are less than 15% of our annual income. Leukaemia Care has undertaken a voluntary commitment to adhere to specific policies that regulate our involvement with the pharmaceutical industry set out in our code of practice here: https://media.leukaemiacare.org.uk/wp-content/uploads/Leukaemia-CARE-Code-of-Practice-pdf.pdf.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	Amgen £15,000 support services Incyte £30,000 core funding Novartis £1,887.95 (£292.95 ASH video and £1,595 honorarium) Pfizer £10,000 support services

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information was gathered through Leukaemia Care's patient survey 'Living with Leukaemia (2017), which included responses from 147 ALL patients. Data and quotes were also gathered from a new survey (2021), conducted for the purpose of this submission, on patients' opinions on treatment options in ALL. Additional information was gathered through one-to-one conversations with 2 patients who have received CAR T therapy. One of these patients was 21 when they received CAR T and the other was in their 50's.
Living with the condition	
6. What is it like to live with the condition? What do carers	Acute lymphoblastic leukaemia (ALL) is a rare and rapidly progressing form of leukaemia. As of 2018 there are 791 new cases of acute lymphoblastic leukaemia in the UK each year. The highest incidence rates of ALL are in children aged 0-4, after which the risk of ALL drops gradually, but starts to increase

experience when caring for someone with the condition?	again at age 50. Five-year survival is approximately 90% in children, but only 30% to 40% in adults and less than 15% in elderly patients, as such outcomes in ALL are poor. Symptoms experienced prior to diagnosis for adults include fatigue (69%); feeling weak or breathless (61%), fever or night sweats (36%), bruising or bleeding (31%), pain in bones or joints (28%), unexplained weight loss (26%), sleeping problems (26%) and swollen lymph nodes (22%). One ALL patient we spoke to who was 21 when she was diagnosed also reported severe headaches and neck pain, claiming that "*nothing would make the headaches go away*". Due to the rapidly progressing nature of the condition, 63% of patients had only experienced symptoms for less than a month before visiting their GP. The NCIN/NCRAS 'Routes to Diagnosis' report shows that 64% of ALL patients are diagnosed via emergency presentation (of which 42% were A&E, 27% emergency GP referral, 5% inpatient emergency and 26% outpatient emergency). This compares to a cancer average of 22% and is the highest of any cancer type in the report. The rapidly progressing nature of the condition means that 86% of ALL patients start treatment within a week of diagnosis. Being diagnosed with ALL can also have a huge emotional impact, prompting patients (and their families) to experience feelings of disbelief, denial, anger, fear, blame, guilt, isolation and depression. In our survey 57% of ALL patients reported that they have felt depressed or anxious more often since their diagnosis, and 7% said they feel constantly depressed or anxious. The emotional impact does not affect the patient in isolation. A diagnosis can place huge emotional strain on families and friends, many of whom may be affected. As such, improvements in a patients' treatment and quality of life will also have a wider impact on the lives of their family and friends. Due to the physical and psychological impact, an ALL diagnosis can also negatively affect a patients' financial situation. In our survey, 78% of patients had to stop working or education as a result of their diagnosis. There is a high rate of relapse in ALL patients, with a relapse rate of nearly 50% in adults with ALL. Evidence indicates that having relapsed from initial treatment worsens a patient's quality of life further. Relapsed patients are more likely to feel isolated all of the time, they are also the most likely group to

	experience anxiety (74%). In addition, relapsed patients are less satisfied with their healthcare teams' support for depression and anxiety. Relapsed patients in particular are the most likely to have experienced a negative impact on their finances (70% vs. 69% of those currently on treatment and 51% of those in remission).
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	When we asked whether ALL patients thought existing treatments for this disease were sufficient, 100% of respondents said no or not sure. Reasons for this included that *"CAR T cell therapy [is] not accessible for T cell ALL patients*". Another patient commented "*I was treated on a paed[iatric] trial as an adult, causing me to feel that adult treatment was insufficient. Also as a young adult I felt out of place and isolated on a ward with older haematology patients. My mental and emotional health suffered massively and still suffer to this day*". Another major reason for adults with ALL to claim that current treatments available on the NHS are insufficient is that there is currently no potential cure in this setting. Other therapies and comparators available in the adult relapsed/refractory setting include salvage chemotherapy, which is used if a patient has not responded to prior chemotherapy treatments. However, salvage chemotherapy only extends patient lives by a matter of months.
8. Is there an unmet need for patients with this condition?	Yes. Adult ALL is rapidly progressing with poor prognosis and as there are currently no potentially curative treatments available in this setting, many patients who have relapsed and have no other treatment options are considered terminal. At this stage patients' only remaining option is best supportive care. CAR T therapy is currently approved in under 25's with relapsed/refractory ALL. One ALL patient we spoke to who was under 25 and received CAR T therapy said, "*my consultant said to my sister "how old are you", and she said I think she was, how old was she at the time… 29… 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*".

	She went on to talk about the impact of people not being able to get CAR-T, either due to age or because CAR-T wasn't routinely available when she was diagnosed, and said "*It's just devastating to think that people like before me and friends that I had who I'd met on the ward who passed away, if it [CAR-T] had been around a little bit sooner then things might have been a little bit different for them. I know you can't change the past but hopefully if it's sorted for the future it'll help a lot more people*". There is therefore a strong unmet need in potentially curative treatment options for adults over 25 with relapsed/refractory ALL.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	CAR T provides a potential cure to ALL for those who have run out of other treatment options. We spoke to two ALL patients who had both relapsed after a stem cell transplant (SCT) and who had received CAR T therapy (one patient was 21, and the other was in their 50's). Both patients achieved complete remission following CAR T therapy, which meant CAR T therapy was a cure for them both. The younger patient explained "*there is actually nothing really bad about CAR T, it was such a stark contrast to what I had already been through with my stem cell transplant*". This is due to the less severe, short-term and more manageable side effects this patient experienced after CAR T in comparison to SCT. After CAR T she says, "*everyone was asking me how I felt and it was the first time I was able to say that I actually felt b*etter." The other CAR-T recipient also experienced fewer side effects than with previous treatments commenting "*CAR-T means that I get a third chance at life. The doctors had said that I could continue with chemo but it would only be effective for a limited time so it's likely that I wouldn't be here without it* [CAR T]*. For me, it was 100 times easier than a transplant with less side effects and a quicker recovery time*". As this patient mentioned, another key advantage of CAR T therapy is the treatment time and recovery time. The actual infusion takes up to 30 minutes and within 10 days after infusion the younger patient was discharged from hospital, commenting "*it all just felt so quick*". While she initially had to go back into hospital for blood tests 3 times a week she said, *"I didn't mind that so much, because when you've been*

	on treatment for as long as I have you know everyone in the clinic and it's like going to see some friends". The appointments were gradually spaced out more over time and now 4 years post treatment she goes in once every 3 months. She was a university student at the time and just 3 months after CAR T treatment she went back to university and carried on with her degree. By comparison, 3 months after her SCT this patient was very ill, regularly being sick and unable to study. Similarly, the older CAR T recipient commented "*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.*" The long-term side effects in this case were therefore easier to manage/tolerate than with other treatments and had less of an impact on the patients' lives.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects of CAR T can be a disadvantage of the therapy. According to the ZUMA-3 clinical trial anemia (49%) and neutropenia (49% [febrile 13%] occurred in 95% of patients who received CAR T therapy. Clinicians have also informed us of more severe short-term side effects, e.g., cytokine release syndrome (CRS) and neurological changes which manifest in an inability to write clearly, for example. CRS occurred in 24% of patients and neurologic events occurred in 25% of patients, but clinicians and clinical trials have reported that these side effects are temporary and reversible. In the ZUMA-3 clinical trial there were two Grade 5 KTE-X19–related events: brain herniation (n = 1) and septic shock (n = 1), but these were very rare. The younger recipient of CAR T who we spoke to explained that even though she had few side effects, she was taken to ICU due to low blood pressure. However, this was for monitoring purposes only and her low blood pressure was reversed quickly with the drug Tocilizumab. Majority of the side effects of CAR T can be managed/reversed and as previously mentioned, the younger recipient of CAR T said that her experience of it and the side effects were *"a stark contrast to what I had*

	already been through with my stem cell transplant". This is partly because of the duration of time which she experienced the side effects of SCT, telling us that she was sick regularly for 3 months post-transplant. For the patients we spoke to the side effects of CAR T were felt for a much shorter period, partly due to their nature of being quickly managed and reversible. CAR T therapy is only administered in a handful of existing CAR T centres in the UK (8 centres for adults). This means that many patients who are eligible to receive CAR T would have to travel in order to be treated. This could add an extra financial burden on patients and their families, as well as taking up a significant amount of time and having a potential impact on a patients' stress/anxiety levels. However, when we recently surveyed ALL patients and asked if they would be willing to travel further than usual (within the UK) to receive a more effective treatment, 66.7% of patients said yes, 33.3% were not sure as it would depend on the situation, and 0% said no. In addition, the most important feature of a treatment for respondents was that it improved/lengthened survival. This was above any other characteristic, including tolerable side effects, showing that patients generally value a potential cure more than any of the disadvantages of CAR T therapy. A final disadvantage is that CAR T therapy does not guarantee a cure in every patient. In fact, it only works as a cure in 50% of patients who are treated. But, given that this is already in the relapsed/refractory setting and the outcomes for patient's survival at this stage are poor, 50% of people achieving a cure is a significant improvement compared with the alternative of best supportive care and death.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All relapsed patients deserve to be offered a potential cure if one is medically possible.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	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.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- ALL is an aggressive disease with severe symptoms, rapid progression and very poor prognosis. A diagnosis therefore has a significant emotional strain on patients and their loved ones.

- CAR T can provide a potential cure to the patients who have run out of options and whose alternative is salvage chemotherapy (only extending life by a matter of months), and/or best supportive care until death. Patients in our survey said they value improved/lengthened survival more than other disadvantages of a treatment. CAR T can save lives.

- CAR T side effects are reportedly manageable and tolerable in comparison to other treatments such as SCT. More severe short-term side effects can be reversed.

- Both the actual treatment time (infusion) and recovery time from the therapy and side effects are reportedly quick, allowing patients to leave hospital and continue with their lives as normal not long after treatment.

- CAR T therapy is currently approved in this setting for under 25's but not for over 25's, presenting an age inequality issue. Patients of all ages deserve access to a potentially curative treatment.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults [ID1494]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**None**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Cure is the main aim of treatment for patients with acute lymphoblastic leukaemia (ALL), although chances of achieving a cure vary substantially depending on age of the patient and other disease characteristics. Patients with relapsed or refractory ALL typically have a dismal prognosis. One year overall survival post 1st salvage regimen is approximately 25%. Currently the only potentially curative option for relapsed adults over 25 is being bridged to a haemopoietic stem cell transplant. Treatment with CAR-T for this indication would have the aim of curative potential.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	In relapsed refractory ALL a clinically significant response would be durable complete remission (<5% blast in bone marrow), a complete remission with incomplete haematological recovery, and negativity for measurable residual disease.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	This is an area of considerable unmet clinical need. Chances of cure and long term survival in adult patients with relapsed/ refractory ALL are poor and there are very few clinical options for adults. Licensed therapies include Blinatumomab and Inotuzumab. These have a median overall survival of only 8 months. Even though availability of these novel agents have improved remission rates, cure is not achievable without consolidation with an allogeneic stem cell transplant. The majority of patients however do not receive a transplant either because they are not in remission or because they are not eligible due to their age or fitness levels or donor availability. Post stem cell transplant relapses are almost universally fatal.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Blinatumomab is available on the NHS for Philadelphia negative relapsed / refractory CD19+ B-ALL. Inotuzumab is available on the NHS for Philadelphia negative and positive relapsed / refractory CD22+ B-ALL. These drugs are optimally used as a bridge to allogenic stem cell transplant if patients are responding and are transplant eligible. Donor lymphocyte infusions may be offered to some patients relapsing post allogeneic stem cell transplant if they achieve a remission with further treatment, with poor evidence of long term efficacy. Rarely chemotherapy combinations are considered, such as FLAG or FLAG-Ida, although far less commonly due to poor response rates. For Philadelphia positive relapsed / refractory B ALL patients can be prescribed ponatinib. This is usually prescribed alongside a chemotherapy backbone. For adult patients under 25 with Philadelphia negative and positive relapsed / refractory B ALL Tisagenlecluecel (Kymirah) is available according to the pre-conditions of the cancer drug fund rules.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Pan-London Haemato-Oncology Clinical Guidelines Acute Leukaemias and Myeloid Neoplasms. Part 1: Acute Lymphoblastic Leukaemia

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The choice of salvage option depends on disease and patient factors and predicted outcome. For transplant eligible individuals the majority of ALL MDTs will recommend Inotuzumab for high burden relapsed disease if patient fits the eligibility criteria. Blinatumomab is typically reserved for low volume disease or where CD22 negative or those with contraindications to Inotuzumab; for example in the presence of liver disease. For post-transplant relapses and non-transplant eligible relapsed refractory patients there is no standard approach. Low dose chemotherapy / best supportive care might be offered. Use of Inotuzumab or Blinatumomab would be decided on case by case basis with the patients, weighing up the potential benefits and toxicities with predicted outcome. In all relapse scenarios appropriate clinical trial should always be considered. In many cases early palliative care and advanced care planning is recommended
• What impact would the technology have on the current pathway of care?	Availability of autologous CD19-targeting CAR-T therapy for adult patients with relapsed/refractory B-ALL will present a significant step forward. A number of patients who are currently offered palliation only because they are considered to be transplant ineligible (for instance because they are over the age of 65), could be eligible for CAR-T therapy. CAR-T therapy may also be used in preference to Blinatumomab and / or Inotuzumab even in transplant eligible patients as may offer similar or better chance of achieving a response and remissions may be durable without the added toxicity of allogeneic stem cell transplant consolidation. For patients with Philadelphia positive B-ALL relapsing after Ponatinib, currently there are no effective treatment options. CAR-T therapy will present an attractive therapeutic option for these patients. The technology is offering potentially curative option for patients who would otherwise be palliative
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No. Blinatumomab and Inotuzumab are currently mainly delivered in allogeneic transplant centres or large BCSH level 3 centres. Ponatinib is oral treatment and can be delivered in level 2 centres. Palliative treatment can be delivered even in smaller centres closer to patients' home. CAR-T therapy is currently only delivered in a limited number of commissioned FACT-JACIE accredited CAR-T centres. The technology is used in NHS for other indications. KTE-X19 (Tecartus) is currently funded in NHS for relapsed mantle cell lymphoma. Tecartus for mantle cell lymphoma dose is 2×10^6 CAR-positive viable T-

	cells per kg of body weight, with a maximum of 2×10^8 CAR positive viable T-cells. Tecartus for ALL dose is 1×10^6 CAR-positive viable T-cells per kg of body weight, with a maximum of 1×10^8 CAR positive viable T-cells. For mantle cell lymphoma the lymphodepleting chemotherapy regimen is cyclophosphamide 500 mg/m2 intravenously and fludarabine 30 mg/m2 intravenously on each of the fifth, fourth, and third day before infusion of Tecartus. For acute lymphoblastic leukaemia the lymphodepleting chemotherapy regimen is fludarabine 25 mg/m2 intravenously over 30 minutes on the fourth, third, and second day and administer cyclophosphamide 900 mg/m2 over 60 minutes on the second day before infusion of Tecartus
• How does healthcare resource use differ between the technology and current care?	CAR-T therapy specific commissioning, regulatory and governance requirements must be met. Delivering this treatment needs a heavy investment in trained and qualified staff including advanced supportive mechanisms. However, much of this investment is already in place in the NHS within the currently commissioned FACT-JACIE accredited CAR T centres and it is expected more centres are soon to be commissioned.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Approved FACT-JACIE accredited centres only
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Currently approved FACT-JACIE accredited centres will have the facilities and equipment to administer KTE-X19 for a new indication. Training would be required on new protocol of lymphodepletion. The NHS need to consider the investment for further centres for expanding CAR-T cell indications. Delivery of CAR T therapy needs heavy investment in trained and qualified staff including advanced supportive mechanisms from allied specialties such as ICU, neurology, etc. Overall the number of individuals eligible for CAR-T in for this indication will be predicted to be small.
11. Do you expect the technology to provide clinically	Yes. The published phase 2 Zuma-3 trial reports complete remission or complete remission (CR) with incomplete haematological recovery (CRi) in 71% of patients infused (39/55). CR/Cri of the intention to treat

meaningful benefits compared with current care?	population was 55%. The median duration of remission of 12·8 months. A reported 12/39 patients with CR/ CRi were in ongoing remission at time of data cut off. Median relapse-free survival (RFS) was 11·6 months in all treated patients and 14·2 months in responders. The RFS rate at 6 months was 58%. Overall survival (OS) rate at 12 months was 71%. Median OS was 18·2 months in all treated patients and was not reached in responders. Almost all patients (98%) achieving CR were MRD-negative. The ZUMA-3 phase 1 results had a median follow up of 22·1 months by Sept 9th 2020. Median OS was 22·4 months; among responders, median overall survival was not reached. In a combined phase 1 and 2 analysis at the 1×10^6 dose level, the rate of CR/CRi was 74% (58/74) with CR rate of 63% (49/74). Median duration of remission was 13·4 months, median RFS was 10·3 months, and median OS was 22·4 months. Median OS was not reached among responders. This data suggests clinically meaningful benefit over current care. In comparison CR/CRi rates were 35% with Blinatumomab and 80% with Inotuzumab in the phase 3 randomised Tower study and Inovate studies respectively. However remissions with these agents are not durable in the absence of consolidation with allogeneic stem cell transplant with median duration of response of <6 months and median OS of <8 months. In comparison, duration of CR was 12 months and median OS was 18 months with KTE X-19 in the Zuma 3 study even without an allogeneic stem cell consolidation in the majority. It therefore appears KTE X-19 is likely to confer a significant survival benefit to patients and given this can be achieved without allogeneic stem cell transplant consolidation, the therapeutic benefit therefore could be enhanced in the non-transplant eligible patients.
• Do you expect the technology to increase length of life more than current care?	Yes according to the published data available, KTE X-19 is likely to confer a significant survival benefit. The survival benefit is likely to even more for patients who are not transplant-eligible but fit for CAR-T therapy. Acknowledging the follow up is short and there is no definite plateau in the survival curve.
• Do you expect the technology to increase health-related quality of	Yes. Once they recover from any acute treatment related toxicity, health-related quality of life (QoL) for patients receiving CAR-T therapy is generally good and generally much better than QoL following allogeneic stem cell transplant. Specific data not available in ZUMA-3.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Unknown. Publications report CD19 targeting CAR-T therapy appears to be less effective in patients who have heavy marrow infiltration with leukemic blasts. In Zuma-3 study, patients aged >65 and those who only received 1 preceding line of therapy had a much better chance of benefiting from KTE X-19, but patient numbers were too small to be confident of this observation.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	Delivery of autologous CD19-transduced CD3+ cells for treating relapsed or refractory B-ALL in adults will be much more difficult to use for patients or healthcare professionals than current care. Relapsed ALL patients are often already managed in a stem cell transplant centre. The cancer drug fund stipulates that Blinatumomab should only be requested by and administered in either bone marrow transplant centres or in major haematological centres that regularly treat patients with relapsed ALL and who have close and regular ALL multi-disciplinary team meetings and links with bone marrow transplant centres. KTE X-19 would additionally need to be delivered in a CAR-T approved FACT-JACIE centre. There is need for enhanced monitoring, ICU and neurological facilities on site for safe delivery of CAR T therapy. These already exist in current commissioned centres. There may be a need for patients to travel some distance from their home for this treatment and a requirement to stay within an hour of the CAR T centre for 4 weeks post infusion which may present difficulties for some patients.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	First decision will be to commence apheresis. There will then be a clinical decision to proceed to lymphodepletion. Thirdly a decision to administer the product. Once KTE X-19 is administered no stop / start rules apply.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unknown
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes. Current treatments offer only short term remissions. CAR-T therapy is a revolutionary treatment which has produced impressive results in previously untreatable cancers and has the potential to offer cure. It represents a major innovation in cancer immunotherapy and in our ability to treat cancers without resorting to intensive chemotherapy or allogenic stem cell transplants

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Currently there is lack of curative options for patients with relapsed refractory ALL above 25 years of age. Specifically in those relapsed post or that are ineligible for a stem cell transplant, either due to lack of donor availability or other patient or disease related factors. For those patients CAR-T is the only option which offers the chance of a meaningful remission. For the transplant eligible patients it potentially offers the chance of improved survival without added toxicity of allogeneic stem cell transplant.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Significant adverse effects were published in the Zuma-3 dataset. All treated patients had at least one adverse event. The most common adverse events of grade 3 or higher were anaemia and pyrexia. Serious adverse events occurred in 75% of patients. 25% of patients had infections of grade 3 or higher. Cytokine release syndrome occurred in 89% of patients. Vasopressors were given to 40%. One patient had grade 3 tumour lysis syndrome. Neurological events occurred in 60% patients, with 25% events of grade 3 or higher. One patient died of brain herniation. One died of septic shock. This array of adverse events means the management needs to take place in an approved centre with close links and access to intensive care facilities, and specialist neurological services. Most patients recover fully from these. A proportion of patients will have persistent low blood counts needing blood and platelet support for many months. A minority of patients may have recurrent infections and need immunoglobulin replacement therapy.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes the population described in ZUMA-3 reflects the population of relapsed refractory ALL population in the UK. Patients in the Zuma 3 trial were aged >18 and had either primary refractory B-ALL, those relapsing early with remission duration of <12 months or those relapsing after 2 lines of therapy.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Complete remission rate. Levels of measurable residual disease (MRD). Median duration of remission. Relapse free survival. Survival with transplant consolidation. Overall survival. Adverse events. Yes these data sets are available in ZUMA-3
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Median follow up at publication of trial results was only 16 months. It is not clear if there is a plateau in survival curve at this stage. Further follow up is needed to know the long term survival benefit.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	There is a reported high mortality with Covid-19 infection in patients post CAR-T therapy. New treatments such as Ronapreve may prove useful in these patients who often lack the ability to mount an antibody response to vaccination.
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	Not available for KTE X-19. In the setting where Tisagenlecluecel is NICE approved, for paediatric and young adults under 25, the real world datasets from UK and worldwide are broadly in keeping with data from the pivotal Eliana trial.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes. Individuals from non-Caucasian backgrounds are less likely to have a matched unrelated donor on the international stem cell transplant registries. According to the Anthony Nolan, 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. As stem cell transplant was previously the only potentially curative treatment for individuals with relapsed refractory ALL, individuals from minority ethnic backgrounds are disadvantaged. This technology would potentially improve equality. Currently there are few FACT-JACIE accredited CAR T centres in England, making access and travel to approved centres potentially layering in equality. The NCCP panel has addressed this for other CAR-T indications and the landscape is expected to change with more allogenic transplant centres being commissioned for providing cellular therapies in the future.
21b. Consider whether these issues are different from issues with current care and why.	Yes. Currently the number of FACT-JACIE accredited CAR T centres is much less when compared to the number of allograft centres where patients are currently treated. However, the difference is expected to narrow down in future.
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for treatments for adults with relapsed refractory acute lymphoblastic leukaemia
- Current treatment options for adults with relapsed refractory B-ALL are inadequate and produce responses which are not durable in the absence of allogeneic stem cell transplant
- CAR T therapy is an innovative form of advanced cellular immunotherapy which has revolutionised treatment of B-ALL in children and young adults. Adults over 25 have no access to CAR-T cell therapy outside a clinical trial which offers a potential cure to patients with an otherwise terminal condition
- KTE X-19 improves remission duration and survival for both transplant eligible and ineligible patients, acknowledging the follow up is short and there is no definite plateau in the survival curve.
- KTE X-19 may offer improved outcomes for patients from minority ethnic backgrounds who have less chance of finding a match to enable a curative stem cell transplant

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NICE National Institute for Health and Care Excellence

NHS England CAR-T tariff

Information provided to NICE as of 17 October 2022

Summary

- **Tariff value:** £65,415
- **Relevant technologies and indications:** applies to all CAR-T cell therapy technologies and indications currently used for people aged 18 or over
- **Methods overview:** Rapid review of financial inputs and costings of 6 NHS providers of CAR-T services
- **Confidentiality status:** not confidential

Description

Rationale: there is not a 22-23 HRG tariff price that could be used as a proxy for CAR-T tariff

Methods:

- Not a micro-costing approach
- Considered costs over pre-infusion, treatment and post-infusion phases
- Removed overheads from the calculations (about 30% reduction from initial tariff value)
- Adjustments to:
    - Length of stay and acuity of patient cohort
    - Proportion of patients who are able to receive their preconditioning in an ambulatory setting
    - Rebalanced the treatment phase to reflect more recent percentage of patients who are well enough to spend some of the first 28 days post infusion outside of hospital (often in a local hotel instead)
- Adjustments are applied as:
    - 20% reduction to pre-conditioning costs (-£1,734)
    - 33% reduction to inpatient admission costs (-£9,749)
    - 171% increase in the costs associated with hotel stays near the treating centre resulting from reduced hospital length of stay (room and subsistence) (+£1886)
    - Net reduction from original costing of £9,597

25th October 2022

Celia Mayers
Project Manager, Technology Appraisals & HST
+44 (0) 161 413 4116

RE: Kite/Gilead response to NHS England CAR T Tariff

Dear Celia,

Thank you for the opportunity to respond to the proposed use by NICE of the revised NHS England CAR-T Tariff (**Revised NHS Tariff**) and related information provided to NICE by NHS England.

In the limited time available, we have reviewed the documents titled "*CAR-T tariff summary to stakeholders*" and "*CAR-T NHSE national costing summary reworked for NICE ID3980 FINAL with % distribution*" (both received on 18 October 2020) together with "*Car-T NHSE national costing original tariff by provider*" (received on 20 October 2022). We note with surprise that the breakdown included in this third document was not included in NHS England's response under the Freedom of Information Act on 1 September 2022 (**FOIA response**), despite the fact that our request specifically asked for an itemised breakdown of pathway costs.

We would be deeply concerned if NICE were to include the Revised NHS Tariff in its assessments as the cost of treatment for CAR-T. For the reasons set out below, we would consider this approach to be procedurally unfair and unreasonable, and with potential adverse ramifications on patient access.

The NHS tariff for CAR-T treatment is used primarily as a mechanism for NHS England to fund individual hospitals for CAR-T treatment and is not designed to represent the cost base that is evaluated by NICE in an appraisal. The current tariff has been embedded within NHS England for three years, without external consultation or validation. In their FOIA response, NHS England explained that "*a CAR-T Finance Working Group used the SmPC for individual products and trial experience of the initial products to establish the individual components of the pathway to build an overall projection of the costs associated with each patient. These overall estimations were then subject to national negotiation discussions between the provider cohort and NHS England to agree an overall tariff, which was considered acceptable to all parties*". The FOIA response further explained that the resulting tariff is a standard value to ensure "*appropriate service reimbursement overall without excessive administrative burden*."

Further, the FOIA response also explains that this service was developed by building on the requirements for allogenic blood and bone marrow transplantation. The proposed tariff is aligned with an allogenic transplant, rather than the autologous transplant, which is a closer match to the cost and treatment burden of CAR-T treatment.

We appreciate that there may be broader reasons why NHS England and trusts might favour retaining the current high level of tariff: for example, there may have been reasons to pay a higher tariff to introduce a new technology into the NHS England. There is a potential conflict in the construction of the tariff, in that it is in the interest of the trusts who provided the estimates to have a higher tariff, and for NHS England to maintain the existing tariff

structure which has been paid for since 2019 without external consultation or validation. How has NICE anticipated and adjusted for this potential conflict?

In line with its Methods Guide, NICE must consider what the true cost of treatment is to the NHS. NICE may consider, but is not bound to apply, the NHS England tariff when determining that cost of treatment. The recommendations that NICE make must apply a clear methodological approach, be evidence based and transparent.

The information provided by NHS England does not:

- provide sufficient transparency on the methods used to calculate the Revised NHS Tariff (or the original tariff on which it is based)
- indicate the evidence on which the calculation, including recent adjustments, was based

To the extent that information has been provided, it raises questions on whether the Revised NHS Tariff includes costs that are not relevant.

We have set out our detailed questions and concerns in the schedule to this letter.

Generally, the concerns that we raised in our response to NICE's ACD ID1685 continue to apply. The information provided does not allow potential issues of double counting to be explored, or a proper assessment of whether all costs reflected are appropriate for inclusion in a NICE assessment. There remain significant questions as to whether the Revised NHS Tariff reflects the true cost of treatment.

We ask that NICE does not incorporate this Revised NHS Tariff and instead applies the cost structure already agreed in the previous appraisals, ID3980 and ID1313.

As noted above, the NHS tariff for CAR-T has not been subject to external consultation or validation. Given its potential impact on access to CAR-T therapies generally (and not just those provided by Kite), full external consultation should take place before any NHS tariff is included in any NICE appraisals.

The requested base case analyses are provided in Appendix A-D of this response.

Please contact me if you have any further queries.

Yours sincerely

A. G. Lundie

Gordon Lundie

Executive Director, Market Access and Reimbursement

Schedule

True cost of treatment

NICE must consider the true cost of treatment that is relevant to the NICE appraisal, which may be different from the tariff cost paid by NHS England.

The information provided by NHS England shows a calculation that starts with the average of costs apparently reported by six Trusts in 2019/20. From the FOIA response, we understand that the original tariff was the result of negotiations to achieve a service reimbursement that was acceptable to all parties. This value has been uplifted to reflect costs in 2022/2023, and then reduced by 30% to remove overheads and further adjusted to reflect certain factors outlined in the *CAR T tariff summary to stakeholders.*

To assess if the Revised NHS Tariff reflects the current, true cost of treatment to the NHS, a number of questions should be addressed, including the following:

1. The Revised NHS Tariff is based on the original tariff, which, as the FOIA response explains, was the result of negotiations to achieve a service reimbursement that was acceptable to all parties. What factors were taken into account in this negotiation, beyond the true cost of treatment? How can the value of these factors be assessed and discounted when determining the appropriate cost of treatment for a NICE appraisal?

2. The original cost information was collected in 2019 and the FOIA response explains that it was based on trial experience of the initial products. Is this sufficiently reflected in the reduction of in-patient costs, or should there be further adjustments? Clinical opinion accepts that the initially anticipated patient burden and costs of CAR-T have not been realised, due to early advances in patient care and identification, and the wider, earlier use of steroids and tocilizumab [1]. Does the Revised NHS Tariff reflect the evolution of clinical practice since 2019?

3. The document *CAR-T NHSE national costing original tariff by provider* shows a breakdown of costs across six Trusts that supports the calculation of the original NHS tariff for CAR-T.
   If this breakdown was used to calculate the original NHS CAR-T tariff in 2019, why was this break down not provided in the FOIA response?

If this breakdown was not provided in the FOIA response because it was only produced after 1 September 2022, why was it produced to support the result of the 2019 calculation, rather than current CAR-T costs?
Why were only six Trusts asked to provide input?

Which Trusts were asked to contribute to the calculation of the original NHS CAR-T tariff in 2019? Were the same Trusts asked to provide the breakdown shown in CAR-T *NHSE national costing original tariff by provider* and also consulted on the allocation of costs in the document *Car-T NHSE national costing summary reworked for NICE ID3980*?

Was the original NHS CAR-T tariff adapted from the tariff or costing for another treatment? If so, with hindsight from 2022, did this provide a suitable basis?
We note from the FOIA response that the CAR-T service was developed by building on the requirements for allogeneic Blood and Marrow Transplantation (BMT) (see section 1.1 of the Service Specification provided with the FOIA response.) A number of elements of the breakdown of the original NHS CAR-T tariff reflect the complexity of bone marrow transplant (allogeneic stem cell transplant) – such as length of hospital stay, nature of apheresis and invasiveness of treatment (and associated costs). However, it has been recognised that CAR-T treatment is not as complex as bone marrow transplant but is more similar to autologous stem cell transplant (see below).

4. The clinical treatment most similar to CAR-T treatment in terms of complexity and NHS activity is autologous stem cell transplant – which has a tariff rate of £17,181 (inflated from 2019/2020 HRG tariff elective SA26A £16,668). What is the explanation for the significant difference that still remains between this tariff and the Revised NHS Tariff for CAR-T?

5. Is it possible to validate the proposed NHS Revised Tariff as the true cost of treatment? (See further questions under **Evidence** below.)

6. Why has a Patient Level Information and Costing System (PLICS) level analysis of patient costings not been carried out, to provide an evidence-based NHS England CAR-T tariff?

7. We understand that the Revised NHS Tariff applies to all CAR-T treatments, and leukapheresis. Leukapheresis is a standard practice for many treatments such as autologous stem cell transplant and we would like to know how the costs applied to CAR-T differ to that used in ASCT for Leukapheresis?

8. How does the Revised NHS Tariff reflect that some patients will reside within a standard patient pathway, and others a complex pathway? The comments in the calculation suggest that the estimates used are based on highly complex patients.

9. What is the basis for the increase of the original £92,000 (for 2019/2020) to £97,598 for 2022/2023? It is not clear how the formula revealed in the calculation reflects inflation.

Evidence

1. What evidence is available to support the cost estimates provided by the six Trusts, on which the Revised NHS Tariff is ultimately based? Did each Trust take a consistent approach in allocating their cost? How has this been derived? Is it based on estimates or actual costs?

2. Is it possible to validate the Revised NHS Tariff, with reference to specific activities and time spent by NHS staff?

3. In determining the cost of treatment to be included in a NICE appraisal, is it sufficient to rely on estimates, or should the cost be calculated by (for example) each provider following a number of patients, and costing each patient across the pathway to arrive at the allocations?

4. In the calculation of the Revised NHS Tariff, it appears that the gross cost of £97,598 has been reduced to £75,076 and then allocated across 105 different cost fields. What evidence supports the cost distribution differentially applied into each field?

   This evidence should be reviewed in order to identify any potential issues of double counting, the relevance of the cost in practice and patient care, as well as its relevance to the NICE appraisal.

Would NICE accept this method of allocation in a manufacturer's submission?

5. How does the calculation of the Revised NHS Tariff reflect significant variations in practice, experience and capacity between provider in the delivery of CAR-T? For example:

   a. **Location of patient in 28 days post-infusion**

   Under the Gilead/Kite CAR-T marketing authorisations, patients are required to remain within proximity of a qualified clinical facility for four weeks. In practice, some London hospitals will discharge patients after 10 days to a local hotel whereas hospitals without this social care arrangement may retain patients in hospital at greater cost. In other instances, the patient's home may be within proximity of the hospital.

   What assumptions have been incorporated in the Revised NHS Tariff about where a patient will stay after infusion, and what evidence supports that this reflects current practice?

   We note that the calculation of the Revised NHS Tariff includes a 33% reduction to in-patient admission costs, and a 171% increase in the costs associated with hotel stays near the hospital resulting from reduced hospital length of stay. What evidence is available to support this level of adjustment? What are the base and revised number of days (i) in hospital and (ii) in a hotel that are reflected in the NHS Revised Tariff?

   b. **Variation**

   There is significant variation between the costs estimated by the six Trusts in the 2019 exercise.

   For example:

   - Trusts A, B and D estimated no cost for radiographers, while Trust E estimated £2,447.
   - For radiologists, the estimated costs spanned from £2,876 (Trust D) to £0 (Trust B)
   - On pathology laboratories, Trust E estimated £1,409, Trust A £11,250 and Trust D £28,497

Where there is such divergence, is it appropriate for the cost of treatment applied by NICE to apply a figure based on a simple average of these estimates?

This variety highlights the need for more evidence-based assessment.

6. How has the thirty percent (30%) reduction in the original NHS tariff, intended to remove overhead costs, been calculated? What is the rationale or evidence for this level of reduction? Were figures other than 30% modelled?

Costs included that may not be relevant

To the extent that it is available, the information provided suggests that the Revised NHS Tariff includes costs that are not relevant to a NICE appraisal:

1. The calculation of the Revised NHS tariff includes £6,514 under the heading of "Identification and work up". It is not clear what this cost represents. To the extent that it reflects the failure of prior treatments (for example biopsy to assess progression) and is not relevant to the decision to prescribe CAR-T, it is not relevant to a NICE appraisal.

   To the extent that it reflects the cost of a second biopsy, it should not be considered in the cost of treatment used in the cost effectiveness model. This is because a second biopsy is not required by clinical practice nor by our marketing authorisations. We note that the second biopsy is not required in other countries and is only a requirement of NHS England.

2. Therapists and counsellors are not routinely considered in the costing of other treatments, for example in the recent appraisal for Trodelvy, despite their services often being provided to patients.

   Would these medical professionals be likely to be allocated to these cancer patients (as a result of their disease) regardless of the decision to treat with CAR-T? If so, is it appropriate for their costs to be included in the NICE appraisal? These costs are highly unlikely to be a marginal additional cost of CAR-T.

3. There is a recognised patient drop-out rate at each stage, with survival at 12 months at approximately sixty percent (60%) [2] [1] [3] [2] [4] [3] [5][4] [6] [5]. How will you apply the tariff to the NICE assessment to accommodate for patients who drop-out at each stage?

4. In the treatment phase, the calculation shows a total of £21,573 of allocated nursing and medical staff cost. What supporting evidence has been collected to validate this number?
   This represents a significant level of care that is equivalent to ITU treatment. However, this is not required for the majority of patients treated with CAR-T, where general ward care following the first week of treatment more regularly occurs. The latest panel data [7] [6] gives us an indication of the real-world ITU admissions rate at 27.8% of all CAR-T patients, where for the majority this was limited to observation/inotropes only.

5. In the treatment phase the calculation includes £9,586 of clinical supplies and pathology costs. It is not clear what this significant sum relates to. Is there evidence to support this cost? For example, there is significant disparity in the costs allocated to clinical supplies and pathology costs by different Trusts (e.g. Trust C: £35,264 v Trust E: £1,409 [See *Car-T NHSE national costing original tariff by provider*]).

6. At the recent review meeting [ID1494], the patient expert described their experience of minimal hospital care after discharge. The calculation of the NHS Revised Tariff allocates a significant cost to the period from Day 28 to Day 100, of £5,351, including a pathology laboratory allocation of £1,144. What activities does this relate to? What proportion of patients require this care?

Technical query

1. Does the figure in C33 of the excel sheet (£75,076) relate to Z33 (£65,415) through a translation of changes? We have analysed these changes, showing of a net reduction of £9,597, however there is a small discrepancy (£64) that is unaccounted for.

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Appendix A – ID3980

In response to the request for ID3980 (Yescarta 3L DLBCL CDF exit), Table 1 presents the deterministic cost effectiveness results with the tariff applied. Compared to the company and ERG base case ICER of £50,480, presented in the public committee slides on 6 September, the use of the NHS England tariff results in an increase to the ICER of ~£9,000.

Table 1: Base-case results (with NHS tariff for CAR T) - ID3980

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,253

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHSE, National Health Service England; QALYs, quality-adjusted life years.

Notes: [redacted] PAS applied

Appendix B – ID1684

In response to the request for ID1684 (Yescarta 2L DLBCL),

Table ***2*** presents the deterministic cost effectiveness results of ID1684 with the tariff applied. Compared to the company base case ICER of £51,154, the use of the NHS England tariff results in an increase to the ICER of ~£10,000, to £60,289 per QALY gained.

Table 2: Base-case results (with NHS tariff for CAR T) - ID1684

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
SOC	[redacted]	[redacted]	[redacted]				
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£60,289

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Appendix C – ID1685

In response to the request for ID1685 (Yescarta 4L FL), Table 3 presents the deterministic cost effectiveness results with the tariff applied. Compared to the company base case ICER of £40,584, presented in the public committee slides on 6 September, the use of the NHS England tariff results in an increase to the ICER of ~£11,000.

Table 3: Base-case results (with NHS tariff for CAR T) - ID1685

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Current 4L+ care	[redacted]	[redacted]	[redacted]	–	–	–	–
Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,297

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHSE, National Health Service England; QALYs, quality-adjusted life years.

Notes: [redacted] PAS applied

Appendix D – ID1494

In response to the request for ID1494 (Tecartus ALL), Table 4 -Table 6 presents the deterministic cost-effectiveness results with the tariff applied.

Table 4: Base-case results (with NHS tariff for CAR T) - ID1494 Overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	13.686	[redacted]	[redacted]	-	[redacted]	-
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	6.934	[redacted]	£27,748
FLAG-IDA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,855

Table 5: Base-case results (with NHS tariff for CAR T) - ID1494 Ph- population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	12.641	[redacted]	[redacted]	-	[redacted]	-
BLINATUMOMAB	[redacted]	4.582	[redacted]	[redacted]	8.059	[redacted]	£38,951
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	9.419	[redacted]	£46,773
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	5.889	[redacted]	£31,236

Table 6: Base-case results (with NHS tariff for CAR T) - ID1494 Ph+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
KTE-X19	[redacted]	13.614	[redacted]	[redacted]	-	[redacted]	-
PONATINIB	[redacted]	5.388	[redacted]	[redacted]	8.226	[redacted]	£45,321
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	10.392	[redacted]	£42,474
INOTUZUMAB	[redacted]	6.752	[redacted]	[redacted]	6.862	[redacted]	£27,042

Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

Dr Sara Ghorashian was involved in patents and royalties for contributing to the development of another CD19 CAR-T product. She is also a speaker and on the advisory board for Novartis.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Chris Carroll summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Geoff Holmes critiqued the statistical aspects of the submission. Dr Sara helped with interpreting the clinical data and providing clinical advice. Andrew Metry and Matt Stevenson critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AEs	Adverse events
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
Allo-SCT	Allogeneic stem cell transplantation
ANC	Absolute neutrophil count
BIC	Bayesian Information Criterion
BM	Bone marrow
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CEAC	Cost-effectiveness acceptability curve
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CR	Complete remission
CRD	The Centre for Reviews and Dissemination
CRi	Complete remission with incomplete haematologic recovery
CRS	Cytokine release syndrome
CS	Company's submission
CSR	Clinical study report
DLT	Dose-limiting toxicity
DoR	Duration Of Remission
DSA	Deterministic Sensitivity Analyses.
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance score
EF	Event-free
EFS	Event-free survival
eMIT	electronic Market Information Tool
EQ-5D-5L	EuroQol 5 Dimensions 5 level
ERG	Evidence review group
ESMO	European Society of Medical Oncology
ESS	Effective Sample Size
FLAG	Fludarabine, cytarabine (Ara-C) granulocyte-colony stimulating factor
FLAG-IDA	Fludarabine, cytarabine (Ara-C) granulocyte-colony stimulating factor idarubicin

GvHD	Graft versus host disease
HCHS	Hospital and community health services
HER2	Human epidermal growth factor receptor 2
HERC	Health Economics Research Centre
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
IPD	Individual patient data
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MCM	Mixture-cure models
mITT	modified intention to treat
MMRM	Mixed model for repeated measures
MRD	Minimal residual disease
MRD-	Minimal residual disease negativity
NE	Not estimable
NICE	National Institute for Health and Care Excellence
NR	Not reported
OCR	Overall complete remission
ORR	Overall response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PFS	Progression-free survival
PH	Proportional hazard
Ph	Philadelphia chromosome
Ph+	Philadelphia chromosome-positive
Ph-	Philadelphia chromosome-negative
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic Sensitivity Analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QIC	Quasi-likelihood under Independence Model Criterion

R/R	Relapsed/Refractory
RCT	Randomised controlled trial
RFS	Relapse-free survival
SCT	Stem cell transplant
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality rate
SRT	Safety review team
STA	Single Technology Appraisal
TE	Technical engagement
TKI	Tyrosine kinase inhibitor
VAS	Visual analogue scale
VOD	Veno-occlusive disease

1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of cost per quality-adjusted life years (QALYs). However, the ERG is aware that the company will provide a new data cut during the technical engagement process which means that the ICERs presented will be superseded. Furthermore, analyses that the ERG believes would be informative to the National Institute for Health and Care Excellence (NICE) Appraisal Committee have not been provided by the company, meaning that the ERG cannot present its preferred range in the ICER.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest impact on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main report.

All issues identified represent the view of the ERG, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the ERG's key issues

Key issues identified by the ERG that impact on the incremental costs and QALYs are summarised in Table 1. A fuller description of each issue, together with potential alternative approaches, the expected impact on the ICER of such approaches and additional evidence that would resolve the issue are contained in Section 1.5.

Table 1: Overview of the ERG's key issues

ID 1494	Summary of issue (More detail is provided in Section 4.3.3)
Issue 1	Presence of programming and implementation errors in the company's economic model
Issue 2	Uncertainty around the appropriateness of the company's naïve comparison approach
Issue 3	Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data
Issue 4	Exclusion of allo-SCT related costs and QALY loss for patients receiving KTE-X19
Issue 5	Concerns with the life expectancy of cured patients compared to general population
Issue 6	Concerns with cured patients having the same utility values as general population
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 9	Uncertainty of the costs associated with delivering KTE-X19 infusion
Issue 10	Issues with dosing regimens used for FLAG-IDA and ponatinib

OS - overall survival, allo-SCT – allogeneic stem cell transplant

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology improves length (overall survival (OS)) and quality of life, using QALYs. In the company's model, KTE-X19 treatment increases QALYs compared with the comparators by increasing expected OS; the costs associated with KTE-X19 treatment compared with comparators are greater, primarily due to the acquisition cost of KTE-X19.

The assumptions within the company's base case modelling that the ERG believes are either incorrect, or uncertain, and that impact most on the ICER, are provided in Table 1.

1.3 The decision problem: summary of the ERG's key issues

The ERG has no key issues with the decision problem as addressed by the company but notes that there is no direct evidence comparing KTE-X19 with the stated comparators and that in some circumstances some comparators may be preferred to alternative options.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The pivotal study (ZUMA-3) is an international, multi-centre, non-randomised, uncontrolled, unblinded, ongoing single-arm study. The study was assessed by the ERG as being at moderate risk of bias (Section 3.1.5). It is a small study with 78 subjects across two phases, and with a median follow-up duration of 18.1 months. KTE-X19 demonstrated efficacy in terms of overall complete remission (CR), OS and Minimal Residual Disease negativity (MRD-) for the study population (Section 3.2.1). However, adverse events (AEs) related to KTE-X19 treatment were frequent, certain AEs at Grade 3 or higher were also common (pyrexia, hypotension and hypoxia), and four treatment-related deaths were recorded across all patients in the two phases (Section 3.2.4). The study included no UK patients nor patients with Eastern Cooperative Oncology Group performance scores of 2 and it is debatable whether the study population reflects the population of patients who would likely be eligible for KTE-X19 in clinical practice in England (Section 3.2.1).

In an absence of study data directly comparing KTE-X19 with relevant comparator therapies, the company submission (CS) reported a matching-adjusted indirect comparison (MAIC) comparing the non-randomised ZUMA-3 data with data from two randomised controlled trials (RCTs) (TOWER evaluating blinatumomab and INO-VATE evaluating inotuzumab ozogamicin (henceforth referred to as inotuzumab for brevity)) (Sections 3.3 and 3.4). The two RCTs were at high risk of bias and the outcomes compared were OS and relapse-free survival (RFS), which was reported as event-free survival (EFS) (Section 3.3.2). The comparator studies included adult acute lymphoblastic leukaemia (ALL) patients with a number of different characteristics from the ZUMA-3 population and applied slightly different criteria for the complete remission with incomplete haematological recovery (CRi) outcome. A naïve indirect comparison was also conducted that included data from the MAIC trials, plus a small

study of ponatinib (PACE) and individual patient data from an unpublished clinical study report for blinatumumab (SCHOLAR-3). The characteristics of patients in PACE and SCHOLAR-3 were again different from the likely population in clinical practice in England. The ERG acknowledges the existing limitations and remaining bias within the MAICs conducted by the company, but judges the MAIC to be more informative, as the naïve comparisons have a greater possibility of bias (sections 3.3 and 3.4).

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

This section expands on the issues listed in Table 1.

Table 2: Issue 1. Presence of programming and implementation errors in the company's economic model

Report section	Sections 4.3.3 and 4.4.2.1
Description of issue and why the ERG has identified it as important	The ERG identified some errors in the way it was programmed and implemented in terms of vial sharing, drug cost calculations based on body surface area (BSA), cyclophosphamide and fludarabine acquisition cost calculations, blinatumomab administration costs, and linkage of inotuzumab spline selection list to the rest of the model.
What alternative approach has the ERG suggested?	The ERG assumed no vial sharing, corrected calculations for how the vial consumption is calculated based on BSA, corrected the cyclophosphamide and fludarabine dose, removed remaining double counting for blinatumomab administration costs, and amended the links for the spline selection list of inotuzumab.
What is the expected effect on the cost-effectiveness estimates?	Correcting errors had minimal impact, increasing the ICER by less than £200 per QALY gained compared with FLAG-IDA. Assuming vial sharing increased the ICER of KTE-X19 against inotuzumab and blinatumomab by £8000 and £3000 respectively.
What additional evidence or analyses might help to resolve this key issue?	-

Table 3: Issue 2. Uncertainty around the appropriateness of the company's naïve comparison approach

Report section	Sections 4.3.3 and 4.4.2.2
Description of issue and why the ERG has identified it as important	The company's model uses relative treatment effect estimates from the naïve indirect comparisons in preference to those obtained from the MAICs for the comparison of KTE-X19 against each of inotuzumab, FLAG-IDA, and a synthetic control arm matched to the ZUMA-3 population for comparison with blinatumomab. The ERG believes that there were important differences between the ZUMA-3 population and the study populations in pivotal studies for the comparators which need to be accounted for. Analyses estimating ICERs in the ZUMA-3 population by assuming the HRs were transportable from the MAIC conducted in comparator studies are believed by the ERG to be informative to the NICE Appraisal Committee.
What alternative approach has the ERG suggested?	The ERG prefers the MAIC approach to adjust for the differences between study populations. This was only estimated for the overall population as the model did not allow for analysing the results of MAIC by subgroup.
What is the expected effect on the cost-effectiveness estimates?	Using MAICs rather than the company's approach increases the ICER by between £10,000 and £18,000 per QALY gained. ICERs were not generated assuming transportable HRs in the ZUMA-3 population
What additional evidence or analyses might help to resolve this key issue?	MAIC analyses to be provided based on Ph status, assuming that the HRs generated are generalisable to both Ph+ and Ph- patients. MAICs also to be provided compared with TOWER.

Table 4: Issue 3. Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data

Report section	Sections 4.3.3 and 4.4.2.3
Description of issue and why the ERG has identified it as important	The company's model has made reasonable choices for the base case, except for the fit to ponatinib OS data. The ERG believes that the Gompertz model should be used rather than the log-normal as it aligns better with the smoothed observed hazard, keeps with the clear plateau from 25 months onwards, and has comparable statistical fit. Additionally, the company did not perform a separate model selection exercise for the ZUMA-3 MAIC-adjusted populations.
What alternative approach has the ERG suggested?	The ERG uses the Gompertz model for ponatinib OS data. In absence of other evidence, the ERG uses the same preferred models as with the naïve comparisons.
What is the expected effect on the cost-effectiveness estimates?	This had minimal impact on the ICER estimate for Ph+ subgroup decreasing the ICER by £46 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	A formal analysis of which survival models are the most appropriate for use in the MAIC rather than relying on those judged most appropriate in the naïve indirect comparison.

Table 5: Issue 4. Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19

Report section	Sections 4.3.3 and 4.4.2.4
Description of issue and why the ERG has identified it as important	In ZUMA-3, 14 of 78 patients who received a KTE-X19 infusion, went on to receive allo-SCT. The company excluded costs and QALY losses related to the transplant based on clinical expectations and a post hoc analysis of OS by status of receiving allo-SCT. The ERG remains suspicious of the ability of KTE-X19 to offer a standalone curative therapy, and considers the OS analysis to be weak as it was neither pre planned nor powered enough to detect a difference.
What alternative approach has the ERG suggested?	The ERG included the costs and QALY loss associated with allo-SCT for patients who received KTE-X19.
What is the expected effect on the cost-effectiveness estimates?	Inclusion of allo-SCT related costs and QALY loss increases the ICER by £4000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	A study which provides survival outcomes for patients who achieved complete remission after KTE-X19 with one group randomised to receive allo-SCT after and one group who do not undergo the procedure.

Table 6: Issue 5. Concerns with life expectancy of cured patients compared to general population

Report section	Sections 4.3.3 and 4.4.2.5
Description of issue and why the ERG has identified it as important	The company's base case applies an SMR of 1.09 to model the mortality risk of patients considered cured (that is, those patients alive after 3 years) compared to that of the age- and sex-matched UK general population. However, the ERG believes this to be an underestimate being sourced from a study in R/R DLBCL population.
What alternative approach has the ERG suggested?	The ERG reviewed SMR values used in previous NICE appraisals in R/R ALL and used a *'conservative'* value of 4 applied previously for 5-year survivors post-SCT.
What is the expected effect on the cost-effectiveness estimates?	Using the higher SMR value of 4 increases the ICER by £7000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	A study providing long term survival outcomes for R/R ALL patients.

Table 7: Issue 6. Concerns with cured patients having the same utility values as general population

Report section	Sections 4.3.3 and 4.4.2.6
Description of issue and why the ERG has identified it as important	The company's base case assumes that the utility values for cured patients is the same as an age- and sex-matched population. The ERG believes that the cumulative drug toxicity and the impact of having R/R ALL at some point of their lives would mean that the utility would be lower than the age- and sex-matched population.
What alternative approach has the ERG suggested?	The ERG applied a multiplier of 0.92 to the utility values of general population. This was estimated from the ratio of utility in the relapse-free health state recorded in ZUMA-3 and the utility of an age- and sex-matched population.
What is the expected effect on the cost-effectiveness estimates?	Assuming lower utility values for patients with a history of R/R ALL increases the ICER by £2,400 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	A study collecting HRQoL data for patients with history of R/R ALL.

Table 8: Issue 7. Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab

Report section	Sections 4.3.3 and 4.4.2.7
Description of issue and why the ERG has identified it as important	The company's estimate of costs for management of AEs associated with KTE-X19 does not align with clinical expectations. The ERG suspects all aspects of treating AEs were captured. For inotuzumab, estimating costs and QALY loss associated with VOD includes a degree of double counting as it involves the full cost of defibrotide injections, and a disutility representing untreated patients.
What alternative approach has the ERG suggested?	The ERG assumes AE-related costs for KTE-X19 to be the same as that for inotuzumab. Half the costs and associated disutility were removed for VOD.
What is the expected effect on the cost-effectiveness estimates?	This had a modest impact of increasing the ICER by less than £1000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Accurate calculation of costs incurred for treating AEs for patients in ZUMA-3 and those on inotuzumab. The tariff for CAR-T delivery has been used in an additional analysis to approximate the costs required to treat potential AEs after a KTE-X19 infusion.

Table 9: Issue 8. Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA

Report section	Sections 4.3.3 and 4.4.2.8
Description of issue and why the ERG has identified it as important	The company estimates separate AE costs for patients on either blinatumomab or FLAG-IDA. Both are administered within hospital care with costs captured as administration costs. The ERG believes that AEs that will develop would be already treated within the hospital stay in line with previous NICE appraisals. Thus, costing AEs separately introduces double counting.
What alternative approach has the ERG suggested?	The ERG removes AE-related costs for blinatumomab and FLAG-IDA.
What is the expected effect on the cost-effectiveness estimates?	This had a minimal impact on the ICER by increasing it approximately £300 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	Accurate calculation of costs incurred for treating AEs in both the inpatient and outpatient settings.

Table 10: Issue 9. Uncertainty of the costs associated with delivering KTE-X19 infusion

Report section	Sections 4.3.3 and 4.4.2.9
Description of issue and why the ERG has identified it as important	The ERG was made aware of a tariff available for the delivery of a CAR-T therapy. Based on expert advice, this was assumed to cost [redacted].
What alternative approach has the ERG suggested?	The ERG applies this tariff to its base case.
What is the expected effect on the cost-effectiveness estimates?	This had a large impact on the ICER by increasing it around £12,000 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	-

Table 11: Issue 10. Issues with dosing regimens used for FLAG-IDA and ponatinib

Report section	Sections 4.3.3 and 4.4.2.10
Description of issue and why the ERG has identified it as important	The company's model allows FLAG-IDA to be administered for a maximum of 4 cycles which was neither in line with clinical advice nor evidence from studies. The model also assumes FLAG-IDA is administered with ponatinib which was not in line with the PACE study.
What alternative approach has the ERG suggested?	The ERG applies a cap of two cycles for FLAG-IDA, and removes the costs of FLAG-IDA for patients on ponatinib.
What is the expected effect on the cost-effectiveness estimates?	This had a large impact on the ICER for the Ph+ subgroup by increasing it around £7000 per QALY gained. The impact was modest on the Ph- subgroup as the ICER only increased by £800 per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	-

1.6 Summary of ERG's preferred deterministic exploratory analyses

Table 12 and Table 13 provide a reference of the results from the ERG's exploratory analyses for the Ph subgroups. However, these results, detailed in Section 4.4, are based on naïve indirect comparisons that the ERG does not believe is appropriate. Table 14 illustrates the impact of using MAICs which is the ERG's preferred method as it explicitly tries to adjust for key differences in patient populations. The ERG-adjusted results from the naïve comparison suggested that KTE-X19 has a deterministic ICER in Ph- patients of £70,545 compared with FLAG-IDA (probabilistic ICER = £71,638) with blinatumomab and inotuzumab being extendedly dominated in the probabilistic analysis. In Ph+ patients the deterministic ICER was £73,316 compared with ponatinib with inotuzumab being extendedly dominated (probabilistic ICER = £74,576).

MAIC results could only be produced for KTE-X19 against FLAG-IDA and inotuzumab in the entire population. Further details are provided in Section 4.4. A full incremental analysis could not be provided as the patients in ZUMA-3 were matched to those in the studies of each comparator. The ERG's most plausible ICER is £100,143 for KTE-X19 against FLAG-IDA (probabilistic ICER = £100,982), and £81,978 for KTE-X19 against inotuzumab (probabilistic ICER = £82,321) in the overall population. A full incremental analysis could be provided if the HRs in the MAIC were assumed transportable to the ZUMA-3 population, but the company did not present ICERs using this approach; the ERG believes that these results would be informative to the NICE Appraisal Committee.

Table 12: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph- subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,380
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £18,108 and £34,753 respectively.							
ERG exploratory analysis 1: Correcting programming and implementation errors in the company's economic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.54	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,566
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £17,797 and £32,460 respectively.							
ERG exploratory analysis 2: Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population							
Blinatumomab	5.07	[redacted]	[redacted]				
KTE-X19	14.03	[redacted]	[redacted]	8.96	[redacted]	[redacted]	£31,690
ERG exploratory analysis 3: Not applicable as ponatinib is not used for the Ph- subgroup							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£40,717
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £24,209 and £40,473 respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]				ED
Inotuzumab	5.46	[redacted]	[redacted]				
KTE-X19	10.06	[redacted]	[redacted]	7.39	[redacted]	[redacted]	£43,829
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £21,649 and £42,046 respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£39,021
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £19,357 and £37,322 respectively.							
ERG exploratory analysis 7: Exploring different cost assumptions for VOD and KTE-X19 and QALY loss assumptions associated with VOD							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£37,168
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £21,747 and £35,554 respectively.							
ERG exploratory analysis 8: Removing costs of AE management for blinatumomab and FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,827
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £18,009 and £34,881 respectively.							
ERG exploratory analysis 9: Using the tariff associated with delivering KTE-X19 infusion							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]	2.45	[redacted]	[redacted]	£41,457
Inotuzumab	7.52	[redacted]	[redacted]				ED
KTE-X19	14.08	[redacted]	[redacted]	8.08	[redacted]	[redacted]	£50,681
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £36,578 and £48,443 respectively.							
ERG exploratory analysis 10: Assuming maximum of 2 cycles for FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£37,184
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £17,627 and £34,338 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 4-10) – deterministic results							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£70,121
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.06	[redacted]	[redacted]	5.67	[redacted]	[redacted]	£70,689
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £58,132 and £70,545 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 4-10) – probabilistic results							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.42	[redacted]	[redacted]				ED
Inotuzumab	5.49	[redacted]	[redacted]				
KTE-X19	10.06	[redacted]	[redacted]	7.30	[redacted]	[redacted]	£71,638
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £58,454 and £71,382 respectively.							
ERG scenario analysis 1 (combining ERG preferred naïve comparison + allowing for vial sharing)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£59,777
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.06	[redacted]	[redacted]	5.67	[redacted]	[redacted]	£73,796
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £66,590 and £70,247 respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate, VOD - veno-occlusive disease

Table 13: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph+ subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic)							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£33,972
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,396 and £29,508 respectively.							
ERG exploratory analysis 1: Correcting programming and implementation errors in the company's economic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.54	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,052
ICERs of KTE-X19 versus inotuzumab and ponatinib are £15,974 and £29,681 respectively.							
ERG exploratory analysis 2: Not applicable as blinatumomab is not used for the Ph+ subgroup							
ERG exploratory analysis 3: Using Gompertz curve to fit ponatinib OS data							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.99	[redacted]	[redacted]				ED

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.89	[redacted]	[redacted]	11.33	[redacted]	[redacted]	£33,926
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,363 and £30,457 respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£37,958
ICERs of KTE-X19 versus inotuzumab and ponatinib are £21,811 and £34,183 respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.17	[redacted]	[redacted]				ED
Inotuzumab	5.46	[redacted]	[redacted]				
KTE-X19	10.62	[redacted]	[redacted]	7.95	[redacted]	[redacted]	£40,927
ICERs of KTE-X19 versus inotuzumab and ponatinib are £19,615 and £35,467 respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£36,440
ICERs of KTE-X19 versus inotuzumab and ponatinib are £17,534 and £31,613 respectively.							
ERG exploratory analysis 7: Exploring different cost assumptions for VOD and KTE-X19 and QALY loss assumptions associated with VOD							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,706
ICERs of KTE-X19 versus inotuzumab and ponatinib are £19,667 and £30,183 respectively.							
ERG exploratory analysis 8: Removing costs of AE management for FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,396
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,318 and £29,445 respectively.							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ERG exploratory analysis 9: Using the tariff associated with delivering KTE-X19 infusion							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£45,210
ICERs of KTE-X19 versus inotuzumab and ponatinib are £33,000 and £42,943 respectively.							
ERG exploratory analysis 10: Assuming maximum of 2 cycles for FLAG-IDA and no chemotherapy with ponatinib							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]	2.09	[redacted]	[redacted]	£23,919
Inotuzumab	7.52	[redacted]	[redacted]				ED
KTE-X19	14.87	[redacted]	[redacted]	9.22	[redacted]	[redacted]	£36,818
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £15,946 and £34,709 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 3-10) – deterministic results							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.39	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£31,687
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.64	[redacted]	[redacted]	6.24	[redacted]	[redacted]	£73,316
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £51,962 and £65,494 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 3-10) – probabilistic results							
FLAG-IDA	2.72	[redacted]	[redacted]	-	-	-	
Ponatinib	4.51	[redacted]	[redacted]	1.78	[redacted]	[redacted]	£30,418
Inotuzumab	5.50	[redacted]	[redacted]				ED
KTE-X19	10.67	[redacted]	[redacted]	6.16	[redacted]	[redacted]	£74,576
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £52,348 and £65,936 respectively.							
ERG scenario analysis 1 (combining ERG preferred naïve comparison + allowing for vial sharing)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.39	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£33,815
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.64	[redacted]	[redacted]	6.24	[redacted]	[redacted]	£72,647
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £59,726 and £65,350 respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate, VOD - veno-occlusive disease

Table 14: Results of the ERG's deterministic MAIC exploratory analyses – overall population

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
KTE-X19	14.96	[redacted]	[redacted]	11.41	[redacted]	[redacted]	£34,378
ERG preferred analyses (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
KTE-X19	10.69	[redacted]	[redacted]	8.02	[redacted]	[redacted]	£65,857
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
KTE-X19	10.89	[redacted]	[redacted]	7.33	[redacted]	[redacted]	£52,380
ERG preferred analyses – MAIC-adjusted ZUMA-3 to FLAG-IDA population (deterministic results)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
KTE-X19	7.87	[redacted]	[redacted]	5.19	[redacted]	[redacted]	£100,143
ERG preferred analyses – MAIC-adjusted ZUMA-3 to FLAG-IDA population (probabilistic results)							
FLAG-IDA	2.75	[redacted]	[redacted]	-	-	-	
KTE-X19	7.92	[redacted]	[redacted]	5.18	[redacted]	[redacted]	£100,982
Company base case (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	7.52	[redacted]	[redacted]	-	-	-	
KTE-X19	14.96	[redacted]	[redacted]	7.44	[redacted]	[redacted]	£17,203
ERG preferred analyses (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	5.47	[redacted]	[redacted]	-	-	-	
KTE-X19	10.69	[redacted]	[redacted]	5.22	[redacted]	[redacted]	£52,637
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population							
Inotuzumab	7.52	[redacted]	[redacted]	-	-	-	
KTE-X19	12.09	[redacted]	[redacted]	4.56	[redacted]	[redacted]	£27,097
ERG preferred analyses – MAIC-adjusted ZUMA-3 to inotuzumab population (deterministic results)							
Inotuzumab	5.47	[redacted]	[redacted]	-	-	-	
KTE-X19	8.70	[redacted]	[redacted]	3.23	[redacted]	[redacted]	£81,978
ERG preferred analyses – MAIC-adjusted ZUMA-3 to inotuzumab population (probabilistic results)							
Inotuzumab	5.51	[redacted]	[redacted]	-	-	-	
KTE-X19	8.77	[redacted]	[redacted]	3.25	[redacted]	[redacted]	£82,321

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Section B.1.3 of the company submission (CS)[1] contains an accurate overview of acute lymphoblastic leukaemia (ALL). ALL is a haematological malignancy which is characterised by a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites.[2] The incidence of ALL is bimodal with a peak occurring in childhood and a second peak occurring at approximately 50 years of age.[3] Patients with ALL often presents with non-specific symptoms, which include a combination of constitutional symptoms and signs of bone marrow failure (anaemia, leukopenia and thrombocytopenia).[2] The severity of symptoms can develop rapidly with diagnosis commonly made following an emergency admission.[4]

In adults, 82% of incident ALL cases are reported by the company to have developed from progenitors of the B-cell lineage, and of these 87% are B-precursor cell ALL. Such patients have fever, weight loss, night sweats, propensity to bruise or bleed, fatigue, weakness, dyspnoea, bone/joint pain, dizziness and frequent infection.[5] Within the precursor B-cell ALL group, the company estimates that almost half (49%) will relapse or become refractory to treatment (Figure 3 of the CS).

Adult patients with ALL can be categorised by the presence, or not, of the Philadelphia chromosome. Patients with the chromosome are denoted as being Philadelphia-chromosome-positive (Ph+) and those without are denoted as being Philadelphia-chromosome-negative (Ph-). Historically, the prognosis for Ph+ patients has been poor, and remains so despite the development of targeted treatments.[6]

Without treatment ALL can result in death within a few weeks or months.[7] With treatment, survival appears conditional on age at diagnosis. Data from the Surveillance, Epidemiology, and End Results Program in the USA indicate that the 5-year survival was 81% for those diagnosed below the age of 45 years, steadily decreasing to 11% for patients aged 75 years and over.[8] In the UK, there is an estimated 40% survival rate for new cases of ALL in patients aged 25 to 64 years, with an estimated 15% survival in those aged 65 years and over.[9] Overall prognosis for ALL in adults is poor with less than 40% of patients with ALL estimated to achieve long-term remission[10] and with median survival for relapsed/refractory (R/R) patients likely to be less than one year based on studies of blinatumomab and inotuzumab.[11, 12]

Allogeneic stem cell transplant (allo-SCT) is a potential option for patients, although the majority of patients do not receive this option due to factors including donor availability, remission status, depth of remission and comorbidities. Autologous stem cell transplant has been used historically but has not been shown to be as effective as allo-SCT when this is an option.[13] An estimated 5 to 30% of adults

with R/R ALL are eligible for allo-SCT,[14] although this proportion has increased with the introduction of newer treatments that provide greater clinical benefits and allow a bridge to transplant. The risks of death following allo-SCT are high with a reported survival at five years for adults with R/R ALL following sibling allograft of 23%.[15] Following relapse after SCT, survival at five years is estimated to be 8% with a median survival time of less than six months.[16] Clinical experts providing advice to the company stated that second allo-SCTs are not perceived to be a viable treatment option. Morbidity following allo-SCT is also frequent, with a common complication being chronic graft versus host disease (GvHD), which is estimated to be 43% five years after transplant.

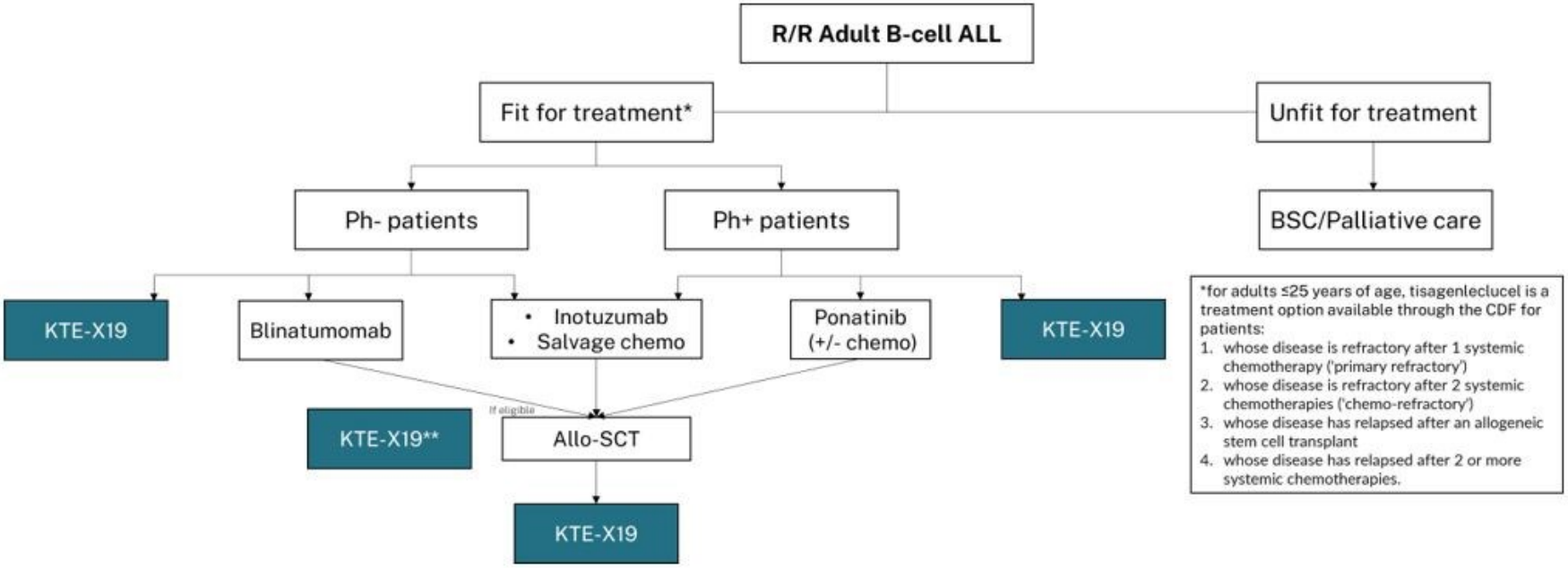
2.2 Critique of company's overview of current service provision

The primary goal of current treatments for ALL is to extend survival with a good quality of life. Correlated with survival is the level of observed treatment response which include complete remission (CR), complete remission with incomplete haematological recovery (CRi) and minimal residual disease negativity (MRD-).

The European Society for Medical Oncology (ESMO) produced guidelines for ALL treatment in 2016, although this was before the European approval of inotuzumab whilst the approval for blinatumomab occurred during the development of the ESMO guidance and it was classified as '*under investigation*'. NICE has published more recent guidance related to the treatment pathway for R/R adult B-cell ALL which includes newer treatment options. The company adapted this pathway in the CS (see Figure 1) and included the proposed positioning of KTE-X19. As shown in the figure, the treatments provided are dependent on whether a patient has Ph+ or Ph- disease. More than one line of therapy can be received from the technologies indicated for patients fit for treatment if they failed to respond. However, when a patient becomes unfit for treatment, they can only receive best supportive (palliative) care.

Allo-SCT is reserved for eligible patients as a consolidation treatment following complete remission with blinatumomab, inotuzumab, ponatinib, or salvage chemotherapy. After allo-SCT, patients may be cured or relapse and require further treatment.

Figure 1: Company's representation of the NICE treatment pathway for R/R adult B-cell ALL and proposed position of KTE-X19 (reproduced from Figure 7 of the CS)



Key: ALL, Acute lymphoblastic leukaemia; BSC, best supportive care; CDF, cancer drug fund; Chemo, chemotherapy; Ph, Philadelphia chromosome; R/R, relapsed/refractory; SCT, stem cell transplant.
Notes: **where ineligible for stem cell transplant.

Blinatumomab is recommended for R/R Ph- precursor B-cell ALL in adults, whereas ponatinib, with or without chemotherapy, is recommended for R/R Ph+ precursor B-cell ALL in adults when the disease is resistant to dasatinib, or dasatinib cannot be tolerated and where imatinib is not clinically appropriate, or the T315l gene mutation is present. The ERG notes that NICE was unable to make a recommendation on dasatinib for Ph+ ALL as the company did not provide an evidence submission (TA714). Inotuzumab is recommended for R/R CD22-positive precursor B-cell ALL in adults, additionally, people with R/R Ph+ should have had received at least one tyrosine kinase inhibitor (TKI). The NICE recommendations for blinatumomab, ponatinib and inotuzumab are each subject to the companies providing these products according to confidential Patient Access Scheme (PAS) discounts.

Tisagenlecleucel, which is also subject to a confidential discounted price, is recommended by NICE for use within the Cancer Drugs Fund; as such, this would not be considered a comparator for this STA following NICE guidelines for company submissions.[17]

The company proposes that its product, autologous anti-CD19-transduced CD3+ cells, (henceforth referred to as KTE-X19 for brevity) should be positioned for use in adults with R/R B-precursor ALL who: have relapsed following allo-SCT; are ineligible for SCT; or who are unlikely to achieve SCT via existing bridging therapies. The company states that these criteria are consistent with the inclusion criteria for the ZUMA-3 study.[18, 19]

2.3 Company's definition of the decision problem

A summary of the company's adherence to the decision problem set out in the NICE scope is provided in

Table 15. The ERG's critique of the company's deviations from the NICE scope are discussed in Section 4.3.

Table 15: Decision problem (adapted from Table 1 of the CS)

	Scope issued by NICE	Decision problem addressed in the company submission	Company's rationale if different from the final NICE scope
Population	Adults with relapsed or refractory B-precursor acute lymphoblastic leukaemia	As final scope	-
Intervention	KTE-X19	KTE-X19	-
Comparators	•Ph- ALL Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy Inotuzumab Blinatumomab •Ph+ ALL Inotuzumab A TKI (such as imatinib, dasatinib, or ponatinib) alone or in combination with FLAG-based chemotherapy best supportive care	•Ph- ALL Fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy Inotuzumab Blinatumomab •Ph+ ALL Inotuzumab Ponatinib + FLAG plus idarubicin (FLAG-IDA) FLAG-IDA	Clinical advice received by the company states that imatinib is used as the first-line TKI for Ph+ patients and would not be used for R/R patients. Dasatinib has no recommendation from NICE in ALL as the company did not make a submission Clinical advice received by the company states that ponatinib would be used in combination with chemotherapy in the UK KTE-X19 would only be used in people who are able to tolerate chemotherapy and therefore best supportive care is not a comparator
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including relapse-free and event-free survival) • treatment response rate (including minimal residual disease, haematologic responses and complete remission) • rate of allo-SCT • adverse effects of treatment • health-related quality of life	As final scope	

2.3.1 Population

The patient population considered in the CS is adults with R/R B-precursor ALL (hereafter referred to as R/R ALL), for whom SCT is not indicated due to relapse after a prior SCT, who are ineligible to

receive SCT or who are unlikely to be able to receive SCT with existing bridging therapies. The company provided estimated incremental cost-effectiveness ratios (ICERs) expressed in cost per quality-adjusted life-years gained (QALYs) for an overall population, and separately for patients who are Ph+ and those that are Ph-.

2.3.2 Intervention

The intervention is KTE-X19 which is a second-generation, chimeric antigen receptor (CAR) T-cell (CAR-T) therapy. KTE-X19 is manufactured from a patient's own T-cells and when returned to the patient are designed to target CD19-expressing tumour cells. KTE-X19 treatment consists of this single infusion. Leukapheresis, conditioning chemotherapy, and bridging chemotherapy are used prior to one off infusion with KTE-X19. The company states that T-cell enrichment and activation occur within the manufacturing process. This process is stated to eliminate '*the risk of premature activation and exhaustion of CAR T-cells during the ex-vivo expansion step of the manufacturing process (which can occur if tumour cells are present in the leukapheresis product).*' KTE-X19 is provided as cells dispersion for intravenous (IV) infusion. The company anticipates that the approved dose for adults with R/R B-precursor ALL is 1 million anti-CD19 CAR T-cells per kg of body weight. Conditioning chemotherapy would be provided to patients receiving KTE-X19 which includes fludarabine, at 25mg/m^2, administered IV over 30 minutes on each of the fourth, third and second day prior to KTE-X19 treatment and cyclophosphamide, at 900mg/m^2, two days before KTE-X19 treatment. One hour before KTE-X19 infusion paracetamol (500 – 1000mg) and diphenhydramine (12.5 - 25mg) IV or oral is recommended. The most common adverse events (AEs) reported as Grade 2 or greater were pyrexia, hypotension and anaemia, as shown in Table 30 of the CS. Two patients experienced fatal Grade 5 KTE-X19 related AEs: brain herniation and septic shock.[19]

The company anticipates that the marketing authorisation in adult ALL will be that KTE-X19 is [redacted]. An application for a Type II variation to the marketing authorisation was submitted to the EMA on the [redacted] and is currently ongoing. The company anticipates that a positive opinion from the Committee for Medicinal Products for Human Use will occur in [redacted] and that regulatory approval will occur in [redacted].

The list price for an infusion of KTE-X19 is £316,118 although a PAS has been approved which reduces the list price by [redacted], resulting in a discounted price of [redacted]. When additional costs relating to leukapheresis, bridging therapy, conditioning therapy and administration are considered the company estimate a total cost of [redacted].

2.3.3 Comparators

The comparators chosen by the company depend on whether a patient is Ph+ or Ph-. For patients who are Ph+, ponatinib plus FLAG-I DA, inotuzumab, and FLAG-IDA were the stated comparators in the NICE scope. For patients who are Ph-, blinatumomab, inotuzumab, and FLAG-IDA were the stated comparators in the NICE scope. The company also performed analyses for the overall population using inotuzumab and FLAG-IDA as comparators.

Clinical advice to the ERG stated that some of the comparators are not similar in their indication. For instance, blinatumomab is reserved for chemo-responsive cases where it can be a bridging therapy to allo-SCT as it has high response rates for those cases with low disease burden. In contrast, inotuzumab efficacy is unlikely to depend on disease burden, although efficacy is improved in patients with high CD22 protein expression.

The ERG also notes that imatinib can be used as a subsequent treatment for patients who cannot tolerate dasatinib, and that ponatinib is only used if imatinib is not clinically appropriate.[20] The ERG notes that NICE was unable to make a recommendation on dasatinib for Ph+ ALL as the company did not provide an evidence submission (TA714).

Inotuzumab is administered IV at a dose of 0.8mg/m^2 on day 1, 0.5 mg/m^2 on day 8 and day 15 in cycle 1 (21-day cycle). From cycle 2 onwards (28-day cycles) it is administered 0.8mg/m^2 or 0.5mg/m^2 on day 1, 0.5mg/m^2 on day 8 and day 15. Treatment may continue up to 6 cycles. Blinatumomab is administered IV at a dose of 9µg/day during week 1 of cycle 1 then 28µg/day for the remainder of the cycle and during subsequent cycles (28-day cycles) followed by a treatment-free interval of 2 weeks. Ponatinib is administered orally at a daily dose of 45 mg/day. FLAG-IDA consists of four components: fludarabine (30mg/m^2 for five consecutive days per 28-day cycle); cytarabine (2g/m^2 for six consecutive days per 28-day cycle); filgrastim (0.005mg/kg for 9 days); and idarubicin (8mg/m^2 for 3 days), The company states that there would be a maximum of four 28-day cycles.

The list prices of the comparators are: inotuzumab £8048 per 1mg of powder for concentrate for solution for infusion; blinatumomab £2017 per 38.5 µg vial (of which 28 µg is useable); ponatinib £5050 for a pack of 30 45mg tablets; and FLAG-IDA which is estimated by the company to have a cost per treatment cycle of £3642. Confidential discounts have been agreed for inotuzumab, blinatumomab and ponatinib.

2.3.4 Outcomes

The outcomes reported in the CS match those in the final scope.

2.3.5 Subgroups

The NICE scope did not specify subgroups but the company has provided ICERs for a population who are Ph+ and those that are Ph-, in addition to the overall population due to the different treatment options recommended for these groups, as shown in Figure 1. The ERG believes that this is appropriate.

2.3.6 Special considerations

The NICE scope did not list any special considerations including issues related to equity or equality that should be explored. The company did not claim that special considerations were relevant to this Single Technology Appraisal.

3 CLINICAL EFFECTIVENESS

This section presents a review of the clinical evidence reported in the CS for KTE-X19 for treating adults with R/R ALL.

3.1 Critique of the methods of review(s)

The clinical evidence provided in the CS was informed by a systematic literature review (SLR) of studies assessing the clinical efficacy and safety of KTE-X19 in adult patients with R/R ALL (CS Appendix D). The primary clinical evidence provided in the CS was informed by the Phase 1 and 2 of a single-arm, multi-centre study, ZUMA-3.[18, 19] Eight publications relating to this study were identified by the SLR (CS, Appendix D, Table 96). Unanchored matching-adjusted indirect comparisons (MAIC) were conducted to estimate the relative efficacy of KTE-X19. These used ZUMA-3, two multi-centre randomised controlled trials (RCTs) of blinatumomab (TOWER, 8 publications) and inotuzumab (INO-VATE, 11 publications). Data from two additional studies – PACE and SCHOLAR-3 – were also included in an additional, naïve indirect comparison (CS, section B.2.9.1). The PACE study data were published,[21] but the SCHOLAR-3 data are unpublished.

Safety evidence in the CS comprises a narrative synthesis of data from the ZUMA-3 study (CS, Sections B.2.10.2-6), which is also compared narratively with this evidence from the TOWER and INO-VATE RCTs (CS, Section B.2.10.6).

3.1.1 Searches

The company performed an initial SLR in June 2019 followed by a revised and up-to-date search in September 2021 to identify all clinical effectiveness and safety studies of KTE-X19 or comparator treatments of adult patients who have R/R ALL. The company's revised and updated search superseded the initial systematic literature searches (with population concept terms broadened and no date restrictions applied).

The company searched all the relevant electronic bibliographic databases in September 2021 (Appendix D.1.1 Identification and selection of relevant studies): MEDLINE [via Embase.com], PubMED-not-MEDLINE [via Embase.com], Embase [via Embase.com], Cochrane Database of Systematic Reviews [via Wiley], Cochrane Central Register of Controlled Trials [via Wiley], Database of Abstracts of Reviews of Effects [via the centre for reviews and dissemination (CRD)], NHS Economic Evaluation Database [via CRD] and Health Technology Assessment database [via CRD].

In the revised search, the company switched host platforms from ProQuest to Embase.com. The latter allows MEDLINE, PubMed-not-MEDLINE and Embase to be searched simultaneously. It should be

noted that the controlled vocabulary/index terms in MEDLINE and Embase are not identical and that by contrast to MEDLINE, Embase has more indexing terms attached to records. The company has included both MeSH and Emtree terminology in the ProQuest search strategy and by contrast, the company have only included the Emtree terminology (from the ProQuest search) in the Embase.com search which will automatically include all of MeSH terms because the MeSH terms are mapped to Emtree terms.

The company searched several key conference abstract websites in September 2021 covering the last five years (2016-2021): American Society of Clinical Oncology; American Society of Hematology; European Society of Medical Oncology (ESMO); European Hematology Association; and International Society for Pharmacoeconomics and Outcomes Research. The terms applied and numbers retrieved in the search were fully reported.

The company searched three clinical trials registries in September 2021: clinicaltrials.gov; the EU Clinical Trials Register: and the World Health Organization International Clinical Trials Registry Platform. The terms applied and numbers retrieved in the search were fully reported.

Overall, the ERG considers that the company's search was comprehensive and that there are no consequential errors identified. Minor suggestions on the reporting include:

- Database searches table (CS Appendix D, Table 94) to provide inception dates of the databases (MEDLINE, PubMed-not-MEDLINE and Embase) as the record numbers retrieved per statement suggests that ProQuest has a greater coverage compared to Embase.com.
- Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart (CS Appendix D, Figure 60)
    - suggests that 4102 records from the various conference proceedings sources were searched in addition to the database search (10,806) and it was unclear how this was screened.
    - to include values from the clinical trials registry search.

The search results are reported in CS Appendix D.1.1, and the PRISMA flowchart (Figure 60 in the CS). The final numbers in the original report contained an error; the company provided an updated PRISMA flowchart with the correct numbers (clarification response[22], A15 and Figure 4). Only eight publications satisfied the inclusion criteria for KTE-X19 (Appendix D.1.1 Table 96), and all publications related to the ZUMA-3 study.[18, 19, 23-28] The ERG does not believe that any relevant KTE-X19 studies have been missed.

3.1.2 Inclusion criteria

The inclusion and exclusion criteria for the systematic review reported by the company are reproduced in Table 16 and are slightly more limited than the NICE scope due to the exclusion of two TKIs: imatinib and dasatinib. The rationale stated by the company was that these therapies either would not be used in a R/R population as it was used as a first-line treatment in Ph+ (imatinib) or are not currently reimbursed in the UK (dasatinib). ZUMA-3 was anticipated to be the only study meeting the inclusion criteria in the NICE scope in terms of evaluating KTE-X19. The company therefore undertook a review of randomised and non-randomised studies in adults with R/R ALL. There was no study directly comparing KTE-X19 with other relevant therapies, for example, FLAG-based chemotherapy, blinatumomab, or inotuzumab. For this reason, the inclusion criteria included relevant comparators so that indirect comparisons with these strategies could be performed. The SLR inclusion criteria included the key effectiveness outcomes from the final NICE scope: overall survival (OS), relapse-free survival (RFS), remission rates, minimal residual disease (MRD), rate of allo-SCT; as well as health-related quality of life (HRQoL) and safety outcomes (CS, Section B.1.1 and Table 1).

Table 16: The inclusion and exclusion criteria for the SLR (reproduced from CS, Appendix D, Table 95)

PICOS	Inclusion criteria	Exclusion criteria
Population	R/R B-precursor ALL in adults* defined as one of the following: • Primary refractory disease • First relapse if first remission ≤ 12 months • Relapsed or refractory disease after 2 or more lines of systemic therapy • Relapsed or refractory disease after allogeneic transplant provided individuals are at least 100 days from stem-cell transplant at the time of enrolment	• B-cell precursor ALL that is not R/R • Burkitt leukaemia or lymphoma • Non-human • Other indications not included under inclusion criteria • Biomarker/genetic studies • Paediatric patients • Prior CAR-T cell therapy or other genetically modified T-cell therapy
Intervention	• KTE-X19 • See comparators	• Interventions not included under inclusion criteria
Comparator	• CAR-T cell therapy Tisagenlecleucel (Kymriah®) • Dasatinib ± corticosteroids • Imatinib ± corticosteroids • Ponatinib ± corticosteroids • Nilotinib ± corticosteroids • Bosutinib ± chemotherapy • Dasatinib ± chemotherapy • Imatinib ± chemotherapy • Ponatinib ± chemotherapy • Nilotinib ± chemotherapy • Bosutinib ± chemotherapy	• Comparators not included under inclusion criteria • Studies that investigated SCT only

	Monoclonal antibodies: • Blinatumomab • Cytarabine regimens • Clofaribine regimens • Alkylating agents • MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone with rituximab for CD20-positive disease) • Inotuzumab ozogamicin	
Outcomes†	• Progression-free survival (PFS) • Remission rates • Overall response rate (ORR) • Partial response (PR) • Stable disease (SD) • Progressed disease (PD) • Overall survival (OS) • Allogeneic stem-cell transplant rate • Relapse-free survival (RFS) • Duration of response • Duration of remission (DOR) • Minimal Residual Disease • Discontinuation rates o Reason for discontinuation o Discontinuation due to AEs	• Outcomes not reported under inclusion criteria
Study Design	• Clinical trials • Observational studies	• Any study design not described under inclusion criteria
Publication Type	• Full-text articles	• Notes** • Errata** • Comments** • Editorials** • Review articles***
Language	• Publications in English	• Publications in any language other than English

ALL - acute lymphoblastic leukaemia, SCT - stem cell transplant, AE - adverse event

*Age ≤ 18 years and weight ≥ 6 kg at the time of assent or consent per IRB guidelines. **Notes, errata, comments, editorials were checked for corrections of previous published data, only in case of any corrections of relevant data, these will be included in the review. ***Reviews and network meta-analyses were checked for bibliographic references ONLY and were not extracted. † The CS, Table 95 reported outcomes only in terms of 'response'; certain instances have been revised to the term 'remission', as this was the outcome being reported in for the ZUMA-3 study.

3.1.3 Study selection

Appendix D.1.1 of the CS reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers. No details were provided on what happened in the event of disagreements, but this was clarified in the company response to clarification question A14. The ERG considers independent study selection by two or more reviewers to be best practice in systematic reviewing.

3.1.4 Data extraction

Details regarding the company's data extraction methods are reported in Appendix D.1.1 of the CS. Data were extracted from ZUMA-3 and reported in the CS (Section B.2.3, Appendix D.1.2 and Appendix E). The CS reports that one reviewer extracted data and a quality check of data extracted was performed by a second reviewer. This is an accepted and appropriate strategy, although the nature and proportion of data checked were not reported.

3.1.5 Quality assessment

The CS reports inconsistently that the quality assessment of the ZUMA-3 study was undertaken both by a single reviewer (CS, Appendix D.1.1, p.64) and by two independent reviewers (CS, Appendix D.1.3). The appraisal was conducted using the Downs and Black checklist[29] for non-randomised studies (CS, Appendix D.1.3 Table 102). The ERG considers this an appropriate but non-validated tool for assessing the quality of non-randomised studies. The ERG considers that whilst the key aspects of quality to be considered outlined in the Downs and Black checklist are appropriate for the quality assessment of cohort studies, the application of a validated high-quality assessment instrument such as the Cochrane ROBINS-I tool[30] would have allowed a more focused and robust assessment of the potential risk of bias in the ZUMA-3 study.

The CS reported a single assessment of the ZUMA-3 study, although the two phases recruited different participants, not all participants were exposed to the same dose of KTE-X19 across both phases, and the primary outcome was different for each phase (Table 17). The ERG agrees with the company's responses to most of the checklist's quality assessment criteria. However, the criteria related to probability values and power were judged differently because these were not provided or assessed for the primary outcome, dose-limiting toxicity (DLT), in Phase 1. Overall, this was assessed by the ERG to be a moderate-quality non-randomised study.

Table 17: Quality assessment of the ZUMA-3 study with the ERG critique

Description of criteria	CS	ERG Phase 1[18]	ERG Phase 2[19]
Internal validity			
Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes p.12	Yes Abstract and Methods
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes pp.12-13	Yes p.493
Are the characteristics of the patients included in the study clearly described?	Yes	Yes Inclusion/exclusion criteria p.12, and p.13, Table 1: Baseline characteristics	Yes Inclusion/exclusion criteria p.493, and p.494, Table 1: Baseline characteristics
Are the interventions of interest	Yes	Yes	Yes

clearly described?		p.12	p.493
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N/A	N/A	N/A p.495: "subgroup analysis was based on baseline disease and treatment covariates were done for selected endpoints"
Are the main findings of the study clearly described?	Yes	Yes pp.13-16, and Tables 2 and 3	Yes pp.495-496, and Table 2
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes pp.15-16	Yes pp.495-496, and Table 2
Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes	Yes
Have the characteristics of patients lost to follow-up been described?	No	No 1 lost to follow-up but details not provided, p.16	UTD Appears to be no-one lost to follow-up
Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	No Not applicable to safety data and no p values reported in Shah 2021b (appendices not provided)	Yes p.495 and Figure 4
External validity			
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	UTD	UTD: No details	UTD: No details
Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	UTD	UTD: No details	UTD: No details
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	UTD	UTD: No details	UTD: No details
Internal validity (bias)			
Was an attempt made to blind study subjects to the intervention they have received?	No	No	No
Was an attempt made to blind those measuring the main outcomes of the intervention?	No	No	No
If any of the results of the study were based on "data dredging", was this made clear?	Yes	UTD	UTD No reference to this in the report, but no evidence of data dredging (all outcomes listed in protocol)
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control	Yes	Yes Median data reported	Yes p.497 and Figure 3

studies, is the time period between the intervention and outcome the same for cases and controls?			
Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes p.12	Yes p.495
Was compliance with the intervention/s reliable?	Yes	Yes Data on patients not receiving treatment reported and explained, p.13	Yes Data on patients not receiving treatment reported and explained, e.g. Fig 1
Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes Also, central and investigator assessments
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N/A	N/A	N/A
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	N/A	N/A	N/A
Were study subjects randomised to intervention groups?	N/A	N/A	N/A
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N/A	N/A	N/A
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	No	No	No Subgroup analyses were performed: pp.495-96 and Figure 2
Were losses of patients to follow-up taken into account?	Yes	Yes Full safety analysis set and ITT analysis	Yes ITT (no losses reported); mITT had only 1 loss
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance?	Yes	UTD No power calculation performed for primary safety outcomes	Yes p.495 (for the CR and CRi primary outcome)

CR: Complete remission; CRi: Complete remission with incomplete haematological recovery; CS: Company submission; ERG: Evidence Review Group; ITT: Intention to treat; N/A: Not applicable; UTD, unable to determine

3.2 Included study of KTE-X19 (ZUMA-3)

The clinical SLR presented in the CS identified one study of KTE-X19 which was relevant to the decision problem: ZUMA-3 (NCT02614066). This formed the key evidence for clinical effectiveness and safety of KTE-X19 within the CS. Eight publications were identified and listed for this study (CS, Appendix D Table 96). The ERG believes that no relevant published studies of KTE-X19 that could

have provided data on safety and efficacy in R/R ALL population have been omitted from the CS. There were two main publications reporting detailed efficacy data, one for Phase 1,[18] and the other for Phase 2.[19]

3.2.1 Study design of ZUMA-3

ZUMA-3 is a non-randomised, international, multi-centre, open-label, ongoing single-arm study initiated in March 2016 and conducted in 32 centres across five countries (USA, Canada, France, Netherlands, and Germany). No data were available from the UK. The primary completion date was September 2020, but the final completion date is listed as 2034 (NCT02614066). Overall, 125 adults with R/R ALL were enrolled in the ZUMA-3 study.

The study had two phases. In Phase 1, 54 subjects with high or low disease burden for R/R ALL were enrolled to evaluate the safety and efficacy of KTE-X19, with the primary outcome being DLT. A Safety Review Team (SRT) reviewed safety data and made recommendations regarding further enrolment in Phase 1 or proceeding to Phase 2 based on the incidence of DLTs and overall safety profile of KTE-X19. On the basis of the results from 41 participants followed for at least 2 months, the SRT recommended initiating the Phase 2 portion of the study at the target dose of $1x10^6$ anti-CD19 CAR+ T-cells/kg dose (hereafter referred to as the target dose). Phase 2 was designed to evaluate the efficacy and safety of KTE-X19 at the target dose. In Phase 2, a different cohort of 71 adult patients with R/R ALL who met the criteria listed in Table 16 were enrolled, of which 55 patients received KTE-X19 infusion.

Overall, the ZUMA-3 study enrolled 99 patients for evaluating the safety and efficacy of KTE-X19 at the target dose; 28 at Phase 1, and 71 at Phase 2.

R/R ALL was defined as one of the following:

- First relapse following a remission lasting ≤12 months
- R/R after second-line or higher therapy
- R/R after allo-SCT (provided the transplant occurred ≥100 days prior to enrolment and that no immunosuppressive medications were taken ≤4 weeks prior to enrolment)

Details of study location, treatments, inclusion and exclusion criteria, prohibited concomitant medications and relevant outcomes are reported in Table 18.

Table 18: Summary of methodology for ZUMA-3 (reproduced from Table 6 of the CS)

Trial number (acronym)	NCT02614066 (ZUMA-3)
Location	This study was conducted at a total of 32 study centres across North America (US: 21; Canada: 1), and Europe (France: 4; Germany: 3; Netherlands: 3)
Trial design	ZUMA-3 is a Phase 1/2, multicentre, open-label study evaluating the safety and efficacy of KTE-X19 in adult subjects with R/R B-ALL.
Eligibility criteria for participants	**Inclusion criteria:** 1. R/R B-ALL, defined as 1 of the following: • Primary refractory disease • First relapse if first remission was ≤12 months • R/R disease after 2+ lines of systemic therapy • R/R disease after allo-SCT provided subject was at least 100 days from transplant at time of enrolment and off of immunosuppressive medications for at least 4 weeks prior to enrolment 2. Morphological disease in the bone marrow (>5% blasts) 3. Subjects with Ph+ disease were eligible if they were intolerant to TKI therapy or if they had R/R disease despite treatment with at least 2 different TKIs 4. Aged 18 years or older 5. ECOG performance status of 0 or 1 6. Absolute neutrophil count ≥ 500/μL unless, in the opinion of the principal investigator, cytopenia was due to underlying leukaemia and was potentially reversible with leukaemia therapy 7. Platelet count ≥ 50,000/μL unless, in the opinion of the principal investigator, cytopenia was due to underlying leukaemia and was potentially reversible with leukaemia therapy 8. Absolute lymphocyte count ≥ 100/μL 9. Adequate renal hepatic, pulmonary, and cardia function, defined as: • Creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 cc/min • Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 2.5 x upper limit of normal • Total bilirubin ≤ 1.5 mg/dL, except in subjects with Gilbert's syndrome • Left ventricular ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, no New York Heart Association class III or class IV functional classification, and no clinically significant arrhythmias • No clinically significant pleural effusion • Baseline oxygen saturation > 92% on room air 10. Females of childbearing potential must have had a negative serum or urine pregnancy test 11. In subjects previously treated with blinatumomab, CD19 tumour expression on blasts obtained from bone marrow or peripheral blood must have been documented after completion of the most recent prior line of therapy. If CD19 expression was quantified, then blasts must have been ≥ 90% $CD19^{+}$

	Exclusion criteria: 1. Diagnosis of Burkitt's leukaemia/lymphoma according to World Health Organisation classification or chronic myelogenous leukaemia lymphoid blast crisis 2. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix bladder, breast) unless disease-free for at least 3 years 3. History of severe hypersensitivity reaction to aminoglycosides or any of the agents used in this study 4. CNS abnormalities, defined as any of the following: • Presence of CNS-3 disease, defined as detectable cerebrospinal blast cells in a sample of CSF with ≥ 5 white blood cells (WBCs) per mm^3 with or without neurological changes • Presence of CNS-2 disease, defined as detectable cerebrospinal blast cells in a sample of CSF with <5 WBCs per mm^3 with neurological changes • History or presence of any CNS disorder, such as a seizure disorder, cerebrovascular ischaemia/haemorrhage, dementia, cerebellar disease, any autoimmune disease with CNS involvement, posterior reversible encephalopathy syndrome, or cerebral oedema 5. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment 6. History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment 7. Primary immunodeficiency 8. Known infection with human immunodeficiency virus, hepatitis B virus, or hepatitis C virus. A history of hepatitis B or hepatitis C was permitted if the viral load was undetectable per quantitative polymerase chain reaction and/or nucleic acid testing 9. Presence of fungal, bacterial, viral or other infection that was uncontrolled or required antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis were permitted if responding to active treatment and after consultation with the Kite medical monitor
Settings and locations where the data were collected	• Subjects were to be hospitalised for treatment with KTE-X19 and remain in the hospital for a minimum of 7 days after treatment unless otherwise required by a country's regulatory agency • Subjects were to remain hospitalised until all KTE-X19-related non-haematological toxicities had returned to Grade 1 or lower or baseline. Subjects could be discharged with noncritical toxicities that were clinically stable or slowly improving even if the event was higher than Grade 1, if deemed appropriate by the investigator • Subjects were also to remain hospitalised for ongoing KTE-X19-related fever, hypotension, hypoxia, or ongoing central neurologic toxicity if the event severity was higher than Grade 1 or deemed necessary by the treating investigator
Study periods and trial drugs	• Screening • Enrolment/leukapheresis • Bridging chemotherapy + CNS prophylaxis - Bridging therapy could be administered after leukapheresis and prior to lymphodepleting chemotherapy at the discretion of the investigator,

	and completed at least 7 day or 5 half-lives, whichever was shorter, prior to initiating lymphodepleting chemotherapy - Recommended for all subjects, particularly those subjects with high disease burden at baseline (M3 marrow [>25% leukaemic blasts] or ≥ 1,000 blasts/mm^3 in the peripheral circulation) - Permitted bridging therapies and regimens included attenuated VAD, mercaptopurine, hydroxyurea, DOMP, attenuated FLAG/FLAG-IDA, and mini-hyper CVAD. A full list can be found in the supplementary materials of Shah *et al.,* (2021b) - All subjects were to receive CSF prophylaxis, consisting of an intrathecal regimen according to institutional or national guidelines. CSF prophylaxis was to be administered any time during screening through 7 days prior to KTE-X19 infusion - Additional CSF prophylaxis could be given after the KTE-X19 infusion at the discretion of the investigator in accordance with institutional guidelines but was to be avoided for at least 8 weeks after KTE-X19 infusion, if possible • Lymphodepleting chemotherapy - Subjects were to receive a non-myeloablative lymphodepleting regimen consisting of fludarabine 25 mg/m^2/day administered IV over 30 minutes on Day -4, -3, -2, and cyclophosphamide 900 mg/m^2/day administered IV over 60 minutes on Day -2 - Prior to the initiation of lymphodepleting chemotherapy, the subject must have shown no evidence or suspicion of an infection, and no systemic antimicrobials for a known or suspected infection within 48 hours prior to initiation of lymphodepleting chemotherapy • KTE-X19 treatment - The following medications were to be administered 1 hour prior to infusion i) Acetaminophen 650 mg orally (PO) or equivalent ii) Diphenhydramine 12.5 mg administered PO, IV, or equivalent - All patients were to receive a single IV infusion of KTE-X19 after a 2-day rest period post-completion of conditioning chemotherapy - KTE-X19 was manufactured from each subject's leukapheresis material • Post-treatment assessment: beginning at Day 14 (± 2 days) and ending at Month 3 (± 2 weeks) • Long-term follow-up: starting at Month 6
Prior and concomitant medication	• Corticosteroid therapy at a pharmacologic dose (> 5 mg/day of prednisone or equivalent dose of other corticosteroids) and other immunosuppressive drugs must be avoided for 7 days prior to leukapheresis and 5 days prior to KTE-X19 infusion • Systemic corticosteroids were to be avoided as premedication in subjects for whom CT scans with contrast were contraindicated • Corticosteroids and other immunosuppressive drugs were to be avoided for 3 months after KTE-X19 infusion, unless used to manage KTE-X19-related toxicities. Other medications that could interfere with evaluation of KTE-X19, such as NSAIDs, were also to be avoided for the same time period unless medically necessary • For subjects with Ph+ ALL, all TKIs were to be stopped at least 1 week prior to KTE-X19 infusion. In subjects who achieved CR, a TKI could be resumed 2 months after KTE-X19 infusion

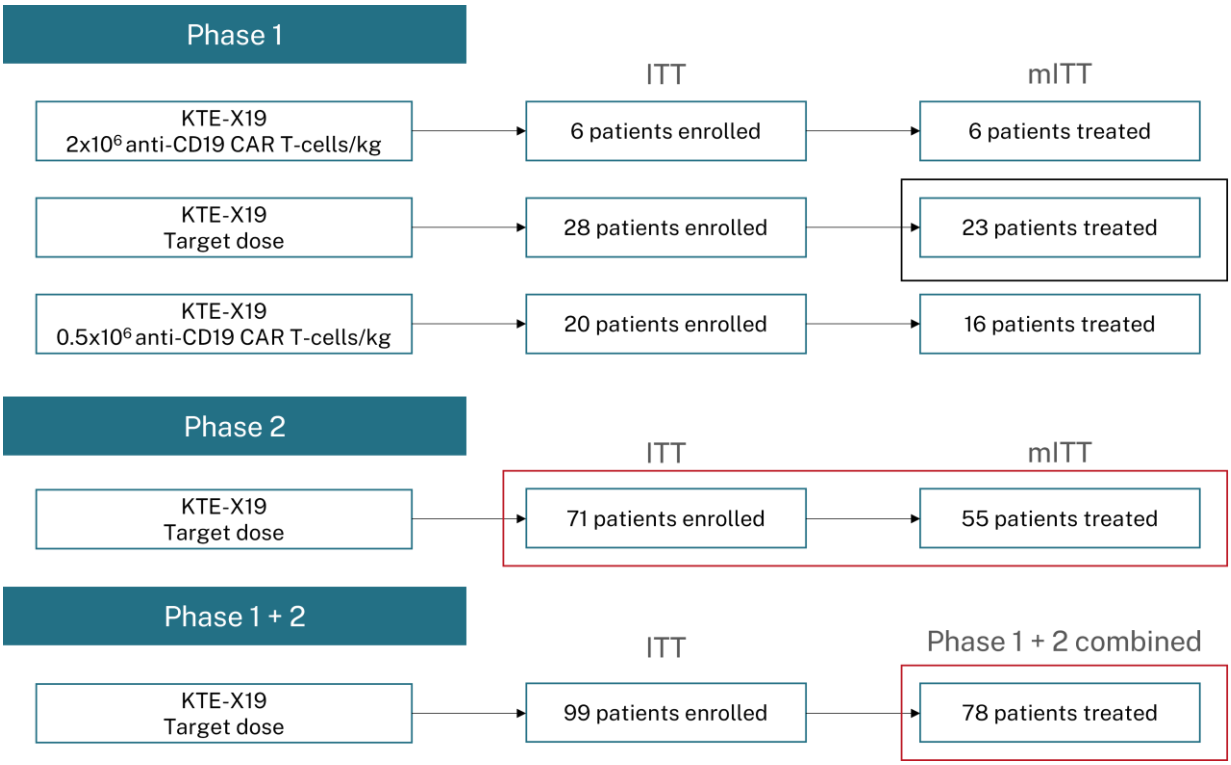
	• Investigators were allowed to prescribe concomitant medications or treatment deemed necessary to provide adequate supportive care, including growth factor support and routine antiemetic prophylaxis and treatment, except for the excluded medications listed above
Primary outcome	• Phase 1: incidence of adverse events defined as dose-limiting toxicities • Phase 2: OCR rate (CR + CRi) per independent review (hereafter referred to as central assessment)
Secondary outcomes used in the model /specified in the scope	• MRD^- rate, defined as the incidence of an MRD^- response, where MRD^- was defined as MRD < 10^{-4} per the standard assessment by flow cytometry performed by the central laboratory. • Duration of remission, defined as the time from the first CR or CRi to relapse or death from any cause in the absence of documented relapse • OCR rate per investigator assessment • Allo-SCT rate • Overall survival, defined as the time from KTE-X19 infusion date to the date of death from any cause - In the ITT population this was defined as time from enrolment to the date of death • Relapse-free survival, defined as time from KTE-X19 infusion date to the date of disease relapse or death from any cause - In the ITT population this was defined as time from enrolment to the date of disease relapse or death from any cause • Incidence of AEs • Changes over time in the EQ-5D and EQ-5D visual analogue scale
Pre-planned subgroups	• Subgroup analyses based on baseline disease and treatment covariates were conducted for selected efficacy and safety endpoints. These included: - Sex - Age - Baseline extramedullary disease - CNS status at screening - Philadelphia chromosome status - Prior lines of therapy - Prior allo-SCT - Prior blinatumomab - Prior inotuzumab - First relapse ≤ 12 months - Primary refractory - Relapsed/refractory post SCT - Relapsed/refractory after ≥2 lines of prior therapy

AE, adverse event; ALL, acute lymphoblastic leukaemia; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNS, central nervous system; CR, complete remission; CRi, complete remission with incomplete haematological recovery; CRS, cytokine release syndrome CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events DOMP, dexamethasone, 6-mercaptopurine, methotrexate, and vincristine; ECOG, Eastern Cooperative Oncology Group; FLAG-IDA, fludarabine, cytarabine, granulocyte-colony stimulating factor; GVHD, graft-versus-host disease; IL, interleukin; IV, intravenous; MRD, minimal residual disease; Ph, Philadelphia chromosome; R/R, relapsed/refractory; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor; VAD, vincristine, doxorubicin, and dexamethasone; WBC, white blood cell.

3.2.1.1 Patient datasets and baseline characteristics

Treatment with the target dose was received by 23 subjects in Phase 1 and 55 subjects in Phase 2. The clinical effectiveness section focuses on a Phase 1 and 2 combined dataset, defined as all subjects in ZUMA-3 to receive KTE-X19 at target dose (n=78). The patient cohorts assessed in the clinical effectiveness review are presented in Figure 2. The modified intention to treat (mITT) populations in each phase were exposed to the target dose and had the opportunity to complete the 6-month disease assessment (for Phase 2, see CS, Appendix D.1.2, Figure 62).

Figure 2: Patient cohorts of ZUMA-3 (reproduced from Figure 10 of the CS)



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

The baseline characteristics of each group (Phase 1, Phase 2 and combined) are reported in

Table **19**.

Table 19: Baseline demographics and characteristics of ZUMA-3 (adapted from CS, section B.2.3.3, Tables 8 and 9, and Appendix L)

Characteristics	Phase 1 (n=23)	Phase 2 (n=55)	Phase 1 + 2 combined (n=78)
Age, median (range), y	[redacted]	40 (19, 84)	[redacted]
Age category, n (%)			
< 65 years	[redacted]	47 (85)	[redacted]
≥ 65 years	[redacted]	8 (15)	[redacted]
Male, n (%)	[redacted]	33 (60)	[redacted]
ECOG performance status, n (%)			
0	[redacted]	16 (29)	[redacted]
1	[redacted]	39 (71)	[redacted]
Philadelphia chromosome t(9:22) mutation, n (%)	[redacted]	15 (27)	[redacted]
MLL translocation t(4:11) of Myc translocation t(8:14), n (%)	[redacted]	2 (4)	[redacted]
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)	[redacted]	14 (25)	[redacted]
Low hypodiploidy (30–39 chromosomes), n (%)	[redacted]	1 (2)	[redacted]
Near triploidy (60–78 chromosomes), n (%)	[redacted]	1 (2)	[redacted]
Number of lines of prior therapy, n (%)			
1	[redacted]	10 (18)	[redacted]
2	[redacted]	19 (35)	[redacted]
≥3	[redacted]	26 (47)	[redacted]
Prior blinatumomab, n (%)	[redacted]	25 (45)	[redacted]
Blinatumomab as the last prior therapy, n, (%)	NR	NR	[redacted]
Prior inotuzumab ozogamicin, n (%)	[redacted]	12 (22)	[redacted]
Prior allogenic SCT, n (%)	[redacted]	23 (42)	[redacted]

Characteristics	Phase 1 (n=23)	Phase 2 (n=55)	Phase 1 + 2 combined (n=78)
Prior autologous SCT, n (%)	[redacted]	2 (4)	[redacted]
Prior radiotherapy, n (%)	[redacted]	13 (24)	[redacted]
Refractory, n (%)			
Primary refractory	[redacted]	18 (33)	[redacted]
R/R after ≥ 2 lines of therapy	[redacted]	43 (78)	[redacted]
R/R post-allo-SCT	[redacted]	24 (44)	[redacted]
First relapse with remission ≤ 12 months	[redacted]	16 (29)	[redacted]
BM blasts at screening, median % (range)	[redacted]	65 (5.01–100)	[redacted]
BM blasts at baseline, median % (range)	[redacted]	60 (0–98)	[redacted]
BM blasts after bridging chemotherapy, median % (range)	[redacted]	59 (0–98)	[redacted]
BM blasts >25% at baseline, n (%)	[redacted]	40 (73)	[redacted]
Extramedullary disease at screening, n (%)	[redacted]	6 (11)	[redacted]
CNS disease at baseline, n (%)			
CNS-1	[redacted]	55 (100)	[redacted]
CNS-2	[redacted]	0 (0)	[redacted]

*clarification response, question A5. BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; MLL, mixed lineage leukaemia; NR, Not reported; SCT, stem cell transplant

The ERG's clinical advisors commented that Phase 1 and Phase 2 participants were not identical or comparable: compared with Phase 1 participants, Phase 2 participants were substantially more likely to be male (60% vs 39%), and had more risk factors for poor prognosis than Phase 1 participants: in Phase 2 there were more Ph+ patients (27% vs 9%), more patients with a complex karyotype (≥ 5 chromosomal abnormalities) (25% vs 0%), more patients had already received prior allo-SCT (42% vs 26%), and more were R/R following allo-SCT (44% vs 26%).

There were no UK patients in either phase of the study. The CS states that a company workshop reported that the combined Phase 1 and 2 population was reflective of the likely patient population in

the UK.[31] However, there are currently very limited published data specifically on patient demographics and characteristics of R/R ALL for the UK.[15] Clinical advice provided to the ERG suggested that the ZUMA-3 population, particularly those in Phase 1, is healthier compared with the patients likely to be eligible for KTE-X19 therapy in practice in the UK (as per the company's positioning statement) if the intervention was recommended. The primary reason for this were that no participants were designated as Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 2 although these patients would potentially be treated with this therapy in clinical practice in England.

3.2.1.2 Endpoints

The study endpoints associated with key treatment definitions are presented in

Table 20. The CS states that the primary endpoint of the study was overall complete remission (OCR). This endpoint was a combined measure of the percentage of patients achieving complete remission (CR) and complete remission with incomplete haematological recovery (CRi). The definition of CR was based on bone marrow (BM) blasts and neutrophil and platelet counts. The reported thresholds for CR are consistent with the definition of remission in other trials (see Table 28). The CS acknowledges that the definition of CRi differs slightly between studies (CS, Section B.1.3.2, Table 3). It should also be noted that the primary endpoint of Phase 1 of ZUMA-3 was DLT, and CR/CRi, DOR, OS, RFS, and MRD were all designated secondary endpoints in this first phase; CR/CRi were designated as the primary endpoint in Phase 2 (

Table 20). Endpoints were assessed every 3 months from the end of the month 3 visit up to 18 months, then every 6 months up to month 60.[19]

Table 20: Definitions of key treatment objectives in ALL (adapted from Table 3 of the CS)

Treatment objective	Abbreviation	Definition
Complete remission (secondary outcome in Phase 1, primary outcomes in Phase 2)	CR	≤5% blasts in the bone marrow and the absence of blood leukaemic blasts, and recovery of peripheral blood counts with neutrophils greater than 1×10^9/L and platelets counts greater than 100×10^9/L
Complete remission with incomplete haematologic recovery (secondary outcome in Phase 1, Primary outcome in Phase 2)	CRi	≤5% blasts in the bone marrow and the absence of blood leukaemic blasts, partial recovery of peripheral blood counts and resolution of any extramedullary disease[a]
Duration of remission (secondary outcome in Phases 1 and 2)	DOR	The time from first complete remission or complete remission with incomplete haematological recovery (central assessment) to relapse or death without documented relapse.
Relapse-free survival (RFS) (secondary outcome in Phases 1 and 2)	RFS	Time from KTE-X19 infusion to date of disease relapse or death from any cause. Participants not meeting criteria for relapse by the analysis data cut-off date were censored at their last evaluable disease assessment date. Participants who had not achieved a CR or CRi at analysis data cut-off were evaluated as an RFS event at Day 0.
Minimal residual disease negativity (secondary outcome in Phases 1 and 2)	MRD-	The presence of leukemic cells not detectable by microscopy and may be measured by standardized methods with a sensitivity of less than 1 x 10^{-4} detectable leukemic cells in bone marrow samples (Shah 2021b: Undetectable MRD, defined as 1 leukaemia cell per 10000 viable cells, was centrally assessed using flow cytometry (NeoGenomics, Fort Myers, FL). MRD was assessed utilizing multicolor flow cytometry to detect residual cancerous cells with a sensitivity of 10^-4. MRD negative remission was defined as MRD < 10^-4 threshold (<0.01%[b]).

Notes: a) the definition of CRi does vary across clinical studies. b) Blinatumomab NICE reimbursement criteria in Philadelphia-chromosome negative adult ALL requires minimal residual disease of at least 0.1%.

Designated secondary endpoints across both phases were OS, RFS, duration of remission (DOR) and minimal residual disease negativity (MRD-). Safety outcomes, including neurological events and symptoms of cytokine release syndrome (CRS), were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. CRS was graded according to the system proposed by Lee and colleagues.[32] All endpoints were investigator-assessed and there was no blinding.

The CS states that the survival advantage of achieving MRD- in both adults and children with ALL has been demonstrated in a meta-analysis of 39 studies[33] (albeit following induction therapy), and that this finding has been reinforced by recent long-term blinatumomab data (CS, Section B.2.6.2). However, clinical advice received by the ERG indicated that thresholds used for detecting MRD, while standard

in trials in this population, are higher than the thresholds used in clinical practice in England, where further treatment would be initiated before the thresholds in the studies are reached. As a result, the efficacy of KTE-X19 in obtaining MRD- in accordance with clinical practice may be overestimated.

3.2.2 Effectiveness study results of ZUMA-3

The primary data cut-off occurred on 09/09/2020, at which point the median follow up was [redacted] months in Phase 1 and [redacted] months in Phase 2. The CS also reported preliminary results from the most recent interim analysis with data cut-off of 23/07/21, at which point the median follow-up was [redacted] months (95% CI: [redacted]) in all treated subjects, that is the combined populations of Phases 1 and 2. The clinical efficacy data for each phase and for Phases 1 and 2 combined are presented in Table 21.

Table 21: Summary of clinical effectiveness: ZUMA-3 (adapted from CS, Section B.2.6, Table 11)

			Primary efficacy endpoint	**Secondary efficacy endpoints**			
Phase	**Analysis set**	**n**	**OCR (CR/CRi)**	**KM median DOR**	**KM median OS**	**KM median RFS**	**MRD-**
1*	Target dose	23	82.6% (65%/17%)	17.6 months	22.4 months	[redacted]	87.0% (20 of 23 subjects)
2*	mITT	55	70.9% (56%/15%)	12.8 months	18.2 months	11.6 months	76.0% (42 of 55 patients)
1+2**	Combined	78	74.4% (62.8%/11.6%)	[redacted]	[redacted]	[redacted]	79.5% (62 of 78 subjects)

DOR, duration of remission, ITT, intent-to-treat; mITT, modified intent-to-treat, MRD, minimal residual disease, OCR, overall complete remission; CR: Complete remission; CRi: Complete remission with incomplete hematological recovery; RFS, relapse-free survival.
Notes: ITT includes all patients enrolled to the relevant phase of the study. mITT refers to subjects who received treatment with KTE-X19, or with regard to the Phase 1 portion the subjects who received KTE-X19 at the target dose of 1 x 10^6 CAR T-cells/kg. *based on data cut-off 09/09/20. **based on data cut-off 23/07/21.

As noted above, there are differences between the Phase 1 and Phase 2 populations exposed to the target dose with the Phase 2 population believed by clinical advisors to the ERG as having potentially more severe disease and worse prognostic factors. This could explain the relatively superior results for the Phase 1 population: for example, OCR of 82.6% vs 70.9%; DOR of 17.6 months vs 12.8 months and an MRD of 87% vs 76%.

Table 21: Summary of clinical effectiveness: ZUMA-3 (adapted from CS, Section B.2.6, Table 11)

			Primary efficacy endpoint	Secondary efficacy endpoints			
Phase	**Analysis set**	**n**	**OCR (CR/CRi)**	**KM median DOR**	**KM median OS**	**KM median RFS**	**MRD-**
1*	Target dose	23	82.6% (65%/17%)	17.6 months	22.4 months	[redacted]	87.0% (20 of 23 subjects)
2*	mITT	55	70.9% (56%/15%)	12.8 months	18.2 months	11.6 months	76.0% (42 of 55 patients)
1+2**	Combined	78	74.4% (62.8%/11.6%)	[redacted]	[redacted]	[redacted]	79.5% (62 of 78 subjects)

DOR, duration of remission, ITT, intent-to-treat; mITT, modified intent-to-treat, MRD, minimal residual disease, OCR, overall complete remission; CR: Complete remission; CRi: Complete remission with incomplete hematological recovery; RFS, relapse-free survival.
Notes: ITT includes all patients enrolled to the relevant phase of the study. mITT refers to subjects who received treatment with KTE-X19, or with regard to the Phase 1 portion the subjects who received KTE-X19 at the target dose of 1 x 10^6 CAR T-cells/kg. *based on data cut-off 09/09/20. **based on data cut-off 23/07/21.

3.2.2.1 Overall complete remission (OCR/CRi)

For the combined Phase 1 and 2 populations (data cut-off 23/07/21), the OCR rate per investigator assessment was 74.4% (58 of 78 subjects, 95% CI: [redacted]), with a CR rate of 62.8% (49 of 78 subjects, 95% CI: [redacted]). The investigator-assessed OCR rate was 82.6% for the Phase 1 population alone and 70.9% for the Phase 2 population alone (both data cut-offs 09/09/20).

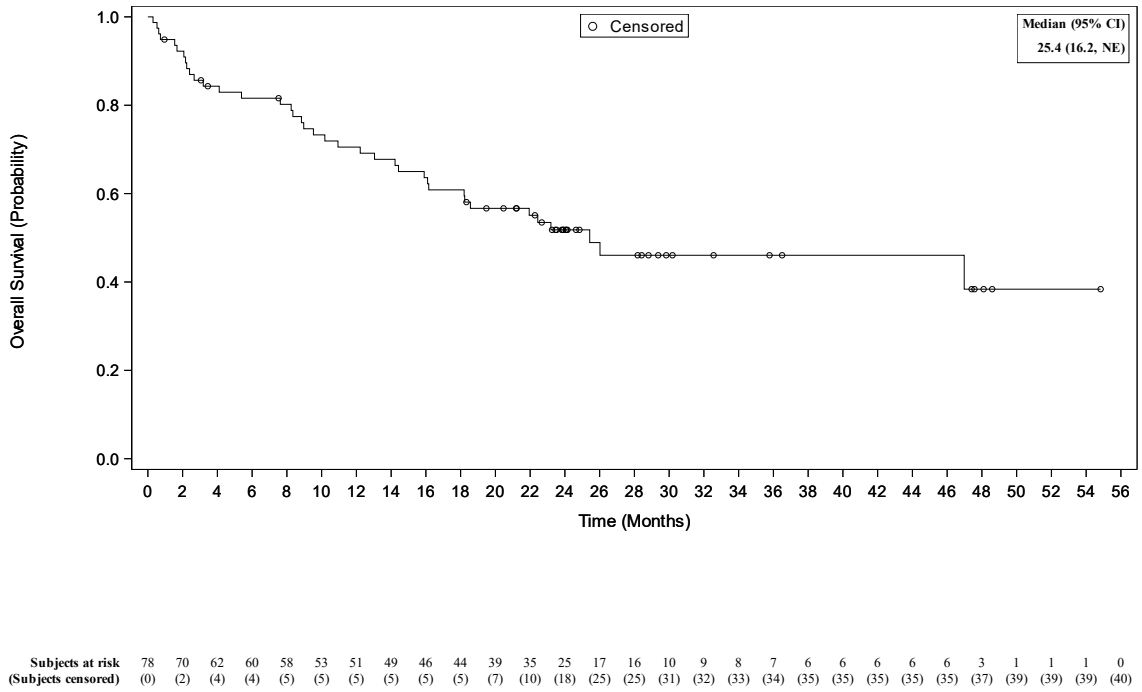
3.2.2.2 Duration of remission

For the combined Phase 1 and 2 populations (data cut-off 23/07/21), among the 58 subjects who achieved a CR or CRi, the median DOR was [redacted] months (95% CI: [redacted]). Overall, [redacted] subjects were censored: [redacted] subjects were in ongoing remission as of the data cut-off date, 14 subjects had an allo-SCT, [redacted] subjects started new anticancer therapy, and [redacted] subject was lost to follow-up. [redacted] subjects relapsed, and [redacted] died. The median DOR was 17.6 months for the Phase 1 population alone and 12.8 months for the Phase 2 population alone (data cut-off 09/09/20).

3.2.2.3 Overall survival

For the combined Phase 1 and 2 populations (data cut-off 23/07/21), the median OS was [redacted] months (95% CI: [redacted]). Kaplan-Meier (KM) estimates of OS at 6 months and 12 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The KM plot for this data cut-off is reproduced in Figure 3. The median OS was 22.4 months (95% CI: [redacted]) for the Phase 1 population alone and 18.2 months (95% CI: [redacted]) for the Phase 2 population alone (data cut-off 09/09/20).

Figure 3: Kaplan-Meier plot of OS (Phase 1 + 2 combined, data cut-off 23/07/21) (CS, Figure 11)



3.2.2.4 Relapse-free survival (RFS)

For the combined Phase 1 and 2 populations (data cut-off 23/07/21), the KM median RFS was [redacted] months (95% CI: [redacted]); KM estimates of the probability of being relapse-free at 6 and 12 months were [redacted] (95% CI: [redacted]) and [redacted] (95% CI: [redacted]), respectively. The KM plot for this data cut-off is reproduced in Figure 4. The CS noted that the rate of censoring is high primarily due to patients either being in remission at time of data cut-off (that is, administratively censored) or because they had received a SCT. The median RFS was [redacted] months for the Phase 1 population alone and 11.6 months for the Phase 2 population alone (data cut-off 09/09/20).

Figure 4: Kaplan-Meier plot of RFS (Phase 1 + 2 combined; data cut 23/07/21) (CS, Figure 14)

In combination, Figure 3 and Figure 4 cause concerns for the ERG if it is assumed that KTE-X19 can be a standalone, curative treatment. Clinical advice provided to the ERG suggested that patients would benefit from allo-SCT or other subsequent treatments. The ERG believes it would not be plausible that patients with relapsed disease post KTE-X19 treatment would live for the time implied in Figure 3 without further treatments. Based on RFS, it appears unlikely that KTE-X19 is a standalone curative treatment.

3.2.2.5 Minimal Residual Disease (MRD)

The threshold for MRD negative remission was defined as MRD < 10^{-4} threshold (<0.01%). For the combined Phase 1 and 2 populations (data cut-off 23/07/21), 79.5% (62 of 78 subjects) achieved MRD- including 57 of 58 patients to achieve CR/CRi (data missing for one patient). The MRD- rate was 87% for the Phase 1 population alone and 76% for the Phase 2 population alone (data cut-off 09/09/20).

As noted above, clinical advice received by the ERG indicated that the threshold used for the outcome MRD, while standard in trials in this population, is higher than the threshold used in clinical practice where further treatment would be initiated before the study threshold is reached. As a result, the efficacy of KTE-X19 in obtaining MRD- in accordance with clinical practice may be overestimated.

3.2.2.6 Subgroups

The CS presented pre-specified subgroup analyses for the primary outcome, investigator assessed OCR, for the following baseline covariates (CS, Section B.2.7 and Appendix E): age; sex; baseline extramedullary disease; Central Nervous System (CNS) status; percentage blasts in BM; Ph status; number of lines of prior therapy; prior therapy (e.g., blinatumomab, inotuzumab, allo-SCT), and RR status. The OCR rate was largely consistent across subgroups. The CS acknowledges that any differences between groups, e.g., presence/absence of extramedullary disease or with/without prior allo-SCT, should be interpreted with caution given the small numbers of patients.

3.2.3 Health-related quality of life

The CS presents a narrative summary of the data from the assessments using the EQ-5D-5L tool. The company clarified the details of these findings in response to a question by the ERG for the following time-points: baseline; 28 days; 3, 6, 9 and 12 months (clarification response, question A6). The trend was consistent across all five domains: mobility; self-care; usual activities; pain/discomfort; anxiety/depression: an initial decline in scores from baseline to day 28 or 3 months, followed by an improvement in scores similar to or slightly better than baseline levels.

Table 22 presents the EQ-5D-5L UK indices by relapse and AE status. Where patients had more than one visit in the time period (pre-injection, pre-relapse or post-relapse), the mean was taken across visits.

Table 22: EQ-5D-5L UK indices by injection, relapse and AE status (adapted from Table 2 of CS, PROs analysis report)

	Pre-Injection			Post-injection, pre-relapse						Post-relapse					
	No AE[a]			No AE			AE			No AE			AE		
	N	Mean	SD	N[b]	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
EQ-5D-5L Index	53	0.78	0.16	29	0.84	0.13	20	0.71	0.27	7	0.79	0.20	7	0.64	0.28

[a] Active grade 3 or 4 treatment-emergent AE (time dependent)

[b] represents the number of patients in this time period category. For patients with more than one visit in the time period, the mean was taken across visits (Screening, Day 0, Day 28, Month 3, Month 6, Month 9, Month 12, Month 15)

Abbreviations: AE - adverse event, SD - standard deviation.

3.2.4 Safety study results of ZUMA-3

The CS reported the safety data for the Phase 2 of ZUMA-3 in Sections B.2.10.3 and B.2.10.4. The Phase 1 data were not reported in the CS; these have been extracted from the primary publication[18] and are presented narratively for comparison below.

A summary of AEs related to KTE-X19 that occurred in ≥10% of subjects in Phase 2 is provided in

Table 23 (CS, Table 31). The most common KTE-X19-related AEs of any grade were [redacted]), [redacted]), and [redacted] ([redacted]). The most common KTE-X19-related AEs that were Grade 3 or higher were [redacted]), [redacted]), and [redacted]). Two patients experienced fatal Grade 5 KTE-X19 related AEs: brain herniation and septic shock.[19]

Table 23: Subject incidence of KTE-X19-related AEs occurring in ≥ 10% of subjects by preferred term and worst grade* (Phase 2, safety analysis set) (reproduced from CS, Table 31)

MedDRA preferred term, n (%)	Any	Worst Grade 1	Worst Grade 2	Worst Grade 3	Worst Grade 4	Worst Grade 5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data cut-off date = 09/09/2020.

AE, adverse event; Medical Dictionary for Regulatory Activities.

Notes: *Worst grade: the worst grade of adverse event for each participant. AEs that occurred during retreatment period are not included. Preferred terms are sorted in descending order of total frequency in the 'Any' column. AEs are coded using MedDRA version 23.0 and graded using the Common Terminology Criteria for Adverse Events version 4.03. Multiple incidences of the same AE in 1 subject are counted once at the highest grade for this subject.

For Phase 1, two datasets were presented in the principal publication for the 23 subjects exposed to the target dose: for subjects managed with the original AE guidelines (n=14) and subjects managed with the revised AE management guidelines (n=9).[18] The revised guidelines involved limiting tocilizumab to the treatment of CRS (and not isolated neurotoxicity) and initiating corticosteroid treatment at Grade 2 rather than Grade 3 for neurological events.[18] The most common Phase 1 KTE-X19-related AEs of

any grade were the same as those observed in Phase 2, but the proportion of patients experiencing these AEs was higher (albeit the number of subjects was smaller). The most common AEs were pyrexia (86% but 100% after revised guidelines); hypotension (79%, but 67% after revised guidelines) and sinus tachycardia (43% and 44%).

As with Phase 2, some of the most common KTE-X19-related AEs in Phase 1 that were Grade 3 or higher were pyrexia (36% but 67% after revised guidelines); hypotension (43% and 33%) and hypoxia (14% and 22%).[18]

3.2.4.1 Cytokine Release Syndrome (CRS)

In the Phase 1 target dose set (n=23), 100% of subjects experienced CRS both before and after the revised AE management guidelines although ≤33% experienced CRS of Grade 3 of higher.[18] CRS-associated events resolved in all but one patient on the target dose who experienced grade 5 KTE-X19–related multi-organ failure secondary to CRS (day 6).[18,26]

In the Phase 2 safety analysis set, 89% of subjects (49/55) had CRS, and 24% (13/55) had CRS that was Grade 3 or higher. No subject had Grade 5 CRS.

In the Phase 1 target dose set (n=23) and the Phase 2 safety set (n=55), the most common CRS symptoms of any grade were pyrexia (≤100% and 94% respectively), hypotension (≤79% and 67%), and sinus tachycardia (≤44% and 37%).

3.2.4.2 Neurological events

In the Phase 1 target dose set (n=23), 93% of subjects (13/14) experienced at least one neurological event of any grade before the revised AE management guidelines, and 78% (7/9) after the revised guidelines were implemented. Common neurological events KTE-X19-related AEs were aphasia (43% but 22% after revised guidelines) and encephalopathy (64% and 22%). Before guideline revisions 64% experienced a neurological event of Grade 3 of higher, but only 11% did so after AE management guideline revision.[18] Common neurological events KTE-X19-related AEs at Grade 3 or higher were aphasia (29% but 11% after revised guidelines) and encephalopathy (43% and 0%).[18] No subject had a Grade 5 neurological event.

In Phase 2, 60% of subjects (33/55) had at least one neurologic AE of any grade, including 25% (14/55) with Grade 3 or higher neurologic AEs. One subject had a Grade 5 neurologic AE of brain herniation.

Across both Phase 1 and 2, the most common neurologic AEs of any grade were tremor (≤44% and 27%, respectively), confusional state (≤67% and 25%), encephalopathy (≤64% and 22%) and aphasia (≤43% and 16%). The most common Grade 3 or higher events were aphasia (≤29% and [redacted]), encephalopathy (43% and 7%), and confusional state, agitation and seizure (≤14% and [redacted]).

3.2.4.3 Treatment-related deaths

In Phase 1 of ZUMA-3, there were two treatment-related deaths as a result of Grade 5 AEs considered related to KTE-X19 either secondary to CRS or in the context of CRS and neurological events outside the DLT-assessment time frame.[18] Two publications suggest that these patients were Phase 1 participants who were not exposed to the target dose. [26, 28]

In Phase 2 of ZUMA-3, there were also two treatment-related deaths as a result of Grade 5 AEs considered related to KTE-X19 either secondary to CRS or in the context of CRS and neurological events: one due to brain herniation and one to septic shock.[19]

3.2.4.4 Safety summary

KTE-X19 produces high frequencies of AEs among patients, with Grade 3 or higher AEs such as pyrexia, hypotension, hypoxia, aphasia and encephalopathy affecting up to 67% of patients in Phase 1 and 36% in Phase 2. Clinical advice received by the ERG suggested that the frequency of the most common CRS and neurological AEs was higher than might be expected for other CAR-T and comparator therapies, for example, the only SAE or Grade 3 or higher treatment-emergent AEs affecting >10% of patients for inotuzumab were febrile neutropenia (11.6%) and veno-occlusive disease (VOD) (11.6%) (INO-VATE FINAL[34]), and for blinatumomab were febrile neutropenia (21.3%) and neutropenia (17.6%) (TOWER Supp[11]). The corresponding figures for FLAG-IDA arm were 18.9% and 2.1% for febrile neutropenia and VOD respectively at >2 years follow-up in INO-VATE, and 34.9% and 26.6% for febrile neutropenia and neutropenia respectively at <1 year follow-up in TOWER.[11, 34] In the PACE study, the only Grade 3 or 4 AEs with an incidence of ≥10% were also neutropenia (12% and 22%), anaemia (12% and 19%) and thrombocytopenia (6% and 19%) at a median follow-up of 6 months and 56.8 months, respectively, compared with 18.1 months for ZUMA-3.[21, 35] Two patients died from treatment-related AEs in each phase of ZUMA-3, with two of these deaths occurring in doses not taken forward to Phase 2 (4/78 subjects, 5%). In the TOWER trial, fatal adverse events considered related to treatment were recorded for 8/267 (3%) of patients in the blinatumomab arm and 8/109 (7%) in the FLAG-IDA arm.[11] In the INO-VATE trial, fatal adverse events considered related to treatment were recorded for 8/164 (4.9%) of patients in the inotuzumab arm and 2/143 (1.4%) in the FLAG-IDA arm).[34] Finally, two deaths (2/32, 6.3%) were attributed by investigators to ponatinib-related adverse events in the PACE trial.[35]

3.2.5 Subsequent Allo-SCT and anticancer therapies used in ZUMA-3

In ZUMA-3, 18% (14/78) of patients ultimately received allo-SCT post-KTE-X19 despite the company's view of how KTE-X19 would be used in clinical practice which is '*we consider it highly unlikely that KTE-X19 would be used as a bridge to allo-SCT, instead being considered as a standalone treatment option in UK clinical practice.*' It is not known how the allo-SCTs observed in ZUMA-3 changed event-free survival (EFS) or OS for patients receiving it, but based on clinical advice provided to the ERG the allo-SCTs could have brought a benefit and the EFS/OS for patients who do not receive allo-SCT after KTE-X19 could be significantly lower. The company presented an analysis of median OS for groups who did, and did not, have allo-SCT and concluded that survival is independent of SCT (

[redacted]

Figure 5). The ERG notes that ZUMA-3 was not designed to show the difference in OS between these two subgroups and that the analysis was under- powered especially for those who received SCT as their KM plot is informed by only [redacted] patients from month 30 onwards. Furthermore, these data may be confounded depending on the reasons for a patient receiving allo-SCT. As such, there is considerable uncertainty in the counterfactual prognosis of patients who received allo-SCT following KTE-X19.

In addition to the 14 patients who received allo-SCT, others accessed subsequent anticancer therapies. In total, [redacted] patients out of the 78 who received a KTE-X19 infusion at target dose received such therapies with [redacted] ([redacted]%) in Phase 1 and [redacted] ([redacted]%) in Phase 2.[36] The most common interventions were inotuzumab ([redacted] patients), cyclophosphamide ([redacted] patients), ponatinib ([redacted] patients), dexamethasone ([redacted] patients), and blinatumomab ([redacted] patients). In addition, [redacted] patients were retreated by KTE-X19 in Phase 2 and had no response.

Based on the number of patients reported in ZUMA-3 who received allo-SCT and/or subsequent treatment, the ERG highlights that the proportion of patients in whom KTE-X19 is a curative standalone therapy may be low.

Figure 5: KM plot of OS for responders by subsequent SCT group (reproduced from CS, Figure 22)

3.3 Critique of studies identified and included in the indirect comparison and/or multiple treatment comparison

In the absence of head-to-head study data for KTE-X19 and the comparators in the NICE scope, the CS reported two forms of indirect treatment comparisons (ITCs): an unanchored MAIC and a naïve comparison (CS, Section B.2.9).

3.3.1 Searches

Appendix D.1.1 of the CS reports the searches conducted for the SLR of clinical efficacy and safety, including the comparator treatments for the ITCs.

The search results are reported in Section Appendix D.1.1 and the PRISMA flowchart Figure 60. The numbers in the original report contained an error and needed clarifying (clarification response, A14 and Figure 4). Only eight publications satisfied the inclusion criteria for KTE-X19 (Appendix D.1.1 Table 96); the identity of the remaining 80 publications, and how they related to the reviews, including the ITCs, was not clear. The company clarified the process and numbers, confirming that the indirect comparison included 19 publications and that the remaining 61 publications were excluded although the reasons for exclusion are not reported (clarification response, question A17). The number of included publications was 27 which related to three studies: ZUMA-3 (8 publications), TOWER and INO-VATE (19 publications).

The naïve indirect comparison included both TOWER and INO-VATE, but also included the PACE study (evaluating the efficacy and safety of ponatinib in chronic myeloid leukaemia [CML] and ALL patients) and individual patient data from the SCHOLAR-3 study (CS, Section B.2.9). The PACE study was identified in the overall searches, but was listed as one of the studies '*evaluated for inclusion in the ITC*' (CS, Appendix, Table 97), and then excluded from the MAIC for sample size issues (CS, Appendix, Table 99). It was also listed in the table of all excluded studies at full text screening (CS, Appendix, Table 100). The SCHOLAR-3 study was not identified in the searches; it is only listed as a clinical study report. Neither PACE nor SCHOLAR-3 are included in the new PRISMA flowchart (clarification response, Figure 4).

3.3.2 Quality assessment

The company used the NICE methods guide tool, adapted from CRD guidance for undertaking systematic reviews in health care to appraise the two RCTs included in the indirect comparisons (TOWER[11] and INO-VATE[12]). The ERG considers that whilst the key aspects of quality to be considered outlined in the NICE user guide are appropriate for the quality assessment of RCTs, the application of a validated quality assessment instrument such as the Cochrane RoB2 tool would have allowed a more robust assessment of the potential risk of bias in the TOWER and INO-VATE studies, and the potential impact of this bias on study outcomes.

The ERG agrees with the company's responses to the eight quality assessment criteria for the TOWER study (Table 24).

Table 24: Quality assessment for TOWER (reproduced from CS, Table 103)

Study name	**TOWER (NCT02013167)**	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**

	CS / ERG	CS / ERG
Was randomisation carried out appropriately?	Yes / Yes	Eligible patients were randomly assigned, in a 2:1 ratio, with the use of an interactive voice-response system to receive open-label treatment with either blinatumomab or standard chemotherapy. Randomisation was stratified according to age, previous salvage therapy, previous allogeneic SCT
Was the concealment of treatment allocation adequate?	No / No	The study was open-label.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes / Yes	The two treatment groups had similar demographic and disease characteristics at baseline when all patients who underwent randomization were assessed as well as when patients who did not receive the trial treatment were excluded / There were some small differences between groups in incidence of relapse post allo-SCT and line of salvage therapy, but these favoured the comparator
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No / No	This was an open-label trial. Given the unique route of administration for blinatumomab as a continuous intravenous infusion over a 28-day period, it would not have been possible to conceal treatment allocation. Given the primary endpoint of overall survival, this is unlikely to present a risk of bias. It is not clear from the publication whether secondary endpoints were performed by central assessment or investigator assessment. Given the open-label nature, the latter may be open to risk of bias.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear / Unclear	Rates of discontinuation due to adverse events were slightly higher in the blinatumomab arm (12%) than the chemotherapy arm (8%). Baseline demographics were considered to be similar, including when patients who did not receive the trial treatment were excluded / Drop-outs due to AEs were substantially higher in the blinatumomab arm (12.2% vs 3.7%), and there was a big difference in the percentage of participants who actually received treatment in the two groups (98.5% vs 81.3%), and characteristics of these drop-outs in the two groups were not reported.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No / No	All the outcomes measured are fully documented in the clinical trial publication / A protocol is available, which lists multiple outcomes, all of which, except safety, are reported.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear / Unclear	The analysis did include an intention-to-treat analysis (all patients who underwent randomisation), and this was the dataset for efficacy analyses. It is unclear from the publication the methods used to account for missing data.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Key: SCT, stem cell transplant

However, the ERG assessments differed from those of the CS across four criteria for INO-VATE, with the ERG judging the trial to be at higher risk of bias due to the lack of details on the randomisation process, potentially important baseline and drop-out imbalances between study arms, and the failure to report some outcomes listed in the protocol (Table 25).

Table 25: Quality assessment for INO-VATE (reproduced from CS, Table 104)

Study name	**INO-VATE (NCT01564784)**	
Study question	**Response (yes / no / Unclear /N/A) CS / ERG**	**How is the question addressed in the study? CS / ERG**
Was randomisation carried out appropriately?	Yes / Unclear	Patients were randomly assigned, in a 1:1 ratio, to receive either inotuzumab ozogamicin or the investigator's choice of standard therapy. Stratification factors at randomization were the duration of the first remission (<12 months vs. ≥12 months), the salvage-treatment phase (first vs. second), and age (<55 years vs. ≥55 years). Of note, 47 additional patients underwent randomisation after the cut-off date, so that additional survival data could be obtained / No details of randomization process
Was the concealment of treatment allocation adequate?	No / No	This was an open-label study.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes / Unclear	The baseline patient characteristics in the remission-analysis population were well-balanced between treatment groups / Some potentially important baseline characteristics were different between groups, e.g. duration of first remission; response to most recent previous induction therapy; median peripheral blast count.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No / No	Given both arms were active treatment, the dosing regimens did not allow for concealment. Inotuzumab ozogamicin was provided as an intravenous infusion on day 1, 8, and 15 of each cycle. Patients in the investigators choice of chemotherapy arm received varying regimens as determined by investigator preference. In addition, given the comparator arm was defined as 'investigator's choice of standard therapy', this required that investigators were aware of allocation. The primary endpoint was assessed by an independent, central end-point adjudication
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear / Yes	Subjects who achieved complete remission could undergo stem-cell transplant at the investigator's discretion. This approach is likely to have biased censoring in favour of inotuzumab due to higher rates of complete remission in this group. More patients in the inotuzumab ozogamicin group than in the standard-therapy group discontinued treatment because of

		complete remission (35% vs. 15%), whereas fewer patients in the inotuzumab ozogamicin group discontinued treatment because of treatment-resistant disease (10% vs. 40%) / It is stated that 13/109 in the standard therapy group did not receive treatment (p.743[12]), so the primary outcome analysis was adjusted to take account of these missing data
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No / Yes	All the outcomes measured are fully documented in the clinical trial publication / A protocol is available, which lists multiple outcomes. Cytogenetic and serum concentration outcomes are listed in the protocol but not in the included studies; the protocol does not list safety outcomes, but these are reported extensively, including individual adverse events [12]
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear / Unclear	The primary analysis was based on the intention-to-treat dataset. It is unclear from the publication the methods used to account for missing data / An 'as treated' analysis was performed for missing data from the standard therapy group for the primary outcome (pp.743-745)[12]

Overall, both TOWER and INO-VATE were at high risk of bias: they were open-label with unblinded outcome assessment, had substantial discontinuation rates and unclear methods for managing missing data.

The data from the PACE study[21] included in the CS were limited to the 32 ALL patients (who were all also Ph+); the remaining 417 were CML patients. Given that the relevant sub-population constituted less than 10% of the entire study population, the ERG decided that the value of conducting a critical appraisal of the study as a whole was questionable. SCHOLAR-3 only exists as an unpublished clinical study report (CSR). In the absence of a recognised appraisal tool for IPD studies, the ERG conducted an assessment drawing attention to the principal potential sources of bias in this study design based on the study details in the CSR provided by the company. The CSR did not report the full details of the search strategy, or the number of reviewers involved in the study selection and data extraction processes. The search for relevant trials interrogated multiple relevant databases, but relevant IPD might have been missed because only trials with IPD in the MediData MEDS database were included. No risk of bias assessments were conducted on included, matched trials, so this was not taken into account in the analyses or results. Only patients from ZUMA-3 phase 2 mITT population were included (n=55), six of which could not be matched and were therefore excluded, and nine matched controls were found to have protocol deviations and so were also excluded (potential attrition bias). The CS did not conduct or report critical appraisals of either the PACE or SCHOLAR-3 studies.

3.3.3 Baseline characteristics

A brief summary of the included studies considered by the company in the ITC is presented in

Table **26**.

Table 26: Summary of studies included in the ITC

Study	Population	Intervention / Comparators
ZUMA-3	Overall	KTE-X19
INO-VATE		Inotuzumab
		FLAG-IDA
TOWER		FLAG-IDA
SCHOLAR-3	Ph-	Blinatumomab
TOWER		Blinatumomab
PACE	Ph+	Ponatinib

FLAG-IDA, Fludarabine, cytarabine, granulocyte-colony stimulating factor, idarubicin; Ph+, Philadelphia chromosome-positive; Ph-, Philadelphia chromosome-negative.

Where comparable baseline data are reported, the patients across the three studies are clinically heterogeneous, particularly in terms of ECOG status, prior therapies (number and types), and percentage of BM blasts at baseline (Table 27). The only baseline characteristics reported across all four trials, i.e. ZUMA-3, TOWER, INO-VATE, and for the 32 ALL patients in the PACE study, were age and Philadelphia chromosome status.[21] The PACE population was much older (mean age, 62 years) than the ZUMA-3, TOWER or INO-VATE populations (median age range 41-47 years across the three studies) and 100% were Ph+ compared with between 0% and 17% in the other three studies (Table 27).

Table 27: Baseline demographics and characteristics (adapted from CS Tables 8 and 135 (ZUMA-3), (TOWER[11] ; INO-VATE[12])

	ZUMA-3	TOWER		INO-VATE§	
Characteristics	**Phase 1 + 2 combined (n=78)**	**Blinatumomab (n=271)**	**Chemotherapy (n=134)**	**Inotuzumab (n=109)**	**Standard therapy (n=109)**
Age, median (range), y	[redacted] †	40.8* (18, 80)	41.1* (18, 78)	47 (18, 78)	47 (18, 79)
Male, n (%)	[redacted]	162 (59.8)	77 (57.5)	61 (56)	73 (67)
ECOG PS					
0	[redacted]	96 (35.4)	52 (38.8)	43 (39)	45 (41)
1	[redacted]	134 (49.4)	61 (45.5)	50 (46)	53 (49)
2	[redacted]	41 (15.1)	20 (14.9)	15 (14)	10 (9)
Philadelphia chromosome positive, n (%)	[redacted]	0 (0)	0 (0)	14 (13)	18 (17)
Salvage treatment phase, n (%)					
1	NR	114 (42.1)	65 (48.5)	73 (67)	69 (63)
2	NR	91 (33.6)	43 (32.1)	35 (32)	39 (36)
≥3	NR	66 (24.4)	26 (19.3)	1 (1)	1 (1)
Prior lines of therapy					
1	[redacted]	NR	NR	75 (69)	69 (63)

	ZUMA-3	TOWER		INO-VATE§	
Characteristics	**Phase 1 + 2 combined (n=78)**	**Blinatumomab (n=271)**	**Chemotherapy (n=134)**	**Inotuzumab (n=109)**	**Standard therapy (n=109)**
2	[redacted]	NR	NR	33 (30)	39 (36)
≥3	[redacted]	NR	NR	1 (1)	1 (1)
Prior blinatumomab, n (%)	[redacted]	N/A	N/A	NR	NR
Blinatumomab as the last prior therapy, n, (%)	[redacted]	N/A	N/A	NR	NR
Prior inotuzumab, n (%)	[redacted]	NR	NR	N/A	N/A
Prior allogenic SCT, n (%)	[redacted]	94 (34.7)	46 (34.3)	17 (16)	22 (20)
Primary refractory	[redacted]	46 (17)	27 (20.1)	NR	NR
R/R after ≥ 2 lines of therapy	[redacted]	NR	NR	NR	NR
R/R post-allo-SCT	[redacted]	91 (33.6)	45 (33.6)	NR	NR
First relapse with remission ≤ 12 months	[redacted]	109 (40.2)	49 (36.6)	62 (57)	71 (65)
BM blasts >25% at baseline, n (%)	[redacted]	60 (22.1)[a] 201 (74.2)[b]	23 (17.2)[a] 104 (77.6)[b]	38 (28)[c] 77 (71)[b]	29 (27)[c] 78 (72)[b]
Extramedullary disease at screening, n (%)	[redacted]	NR	NR	NR	NR

	ZUMA-3	TOWER		INO-VATE§	
Characteristics	**Phase 1 + 2 combined (n=78)**	**Blinatumomab (n=271)**	**Chemotherapy (n=134)**	**Inotuzumab (n=109)**	**Standard therapy (n=109)**
CNS-1	[redacted]	NR	NR	NR	NR
CNS-2	[redacted]	NR	NR	NR	NR

BM, bone marrow; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; MLL, mixed lineage leukaemia; N/A: Not applicable; NR, Not reported; SCT, stem cell transplant. [a]10%-50%; [b] >50% [c]<50% blasts *Mean †clarification response, question A5 §Remission analysis population (Kantarjian 2016)

3.3.4 Endpoints

It should be noted that definition of the CRi outcome according to Absolute Neutrophil Count per microlitre (ANC/μL) and platelet count per microlitre differed between the three trials (Table 28). Otherwise, the remaining outcomes were assessed and measured in the same way across all three trials. All data were extracted from the trial protocols by the ERG.

Table 28: Comparison between outcome measures among different key studies

	ZUMA-3 Protocol: NCT02614066	**INO-VATE** Protocol: NCT02013167	**TOWER** Protocol: NCT01564784
CR	CR: ≤5% blasts by morphology in BM; peripheral blood counts: ANC ≥ 1000/μL and platelet ≥ 100,000/μL	<5% marrow blasts and the absence of peripheral blasts; peripheral blood counts: ANC ≥1000/μL and platelets ≥100,000/μL	≤5% or less bone marrow blasts and no evidence of disease; peripheral blood counts as follows: platelet count of >100,000 per microlitre and absolute neutrophil count of >1000 per microlitre
CRi	≤ 5% blasts by morphology in BM; ANC ≥ 1000/μL and platelet count <100000/μL or ANC < 1000/μL and Plt ≥ 100000/μL	ANC <1000/μL and/or platelets <100,000/μL	ANC of >1000 per microlitre or platelet count of >100,000 per microlitre.
DOR	For subjects who experience a CR or CRi to retreatment was defined as the time from the first complete remission after retreatment to relapse after retreatment or death due to disease relapse	Duration of complete remission, calculated only for participants who achieved a CR, was calculated from the date a CR was first achieved until the earliest date of a disease assessment indicating a relapse event or death, whichever occurred first. Participants who did not have a relapse event were censored on their last disease assessment date	For patients with CR/CRi, remission duration was defined as the duration from remission to progressive disease (objective progression, relapse, treatment discontinuation due to health deterioration) or death
MRD	MRD was assessed utilizing multicolor flow cytometry to detect residual cancerous cells with a sensitivity of 10^{-4}. MRD negative remission was defined as MRD < 10^{-4} threshold.	MRD remission was defined as the occurrence of an MRD level below 10^{-4} measured by quantitative reverse transcription polymerase chain reaction or flow cytometry	MRD negativity was considered to have been achieved if the lowest value of MRD from the first date of CR/CRi to EoT was <1 × 10^{-4} blasts / nucleated cells

CR: Complete remission; CRi: Complete remission with incomplete haematological recovery; DOR: Duration of remission; EoT: End of therapy; MRD: Minimal Residual Disease

3.4 Critique of the indirect comparison and/or multiple treatment comparison

The company's SLR showed that there were no studies comparing KTE-X19 with any of the comparator treatments in the NICE scope. With ZUMA-3 being a single-arm study, no anchored ITCs were possible. For this reason, unanchored analyses using both MAICs and naïve ITCs were conducted by the company.

All evidence for KTE-X19 was drawn from the ZUMA-3 study.[18, 19] Evidence sources for the other comparators were as follows: inotuzumab, INO-VATE;[34] blinatumomab, TOWER;[37] FLAG-IDA, pooled data from INO-VATE and TOWER;[34, 37] and ponatinib, PACE.[35]

In addition, a *post hoc* analysis from the retrospective cohort study, SCHOLAR-3,[38] was used for the comparison with blinatumomab. SCHOLAR-3 created a "synthetic control arm" (SCA-3) by matching patients from historical trials who had not previously received blinatumomab therapy with [redacted] ZUMA-3 patients (full details are stated in CS Section B.2.9). Matching was made on a 1:1 basis. In response to clarification question B22, the company stated *"1:1 matching was used due to a design decision that prioritised the minimisation of heterogeneity between matched cohorts over statistical efficiency"*. Since matching intrinsically reduces heterogeneity between populations, it is not clear to the ERG how 1-to-many matching would compromise this. Patients from ZUMA-3 were included irrespective of whether they had prior treatment with blinatumomab and inotuzumab which may disadvantage the treatment effect of KTE-X19 in this population. The primary purpose of the SCHOLAR-3 analysis was to compare OCR rates and the treatments administered in SCA-3 were either blinatumomab ([redacted]) or SoC chemotherapy ([redacted]). Those receiving SoC chemotherapy were excluded for the KTE-X19 versus blinatumomab comparison, hence that means the N=[redacted] for this dataset as shown in Table 29.

Three categories of ITC were carried out against the various comparators as summarised in Table 29: (i) naïve (unadjusted) comparisons (vs ponatinib, inotuzumab, blinatumomab, and FLAG-IDA); (ii) matched comparison via SCHOLAR-3 population SCA-3 (vs blinatumomab); (iii) MAIC (vs inotuzumab, blinatumomab, FLAG-IDA). For ponatinib, a MAIC was deemed unsuitable due to the already small number of Ph+ ALL patients in the ZUMA-3 study. In each case, rather than estimating a treatment effect which is then used in the economic model, the various approaches resulted in different datasets to which separate survival models were fitted. These models then provided survival estimates, including any extrapolation required, within the economic model. More specifically, for the naïve comparisons independent survival models were fitted to the unadjusted pseudo-individual patient data (IPD) comparator data recreated from digitised KM plots from TOWER and INO-VATE for the comparators and to the unadjusted ZUMA-3 data for KTE-X19. For the matched SCHOLAR-3 analysis,

separate survival models were fitted to the matched populations (although as explained below, the matched ZUMA-3 population was not used in the company's economic model). For the MAIC analyses, the comparator data were the same as for the naïve comparison, whilst the KTE-X19 IPD data were weighted according to the MAIC model as part of the survival model fitting process.

In the company's base case economic analyses, naïve comparisons were used against all comparators except for blinatumomab. The primary reason provided by the company for using naïve comparisons to model the treatment effect of KTE-X19 compared to inotuzumab and FLAG-IDA, was the assertion that the ZUMA-3 population is fully in keeping with the target population in UK practice whereas the TOWER and INO-VATE populations are not; MAIC would therefore adjust away from the target population. For blinatumomab, the matched SCHOLAR-3 comparison was preferred by the company since the company had IPD for both group and could therefore match to the ZUMA-3 population. The company also stated *that "the point estimate of the naïve OS HR for blinatumomab (0.39) was identical to that from the SCHOLAR-3 analysis, whereas that from the MAIC (0.47) diverged. Thus, the naïve ITC appears to have produced more valid results than the MAIC, given the SCHOLAR-3 analysis involved matching individual patients to the correct target population. This also supports, by inference, use of a naïve comparison for inotuzumab in the economic analysis."* The ERG notes that the agreement of two models does not mean they are correct.

Table 29: Summary of key ITCs used in the economic model (reproduced from Table 25 of the CS)

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
ZUMA-3 vs. INO-VATE (inotuzumab)					
• IPD from ZUMA-3 for KTE-X19 • Published AD from INO-VATE for inotuzumab	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup	mITT phase 1+2 (N=78)	ITT (N=164)	• OS (KM curves) • EFS (KM curves) • Response rate	• **Naïve analysis (base case)** • Observed absolute effects by treatment (CR rate, KM curves) • **MAIC analysis** • Propensity score weighted absolute effects for KTE-X19 matched to the population in INO-VATE (CR rate, KM curves)
ZUMA-3 vs. pooled INO-VATE/TOWER (proxy for FLAG-IDA)					
• IPD from ZUMA-3 for KTE-X19 • Published AD from pooled INO-VATE and TOWER for FLAG-IDA	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup	mITT phase 1+2 (N=78)	INO-VATE (N=162) TOWER (N=134)	• OS (KM curves) • EFS (KM curves) • Response rate	• **Naïve analysis (base case)** • Observed absolute effects by treatment (CR rate, KM curves) • **MAIC analysis** • Propensity score weighted absolute effects for KTE-X19 matched to the population in pooled INO-VATE/TOWER (CR rate, KM curves)
ZUMA-3 vs. SCHOLAR-3 (blinatumomab)					

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
• IPD from ZUMA-3 phase 2 for KTE-X19 • IPD from SCHOLAR-3 synthetic control arm (SCA) 3 for blinatumomab	Adult patients with R/R ALL, irrespective of Philadelphia chromosome status or relapsed/refractory subgroup; SCA-3 cohort represents patients from historical clinical trials who had not previously been treated with blinatumomab or inotuzumab	mITT phase 2 (N=[redacted]) *Note: the economic model utilizes the ZUMA-3 mITT phase 1+2 Ph- overall population for the comparison*	SCHOLAR-3 SCA-3 (N=[redacted])	• OS (KM curves) • EFS (KM curves) • Response rate	• **SCHOLAR-3 analysis (base case)** • (SCHOLAR-3 IPD constructed matching to ZUMA-3 IPD) observed absolute effects by treatment (CR rate, KM curves)
ZUMA-3 vs. TOWER (blinatumomab)					
• IPD from ZUMA-3 for KTE-X19 • Published AD from TOWER for blinatumomab	Adult patients with R/R ALL, irrespective of relapsed/refractory subgroup, Philadelphia chromosome negative	mITT phase 1+2 Ph- (N=61)	ITT (N=271)	• OS (KM curves) • EFS (KM curves) • Response rate	• **Naïve analysis** • Observed absolute effects by treatment (CR rate, KM curves) • **MAIC analysis** • Propensity score weighted absolute effects for KTE-X19 matched to the population in TOWER (CR rate, KM curves)

Data sources	Target population	Analysis population		Efficacy outcomes	Indirect comparison method and corresponding output
		ZUMA-3 KTE-X19	**External study**		
ZUMA-3 vs. PACE (ponatinib)					
• IPD from ZUMA-3 for KTE-X19 • Published AD from PACE for ponatinib	Adult patients with R/R ALL, irrespective of relapsed/refractory subgroup, Philadelphia chromosome positive	mITT phase 1+2 Ph+ (N=17) *Note: the economic model utilizes the ZUMA-3 mITT phase 1+2 overall population for the comparison*	PACE (N=32)	• OS (KM curves)	• **Naïve analysis (base case)** • Observed absolute effects by treatment (KM curves)

Key: AD, aggregate data; ALL, acute lymphoblastic leukaemia; CR, complete remission; EFS, event-free survival; HR, hazard ratio; IPD, individual patient data; ITT, intention to treat; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; mITT, modified intention to treat; OS, overall survival; R/R, relapsed or refractory
The mITT phase 1+2 dataset comprises 55 phase 2 patients and the 23 phase 1 patients treated with the target dose of 1 x 10^6 cells/kg.

In clarification question B12, the ERG requested the results of all tests for proportional hazards (PH) between the MAIC adjusted ZUMA-3 and comparator populations together with ICERs for scenarios in which a hazard ratio (HR) obtained from each adjusted comparison is applied to the EFS and OS survival functions from the appropriate ZUMA-3 dataset. The company provided the PH evidence but did not provide the additional economic analyses nor comment on the request. In the CS it was stated that "*the proportional hazard assumption was violated in the comparison of KTE-X19 versus relevant comparators*" (though it was clarified in response to question A8 that this was not the case for the EFS comparison with inotuzumab). The ERG notes that tests for proportional hazards have a tendency to lack power especially for small- or moderately-sized datasets and in the presence of censoring. The ERG's view is that there is no clear evidence against PH for the MAIC OS comparisons in the case of TOWER, INO-VATE or the pooled dataset. As previously noted, the same is true for the EFS inotuzumab comparison. For the EFS comparison with TOWER the evidence is marginal. Only for the pooled TOWER/INO-VATE EFS comparison is there strong evidence that the PH assumption does not hold, although even in this case the PH assumption is not violated to the extent that survival curves or lines on the complementary-loglog plot cross. Given that there is a significant possibility of bias associated with any of the analysis methods that can be employed in this STA, the ERG believes that assuming a transportable HR treatment effect, estimated from the MAIC analysis (as presented in CS Table 26) applied to the ZUMA-3 population, would have been a reasonable approach to take if the company believes that matching to patients in the studies other than ZUMA-3 is inappropriate. In its economic analysis the company assumed patients who survived disease-free to three years were cured (see Section 4.2.3). This means that long-term survival extrapolations are not required and therefore a strong assumption of long-term PH is not necessary when using a transportable HR approach.

3.4.1 MAICs

The company's MAIC analysis involved: (i) assessing feasibility of unbiased comparisons using MAIC based on overlap of population characteristics; (ii) redefining outcome definitions in ZUMA-3 to match those in the comparator studies; (iii) fitting a logistic regression model to estimate MAIC weights using covariates informed by clinical advice; (iv) using the weighted ZUMA-3 population to form KM functions and fit parametric survival functions which were used in the economic model. In addition, the company provided HRs between the weighted ZUMA-3 populations and comparator populations.

The choice of covariates was based on clinical advice regarding prognostic factors and treatment effect modifiers for R/R ALL. However, reduction in effective sample size (ESS), which tends to reduce with every added covariate) and model convergence were also factors in the final choice of model. An initial set of 20 potential covariates were considered, as shown in Table 30. Of these, six were excluded because comparator data were not available. Clinicians' comments (MAIC Technical report Table C1[39]) suggest that these 6 may be potentially important. The remaining 14 covariates were ranked in order of

importance by the company based on previously elicited clinician comments and scores (MAIC report Table C1). Two covariates were then considered to be the same: % BM blasts at screening and peripheral blasts. With the latter removed, the top 9 ranked from the remaining 13 were considered for inclusion in the weighting model. In each case, covariates were removed from the weighting model until convergence was achieved. The company investigated whether a higher level of ESS could be preserved by further reducing the number of covariates. However, it was decided that this could not be done without excluding important covariates. ESS reduction was in the range 69-79% (over the different ZUMA-3 populations) after matching to INO-VATE and in the range 51-64% after matching to TOWER. The salvage status covariate was included in the models in two alternative ways: (i) as a two-category variable, first salvage versus second or higher salvage; and (ii) as a three-category variable, first salvage, second salvage, third or higher salvage. In answer to clarification question B6, the company stated that the tri-partite categorisation was used in the final MAIC analyses as it had a minimal impact on the ESS while providing more stratification of the type of salvage.

The ERG notes that important covariates may have been excluded during this selection process especially among those for which comparator data were not available. However, the ERG recognises the need to maintain ESS and also notes the fact that among many possible important covariates there may be some redundancy. As noted by the company, the inclusion of 6-8 covariates is in keeping with the median of six identified from 16 MAICs included in health technology appraisals for NICE in oncology between 2010 and 2018.[40] It is difficult to quantify the amount of bias that may remain after the matching process but the ERG is satisfied that the company's approach is comparable to other technology appraisals.

Clarification question B7 noted that concerns have been raised about MAIC process by Phillippo *et al*.[41] and requested that an alternative simulated treatment comparison analysis be carried out to further quantify uncertainty and account for possible bias. The company stated that it was not able to carry out this analysis in the time available and that their approach is consistent with previous CAR-T appraisals and in line with NICE guidance, noting that other studies have supported the use of MAIC (e.g. Ramiro-Azocar *et al*.[42]). The ERG notes that the latter study assumes that the assumptions of MAIC are not violated whilst the Phillippo study investigates the robustness of both methods to failure of assumptions. Furthermore, whilst in their response to clarification question B7 the company restated their belief that naïve comparisons were the most appropriate approach, the ERG's contention is that this leaves a strong possibility of bias and that applying a transportable HR to the ZUMA-3 data would be a sensible approach with the HRs ideally being estimated using both MAIC and STC adjustments to fully quantify uncertainties.

Table 30: Covariates considered for inclusion in the MAIC weighting models, their clinical ranking and those that were finally included in each model (adapted from CS, MAIC technical report, Table C1)

Factor	Potentially Important	Comparator data available	Rank	Considered	Matching INO-VATE	Matching TOWER	Matching pooled*
Primary refractory	Y	Y	1	Y		Y	
Duration of first remission <12 month	Y	Y	2	Y	Y	Y	Y
Prior allogeneic stem cell transplant	Y	Y	3	Y	Y	Y	Y
Age at baseline	Y	Y	4	Y	Y	Y	Y
ECOG performance status at baseline	Y	Y	5	Y	Y	Y	Y
Lines of prior therapies/salvage phase	Y	Y	6	Y	Y	Y	Y
% bone marrow blasts at screening	Y	Y	7	Y	Y		
Peripheral blasts	Y	Y	8	N			
Complex karyotype	Y	Y	9	Y	Y		
Philadelphia chromosome	Y	Y	10	Y	Y	Y	Y
Sex	N	Y	11	N			
Race	N	Y	12	N			
Region	N	Y	13	N			
Normal karyotype	N	Y	14	N			
Low hypodiploidy	Y	N		N			
Near triploidy	Y	N		N			
Extramedullary disease	Y	N		N			
Mixed lineage leukemia translocation	Y	N		N			
CD19 expression based on central read	Y	N		N			
Bridging chemotherapy	Y	N		N			

Y: Yes; N: No.

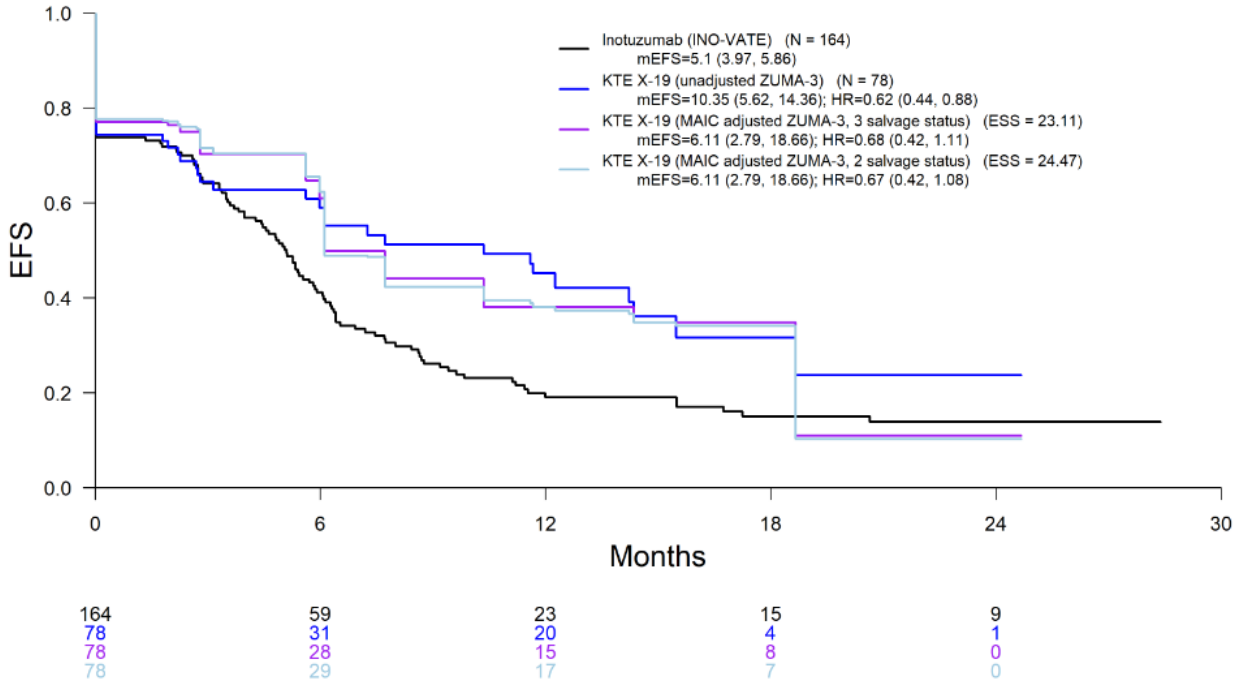
* The column for the pooled matching is the ERG interpretation of the company's statement that "Covariates reported by both trials (INO-VATE and TOWER) were matched for the comparison with chemotherapy.

The MAIC-weighted ZUMA-3 dataset was used together with the comparator datasets to estimate treatment effects in the form of hazard ratios and median survival times. The results are presented in Table 31 and Table 32 for OS estimated by naïve comparisons and MAICs respectively, Table 33 for OS for KTE-X19 versus blinatumomab as estimated from SCHOLAR-3, and

Table 34 and Table 35 for EFS estimated by naïve comparisons and MAICs respectively. All the HRs estimates show a statistically significant treatment advantage for KTE-X19 with the exception of the MAIC comparisons to inotuzumab where the results are in favour of KTE-X19 but are not statistically significant. The ERG suggested during clarification that the company perform an exploratory cost-effectiveness analysis where the HRs from the MAIC were assumed transportable to the ZUMA-3 population so that the comparator survival curves could be derived from those of ZUMA-3. The company did not undertake this analysis.

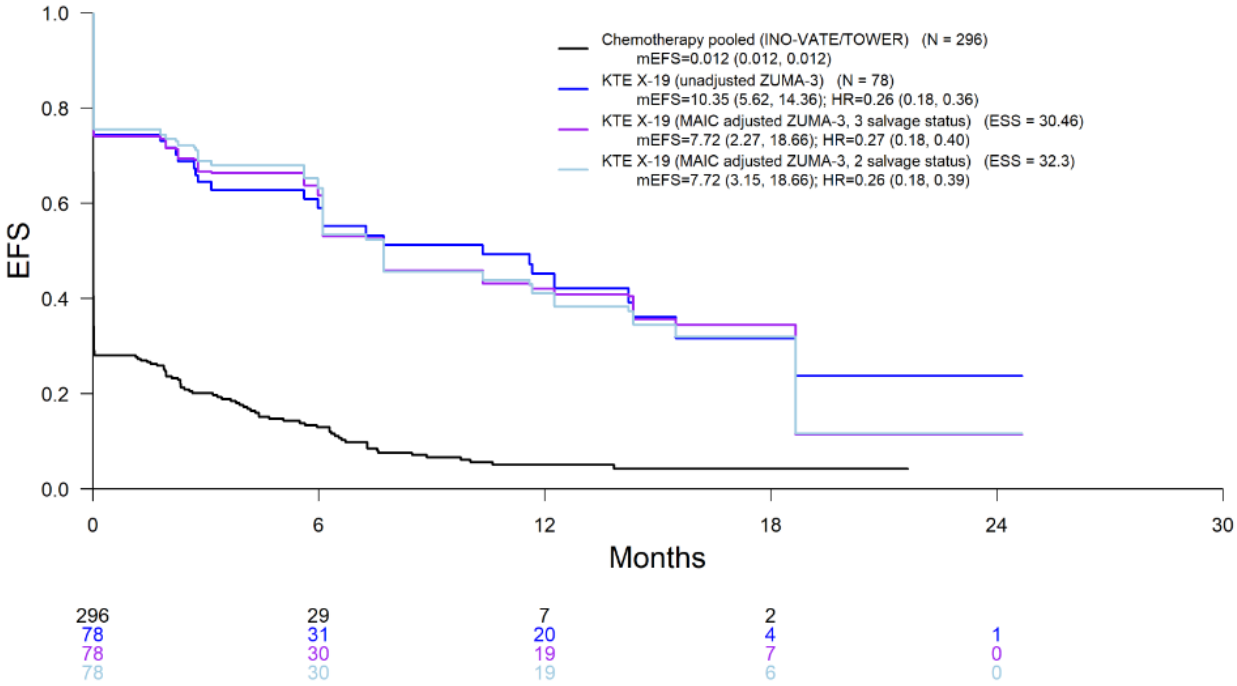
The company used the MAIC analyses in the overall population for inotuzumab and FLAG-IDA to conduct scenario analyses. In these analyses, the same survival models were fitted to the comparator data as with the naïve analyses. For ZUMA-3, survival models were fitted to the MAIC-weighted survival data which is represented in comparison to the naïve KM curves in Figure 6 to Figure 9. The ERG asked for clarification on why scenarios analyses were only carried out using the MAICs for the overall population. The company responded that no Ph subgroup data were available from the INO-VATE study for the FLAG-IDA and inotuzumab comparisons. The ERG remains uncertain, however, why a scenario analysis wasn't carried out using the MAIC for blinatumomab for the Ph- subgroup.

Figure 6: Event-free survival for ZUMA-3 mITT phase 1+2 versus INO-VATE (Reproduced from MAIC report Figure E2)



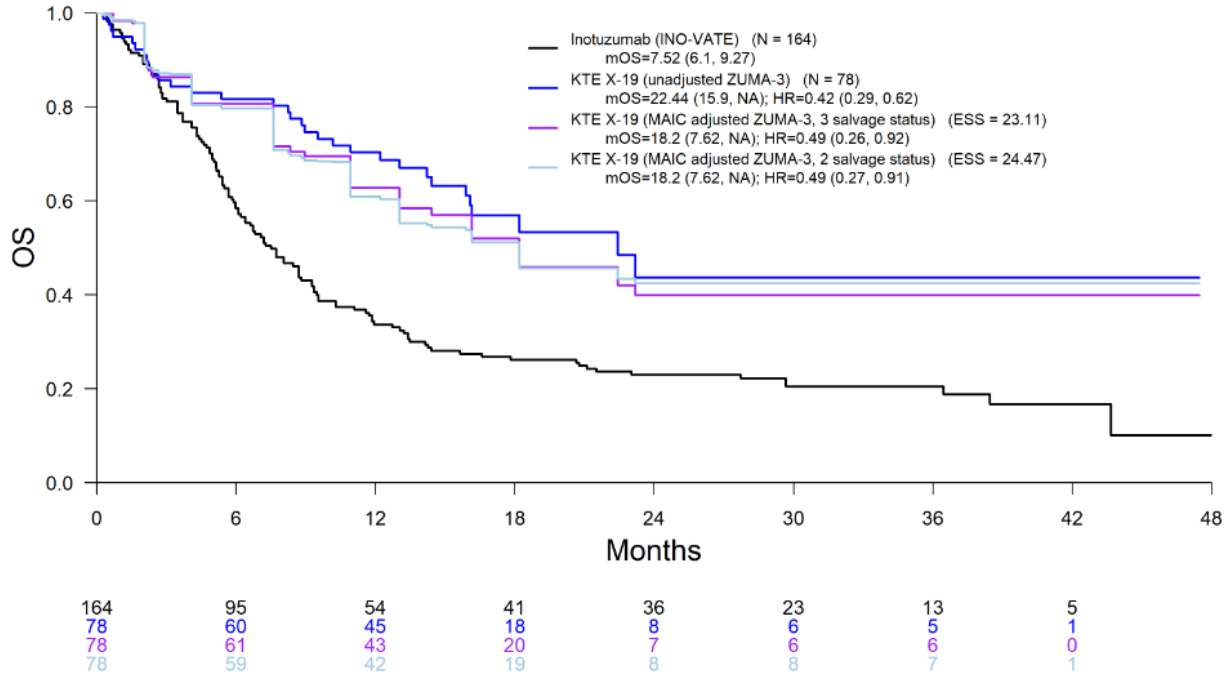
Abbreviations: *EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; m, median; MAIC, matching-adjusted indirect comparison*

Figure 7: Event-free survival for ZUMA-3 mITT phase 1+2 versus stacked IPD in INO-VATE and TOWER (Reproduced from MAIC report Figure E10)



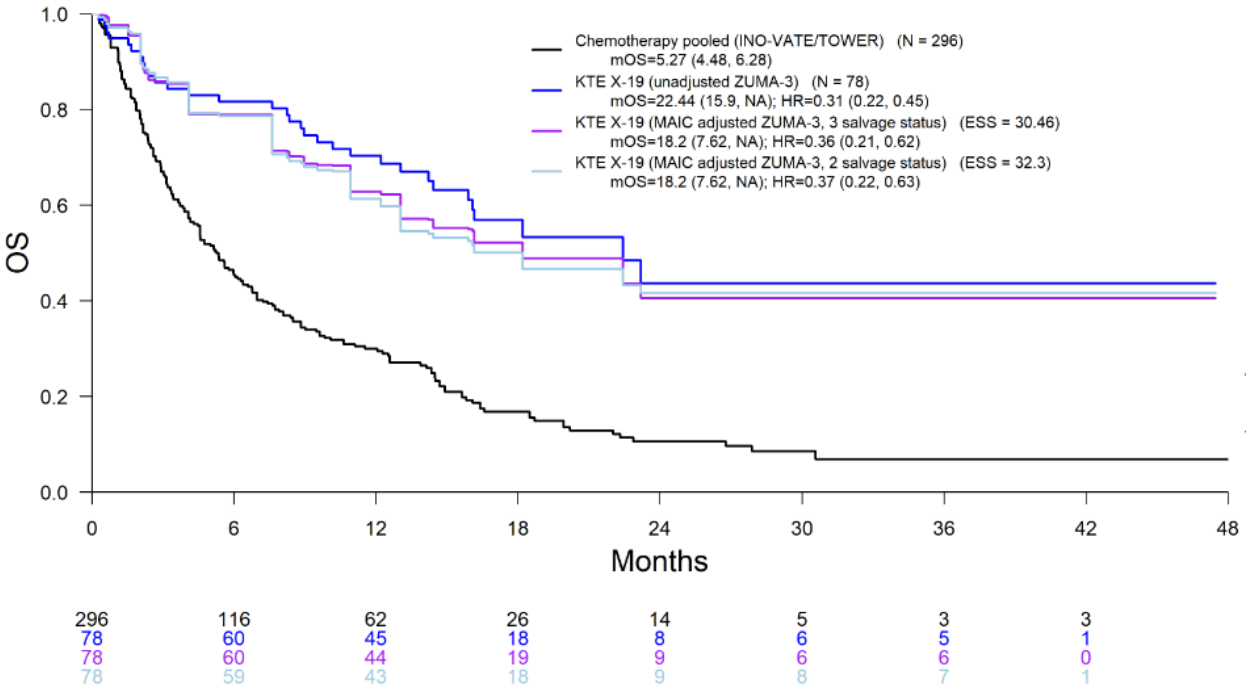
Abbreviations: *EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; m, median; MAIC, matching-adjusted indirect comparison*

Figure 8: Overall survival for ZUMA-3 mITT phase 1+2 versus INO-VATE (Reproduced from MAIC report Figure D2)



Abbreviations*: ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; m, median; OS, overall survival*

Figure 9: Overall survival for ZUMA-3 mITT phase 1+2 versus pooled IPD in INO-VATE and TOWER (Reproduced from MAIC report Figure D10)



Abbreviations: *ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; m, median; OS, overall survival*

Table 31: Summary of naïve ITC results for OS (adapted from CS Table 25 and Table 26).

Comparison	ZUMA-3 analytical set	Median OS in unadjusted ZUMA-3 patients	Median OS for the comparator	HR (CI) from naïve ITC
KTE-X19 vs Blinatumomab (TOWER)	Phase 1+2 mITT (N=78)*	22.44 [redacted]	[redacted]	[redacted]
KTE-X19 vs Inotuzumab (INO-VATE)	Phase 1+2 mITT (N=78)	22.44 [redacted]	[redacted]	[redacted]
KTE-X19 vs pooled chemo	Phase 1+2 mITT (N=78)	22.44 [redacted]	[redacted]	[redacted]
KTE-X19 vs ponatinib	Phase 1+2 mITT Ph+ subgroup (N=17)	[redacted]	[redacted]	[redacted]

Key: CI - confidence interval, ESS - effective sample size, HR - hazard ratio, ITC - indirect treatment comparison, mITT - modified intention-to-treat, NE - not estimable, OS - overall survival.

*This was cited as 61 subjects representing the Ph- subgroup in CS, Table 25 and clarification response, Table 12. However, data presented in CS, Figure 25 and reported here are for ZUMA-3 mITT overall population.

Table 32: Summary of MAIC results for OS (adapted from CS Table 25 and Table 26)

Comparison	ZUMA-3 analytical set	ESS*	ZUMA-3 MAIC median OS (months) (CI) 3 salvage status*	MAIC HR (CI) 3 salvage status*	MAIC median OS (months) (CI) 2 salvage status*	MAIC HR (CI) 2 salvage status*
KTE-X19 vs Blinatumomab (TOWER)	Phase 1+2 mITT (N=78)**	37-39	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs Inotuzumab (INO-VATE)	Phase 1+2 mITT (N=78)	23-24	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs pooled chemo	Phase 1+2 mITT (N=78)	30-32	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI - confidence interval, ESS - effective sample size, HR - hazard ratio, MAIC - matched adjusted indirect comparison, mITT - modified intention-to-treat, NE - not estimable, OS - overall survival.

*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.

** This was cited as 61 subjects representing the Ph- subgroup in CS, Table 25 and clarification response, Table 12. However, data presented in CS, Figure 25 and reported here are for ZUMA-3 mITT overall population.

Table 33: Summary of SCHOLAR-3 results (adapted from CS Table 25 and Table 26)

Comparison	ZUMA-3 analytical set	ZUMA-3 median OS (months) (CI)	Median OS for blinatumomab (months) (CI)	HR (CI)
KTE-X19 vs Blinatumomab (SCHOLAR-3 SCA-3)	Phase 2 mITT (N=[redacted])	[redacted]	[redacted]	[redacted]

Key: CI - confidence interval, HR - hazard ratio, mITT - modified intention-to-treat, NE - not estimable, OS - overall survival, SCA - synthetic control arm

SCHOLAR-3 is a retrospective cohort study utilizing data from the Phase 2 ZUMA-3 investigational study (mITT) and IPD sampled from historical clinical trials in relapsed or refractory adult ALL contained within the Medidata Enterprise Data Store database to create a matched synthetic control arm.

Table 34: Summary of naïve ITC results for EFS (adapted from CS Table 25 and Table 27)

Comparison	ZUMA-3 analytical set	ZUMA-3 Median EFS	Median EFS for the comparator	Naïve HR (CI)
KTE-X19 vs Blinatumomab (TOWER)	Phase 1+2 mITT (N=78)*	[redacted]	[redacted]	[redacted]
KTE-X19 vs Inotuzumab (INO-VATE)	Phase 1+2 mITT (N=78)	[redacted]	[redacted]	[redacted]
KTE-X19 vs Pooled Chemo (TOWER +INO-VATE)	Phase 1+2 mITT (N=78)	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; MAIC, Matching-adjusted indirect comparison.

*This was cited as 61 subjects representing the Ph- subgroup in CS, Table 25 and clarification response, Table 12. However, data presented in CS, Figure 28 and reported here are for ZUMA-3 mITT overall population.

Table 35: Summary of MAIC results for EFS (reproduced from CS Table 25 and Table 27)

Comparison	ZUMA-3 analytical set	ESS*	ZUMA-3 MAIC median EFS (months) (CI) 3 salvage status*	MAIC HR (CI) 3 salvage status*	ZUMA-3 MAIC median EFS (months) (CI) 2 salvage status*	MAIC HR (CI) 2 salvage status*
KTE-X19 vs Blinatumomab (TOWER)	Phase 1+2 mITT (N=78)**	37-39	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs Inotuzumab (INO-VATE)	Phase 1+2 mITT (N=78)	23-24	[redacted]	[redacted]	[redacted]	[redacted]
KTE-X19 vs Pooled Chemo (TOWER +INO-VATE)	Phase 1+2 mITT (N=78)	30-32	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; EFS, event-free survival; ESS, effective sample size; HR, hazard ratio; MAIC, Matching-adjusted indirect comparison.

*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.

**This was cited as 61 subjects representing the Ph- subgroup in CS, Table 25 and clarification response, Table 12. However, data presented in CS, Figure 28 and reported here are for ZUMA-3 mITT overall population.

3.5 Conclusions of the clinical effectiveness section

The pivotal study (ZUMA-3) is an international, multi-centre, non-randomised, uncontrolled, unblinded, ongoing single-arm study. The study was assessed by the ERG as being at moderate risk of bias. It is a small study with 78 subjects at the target dose across two phases, and with a median follow-up duration of 18.1 months. KTE-X19 demonstrated efficacy in terms of overall CR, OS and MRD- for the study population. However, AEs related to KTE-X19 treatment were frequent and certain AEs at

Grade 3 or higher were also common (pyrexia, hypotension and hypoxia), and four treatment-related deaths were recorded across all patients in the two phases, including two treatment-related deaths at target dose.

The study included no UK patients and it is debatable whether the study population reflects the population of patients who would be likely to be eligible for KTE-X19 in clinical practice in England. As detailed in Section 2.3.1, the company is positioning the technology for patients unfit to receive SCT although the ZUMA-3 eligibility criteria did not explicitly state as an inclusion criterion patients who are unfit for SCT. However, the ZUMA-3 population is expected to include those who have a ECOG performance score (ECOG PS) of 2 for whom SCT is inappropriate or contraindicated and these patients were not recruited in ZUMA-3. Whilst the ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status, the lack of Ph+ patients in TOWER, and lower percentage in INO-VATE compared to ZUMA-3 add uncertainty on which study best reflects the population who could receive KTE-X19 in England.

In combination, the KM estimates of OS and RFS cause concerns for the ERG if it is assumed that KTE-X19 can be a standalone, curative treatment. The RFS KM (Figure 4) [redacted] (Figure 3). This survival would not be anticipated in untreated patients and may suggest that many relapsing patients were salvaged with allo-SCT or further subsequent therapy. The ERG remains uncertain of the impact of further lines of therapy used at ZUMA-3 after KTE-X19 and how different the OS outcomes would be without the use of allo-SCT and subsequent treatments.

In an absence of study data directly comparing KTE-X19 with relevant comparator therapies, the CS reported a MAIC comparing the non-randomised ZUMA-3 data with data from two RCTs (TOWER and INO-VATE). The two RCTs were at high risk of bias and the outcomes compared were OS and RFS, which was reported as EFS. The comparator studies included adult ALL patients with a number of different characteristics from the ZUMA-3 population, and applied slightly different criteria for the CRi outcome. A naïve indirect comparison was also conducted that included data from the MAIC trials and from a small study of ponatinib, with a substantially different ALL population (older and exclusively Ph+), and individual patient data from an unpublished clinical study report (SCHOLAR-3).

The main reason stated by the company as to why the naïve comparison approach was adopted in their base case was that *"100% of the ZUMA-3 patients are generalisable to its anticipated UK positioning, ZUMA-3 should provide the target population for any adjustments."* The ERG believes this may not

necessarily be the case as patients with an ECOG PS of 2 were not recruited and that the proportion of patients with Ph+ would likely be higher in English practice, and that the MAICs which match to the populations in TOWER and INO-VATE may be informative. The ERG acknowledges the existing limitations and remaining bias within the MAICs conducted by the company, however judges that the naïve comparisons have a greater possibility of bias.

4 COST EFFECTIVENESS

This section describes the company's economic model and the resulting cost-effectiveness estimates for KTE-X19 versus its comparators. This section also presents the ERG's critical appraisal of the updated model post-clarification and the methods and results of additional exploratory analyses undertaken by the ERG. The ERG was informed by the company that an additional data cut will be presented in the Technical Engagement (TE) process, thus results and conclusions presented here will be superseded before the STA comes to the NICE Appraisal Committee. It is also anticipated that some of the analysis that are missing in the CS but that are requested by the ERG will be undertaken in the TE process.

4.1 ERG's comment on company's review of cost-effectiveness evidence

4.1.1 Company's search objective and methods

Appendix G of the CS reports a combined economic SLR including economic evaluations, healthcare cost and resource use as well as HRQoL evidence related to the R/R ALL in the adult population.

The company performed an initial SLR in June 2019 followed by a revised and up-to-date search in September 2021. The three-in-one systematic literature review search was to identify literature for: (i) published cost-effectiveness studies of treatments for patients who have R/R ALL (CS Appendix G); ii) HRQoL studies (CS Appendix H) and (iii) cost and resource use studies (CS Appendix I).

The company searched all the relevant electronic bibliographic databases in September 2021 (Appendix D.1.1 Identification and selection of relevant studies): MEDLINE [via Embase.com], PubMed-not-MEDLINE [via Embase.com], EMBASE [via Embase.com], Cochrane Database of Systematic Reviews [via Wiley], Cochrane Central Register of Controlled Trials [via Wiley], Database of Abstracts of Reviews of Effects [via CRD], NHS Economic Evaluation Database [via CRD] and Health Technology Assessment database [via CRD]. The ERG commented on the approach for simultaneous searching in Embase.com platform, sources searched in conference abstracts and clinical trials registries at Section 3.1.1. The company searches are fully reported and there were no consequential errors identified in the search strategies.

4.1.2 The inclusion and exclusion criteria used in the study selection

The inclusion and exclusion criteria used by the company are presented in CS Appendix G, Table 105. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant evidence.

4.1.3 Findings of the cost effectiveness review

The results of the SLR were provided in CS Table 35 for identified economic evaluation studies with the results for HRQoL evidence and health care cost and resource use reported in CS Appendices H and I, respectively. The SLR identified 14 publications that reported economic models evaluating blinatumomab, inotuzumab and standard chemotherapy. Twelve of these were conference abstracts and the remaining two were full text articles.[43, 44] Seven publications used a state transition model and five used a partitioned survival model; the remaining two analyses were abstracts of cost-minimisation analysis / budget impact analysis.[45, 46] Six publications involved US settings with one being UK-based,[47] whilst two did not specify the setting and reported only health outcomes.[48, 49]

To supplement these papers, four NICE appraisals, covering other comparators for similar indications were identified which were used to inform the model structure, assumptions, and parameterisation; these are summarised briefly in Table 36 of the CS.

4.1.4 Conclusions of the cost effectiveness review

As no models were identified that fully addressed the decision problem, the company built a *de novo* model. The approach taken was to use a partitioned survival model using the published EFS and OS data from KM curves for the relevant comparators, as detailed in Section 4.2 of this report. The ERG agrees that the modelling approach is appropriate.

4.2 Summary of the company's submitted economic analysis

Following the clarification process, the company submitted an updated version of its executable economic model, programmed in Microsoft® Excel. The updated model includes the following amendments:

(i) The option to select MAIC with PH assumption to model KTE-X19 efficacy relative to comparators using HRs, however, the ERG comments that these values could not be used to generate ICERs.

(ii) Corrections to the model calculations relating to the administration costs of cyclophosphamide, dexamethasone, mercaptopurine, and hydroxyurea

(iii) Amended dosing of CAR-T pre-treatment regimens using the body surface area (BSA) distribution from ZUMA-3 study

(iv) The inclusion of dose reductions for inotuzumab based on evidence reported in INO-VATE

(v) The application of a standardised mortality rate (SMR) to mortality rates instead of probabilities

(vi) The correction of an implementation error for calculating costs and QALY losses associated with AEs

(vii) The inclusion of further AEs for KTE-X19 which were missing from the original model

(viii) A correction relating to the frequency of rash as an AE associated with ponatinib

(ix) The addition of a one-off disutility associated with AEs from conditioning therapy

(x) The correction of IV administration costs associated with changing the pump used for the delivery of blinatumomab
(xi) Amended estimates of the number of vials of filgrastrim required per administration; and
(xii) Correcting administration cost calculations associated with inotuzumab and blinatumomab when used as subsequent therapies.

4.2.1 Model overview

The model evaluates the use of KTE-X19 in the treatment of R/R ALL adults for whom SCT is not indicated against four comparators: inotuzumab, FLAG-IDA, blinatumomab, and ponatinib. Health outcomes for the KTE-X19 group are based on ZUMA-3, with other published evidence used to estimate the effectiveness of the comparators as described in Section 4.2.2.

The economic analysis was performed for the overall population and two subgroups (Ph- and Ph+). The clinical evidence and model parameters used are described separately for each population from Section 4.2.3 onwards.

The base case model adopts an NHS and Personal Social Services (PSS) perspective. The base case model uses a 57-year time horizon with costs inflated to 2020 values using the NHS cost inflation indices published in the Personal Social Services Research Unit (PSSRU) report.[50] Costs and QALYs are discounted at a rate of 3.5% per annum as recommended by NICE.[51]

The model uses weekly cycles without half cycle correction. The ERG does not consider this to be a significant limitation due to the short cycle length used.

4.2.2 Interventions and comparators

The intervention is KTE-X19 in line with the specified decision problem. Treatment with KTE-X19 involves leukapheresis, conditioning chemotherapy, and bridging chemotherapy prior to one off infusion with KTE-X19. The administered dose of KTE-X19 is $1x10^6$ anti-CD19 CAR T-cells/kg as per Phase 2 of the ZUMA-3 study.

The comparators are dependent on the patient's Ph status. Inotuzumab, FLAG-IDA, and blinatumomab were the considered comparators for the Ph- subgroup, whereas inotuzumab, FLAG-IDA, and ponatinib were considered for the Ph+ subgroup. The company also presented cost effectiveness results for the overall population using inotuzumab ozmogamicin and FLAG-IDA as comparators.

Inotuzumab dosing used in the model reflects the INO-VATE study where inotuzumab was IV-administered for an average of three cycles at a dose of 0.8 mg/m^2 on day 1, then 0.5 mg/m^2 on days 8

and 15 in cycle 1 (which was 21 days). Cycles 2 and 3 were 28-days and dosing was either 0.8 or 0.5 mg/m^2 on day 1 (with the lower dose for previous cycle responders), 0.5 mg/m^2 on days 8 and 15.[12] In response to clarification question B57, the company amended the model to account for the dose reductions that could happen on the first day of cycles 2 and 3.

FLAG-IDA was administered until disease progression with the FLAG-IDA EFS curve derived from TOWER and INO-VATE data was used as a proxy for time on treatment, or for a maximum of four 28-day cycles in line with FLAG-IDA protocol from the Royal Surrey NHS Foundation Trust. The dosing for each component of FLAG-IDA (fludarabine, cytarabine, filgrastim, and idarubicin) are listed in the CS Section B.3.2.3. Clinical advice given to the ERG indicated that it is "*phenomenally rare*" to give more than two cycles and the aim is "*just trying to get to allo-SCT as soon as possible if [the] patient responds*".

Blinatumomab dosing used in the model reflects the schedule used in the TOWER study where blinatumomab was IV-administered for an average of 1.45 28-day cycles at a dose of 9 μg/day during week 1 of cycle 1 then 28 μg/day for the remainder of the cycle and during subsequent cycles. Patients spend six weeks per treatment cycle due to the presence of two weeks off treatment between consecutive cycles.

Ponatinib dosing is modelled according to the schedule in the PACE study, whereby an oral daily dose of 45 mg/day is administered until disease progression with the ponatinib PFS curve was used as a proxy for time on treatment, or for a maximum of three months. Whilst the ERG notes that PFS does not always equate to time on treatment, in this instance the median duration of treatment (2.7 months) is close to the median PFS generated in the company's model.

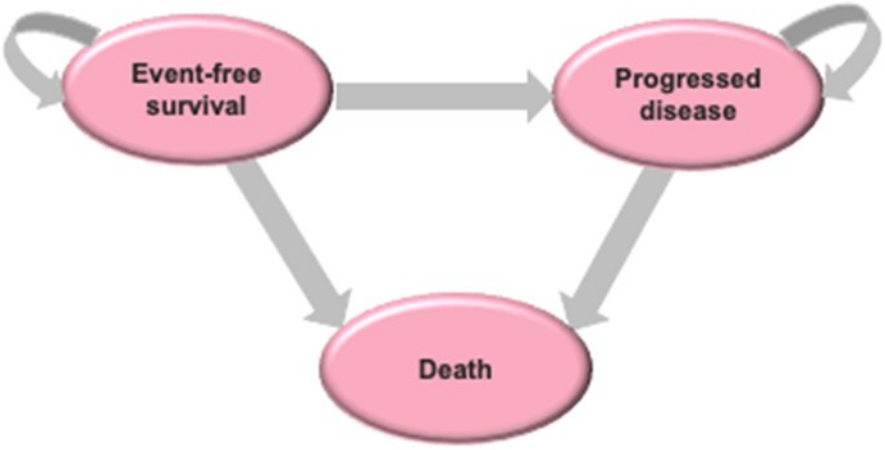
4.2.3 Model structure and logic

The company submitted a partitioned survival model that estimates the long-term outcomes of adult R/R ALL patients over a lifetime horizon. Patients receive either KTE-X19 or one of the comparators detailed in Section 4.2.2. The company justified its model structure based on the progressive nature of disease (patients cannot return to a better health state once they have experienced health deterioration to further states), and on consistency with previous economic modelling of NICE ALL appraisals (TA554[52], TA450[53]).

The model has three mutually exclusive health states: event-free (EF), progressed disease (PD), and death (Figure 10). All patients enter the model in the EF health state. The EFS curve directly informs the proportion of patients remaining in the EF state at each timepoint. The proportion of patients in the PD state corresponds to the difference between the proportion of patients alive (given by the OS curve)

and the proportion of patients in the EF state (given by the EFS curve). The proportion of patients in the dead state is 1 minus the proportion of patients alive.

Figure 10: The company's model structure (reproduced from CS Figure 33)



For the cohort where the intention is to provide KTE-X19 treatment, only a subset (78.8%) proceeded to get the infusion (that is the mITT ZUMA-3 population). The model incorporates the costs of leukapheresis, conditioning, and bridging chemotherapies of the patients who received these but who did not proceed to KTE-X19 infusion using cost multipliers. The cost multipliers used for the company's base case were from the combined datasets of Phases 1 and 2 of ZUMA-3 and included multipliers of 1.27 for leukapheresis costs (out of 99 patients undergoing leukapheresis, 78 had the infusion), 1.05 for conditioning chemotherapy cost (out of 82 patients, 78 had the infusion), and 1.25 for bridging chemotherapy cost (out of 91 patients, 73 had the infusion). Patients who failed to get the infusion were distributed to receive one of the other comparators based on the subgroup under evaluation as per ZUMA-3 CSR[36] (CS, Table 40). The KTE-X19 EFS and OS curves were adjusted such that the probability of survival at any timepoint equals the weighted average of the probabilities of survival for KTE-X19 and the appropriate comparators.

The model applies a structural assumption of cure. From year 3 onwards, patients who are alive are considered cured and accrue general population utility values but have an increased risk of death compared with the general population estimated by using an SMR of 1.09. The SMR value was sourced by the company from a study in diffuse large B-cell lymphoma (DLBCL) patients,[54] and was used by the company in a separate appraisal for KTE-X19 in mantle cell lymphoma (TA677[55]). The company justified using the same SMR value for R/R ALL patients based on data from two studies. The first study (SCHOLAR-1[56]) was claimed by the company to show that "*short-term outcomes (up to 2 years) on current SoC for DLBCL are very similar to those observed in the blinatumomab and inotuzumab*

R/R ALL clinical studies". The ERG notes that is not accurate because whilst SCHOLAR-1 indicates a 2-year survival of 20% for SoC for DLBCL patients, clinical trials report a 2-year survival of 10.6% on inotuzumab, and 4.2% on FLAG-IDA (CS, Table 110). The second study (Kliman *et al.*[57]) showed that "*recipients of allo-SCT who survived to at least 2 years and were disease-free continued to experience long-term outcomes close to the general population*". However, the same study, which included 26% of patients with an indication of ALL, reported a multivariate analysis of risk factors for OS in 2-year survivors, and showed that poor risk disease (such as ALL) renders a hazard ratio of 1.57 compared to the other indications mentioned in the study.

The company noted that there are different plateaus levels in ZUMA-3[19] for RFS at 20-25% and for OS at 40% in the primary data cut-off, implying that a proportion of patients (15-20%) remain in the PD state for a long time, which is not compatible with R/R ALL pathology. The company states that "*is because the way RFS KM are derived does not allow for robustly informative extrapolation*" and can be explained by two factors: (i) that for patients with CR/CRi the "*RFS at 2-3 year is more aligned to the plateau seen for OS (~35-40%)*" and (ii) that there "*is also a high level of censoring 40% consisting mainly of patients in ongoing remission (15%) and patients who received a subsequent allo-SCT (18%), representing a proportion without progression of 33% again much more aligned with the OS plateau ~40%.*". The ERG comments that administrative censoring should not alter the level at which the KM plateaus and that if subsequent treatments are benefitting patients, it is unclear whether these patients could be assumed to be cured at 3 years.

Despite the fact that 18% of patients received allo-SCT in the ZUMA-3 mITT Phases 1 and 2 combined dataset, no KTE-X19 patients are assumed to receive allo-SCT in the model. The two reasons provided by the company were: (i) the positioning of KTE-X19 does not allow patients to receive a second SCT or even receive a first SCT as a consolidation therapy following a CAR T-cell therapy, and (ii) no difference was shown in survival outcomes when patients who had SCT in ZUMA-3 were censored (

Figure 5). The ERG believes that given that the modelled outcomes are based on those observed in ZUMA-3, the costs and health outcomes of allo-SCT should also be included.

The key structural assumptions employed within the company's model are presented in Table 75 of the CS, with key points presented here:

- Patients alive after 3 years in the model are considered to be 'cured' albeit with a heightened mortality risk, however, their quality of life is assumed to be the same as an age- and sex-matched population.
- Naïve ITCs were preferred to MAICs in the company's base case.
- KTE-X19 clinical efficacy is informed by the combined data of the 78 patients receiving KTE-X19 infusion at Phases 1 and 2 of ZUMA-3 (mITT ZUMA-3 Phases 1 and 2 combined).
- The costs of Allo-SCT costs and any detrimental effects on HRQoL associated with allo-SCT were excluded from the KTE-X19 arm calculations.
- Patients who did not receive KTE-X19 infusion due to AEs were assumed to receive FLAG-IDA; the remainder received other comparator therapies.

4.2.4 Evidence used to inform the company's model parameters

Table 36 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections. The ERG highlights that ZUMA-3 related evidence uses the September 2020 data cut, and is expected to be updated at the TE process.

Table 36: Summary of evidence sources used to inform the model parameters

Parameter type	Parameter	Source(s)
Patient characteristics	Age	Zuma-3 mITT Phase 1+2 combined[18, 19]
	Percent male	
	Weight	
	BSA	
EFS and OS – KTE-X19 (up to 3 years)	Log-normal models fitted to survival data and weighted down to reflect non-responders receiving comparators. In scenario analyses, MAICs used to adjust the fitted curves to estimate outcomes for the populations of comparator studies	-Zuma-3 mITT Phase 1+2 combined[18, 19] – Ph- patients for Ph- subgroup -ZUMA-3 mITT Phase 1+2 combined[18, 19] – overall population for Ph+ subgroup
EFS and OS – inotuzumab (up to 3 years)	1 knot hazard and 2 knot normal spline models fitted to the EFS and OS KM plots respectively	INO-VATE ITT[34]
EFS and OS – blinatumomab (up to 3 years)	1 knot hazard spline and log-normal models fitted to the EFS and OS KM plots respectively of SCHOLAR-3 SCA-3 (historical data of patients receiving blinatumomab matched to ZUMA-3 mITT Phase 2 population). In a scenario analysis, the same functions were fitted to survival data of TOWER	SCHOLAR-3[38] (base case) TOWER[11] (scenario analysis)
PFS and OS – ponatinib (up to 3 years)	Log-normal models fitted to survival data	PACE[35] - R/R ALL population
EFS and OS – FLAG-IDA (up to 3 years)	Generalised gamma models fitted to survival data	Aggregate data pooled from INO-VATE[34] and TOWER[11]
EFS/PFS and OS extrapolations beyond 3 years	General population mortality with an SMR of 1.09 applied	England life tables (2018-2020),[58] Maurer *et al.*[54]
AE frequency	Incidence of grade 3 or 4 AEs occurring in ≥2% of the trial population for inotuzumab, ≥20% for ponatinib, and ≥5% of that for KTE-X19 and rest of comparators.	Zuma-3 mITT Phase 1+2 combined,[18, 19] INO-VATE,[34] TOWER,[11] PACE[35]
Health-related quality of life	Utility values for event-free and post-relapse health states (up to 3 years)	ZUMA-3 mITT Phase 2[19]
	Utility values (beyond 3 years) – same as general population	Ara and Brazier[59]
	Utility decrements associated with AEs	Various literature sources as described in CS, Table 46
Resource use	Dosing regimens for pre-treatment chemotherapy and KTE-X19 treatment	Zuma-3 mITT Phase 1+2 combined[18, 19]
	Dosing regimen for inotuzumab	INO-VATE[34]
	Dosing regimen for blinatumomab	Blinatumomab SmPC,[60] von Stackelberg *et al.*[61]
	Dosing regimen for ponatinib	PACE[35]
	Dosing regimen for FLAG-IDA	Expert opinion

	Subsequent treatment distribution	Zuma-3 mITT Phase 1+2 combined for KTE-X19[18, 19] plus assumptions for comparators
	Frequency of monitoring and follow-up	TA554[52]
Unit costs	Leukapheresis, pre-treatment chemotherapy and KTE-X19 treatment	KITE, NHS Reference costs 2019-20,[62] eMIT,[63] NHS drug tariff 2021,[64] BNF[65]
	Drug acquisition – Inotuzumab	NHS drug tariff 2021[64]
	Drug acquisition – Blinatumomab	BNF[66]
	Drug acquisition – Ponatinib	BNF[67]
	Drug acquisition – FLAG-IDA	eMIT,[63] NHS drug tariff 2021,[64] BNF[68]
	Drug administration	NHS Reference costs costs 2019-20[62]
	Monitoring and follow-up	
	Subsequent allo-SCT	
	Management of AEs	
	End of life	Georghiou and Bardsley[69]

AE - adverse event, BSA - body surface area, EFS - event-free survival, ITT - intention to treat, mITT - modified intention to treat, SmPC - summary of product's characteristics, eMIT - electronic market information tool, KM - Kaplan-Meier, MAIC - matched-adjusted indirect comparison, PFS - progression-free survival, Ph - Philadelphia chromosome, R/R ALL - relapsed/refractory acute lymphoblastic leukemia, SCA - synthetic control arm, SmPC - summary of product characteristics, SCT - stem cell transplant, SMR - standardised mortality rate

4.2.4.1 Initial patient characteristics at model entry

The population in the decision problem is adults (≥ 18 years of age) with R/R ALL for whom SCT is not indicated. This is in line with the anticipated market authorisation for KTE-X19 and ZUMA-3 eligibility criteria. Patient characteristics at model entry (that is, at the point at which patients would receive KTE-X19) are summarised in CS, Table 38. The modelled population had a mean age of 43.2 years, were 53.8% male, with a mean weight of 81 kg and BSA of 1.92 cm^2.

These baseline characteristics were used for calculating age-related utility decrements and treatment dosage for both the overall population and the subgroups by Ph expression.

4.2.4.2 Treatment effectiveness and extrapolation in the base case

Table 37 provides a summary of the survival distributions and datasets used in the company's base case analysis for OS and RFS/EFS/PFS. The proportional hazards assumption was checked and judged by the company not to hold; hence, independent models were used for each treatment group. The company fitted a range of survival models including standard parametric models (exponential, Weibull, log-logistic, log-normal, Gompertz, and generalised gamma), Royston-Parmar restricted cubic spline models (with up to 3 internal knots, fitted on the hazard, odds and normal scales) and mixture-cure models (MCMs).

For KTE-X19, the company's base-case analysis uses log-normal models for EFS and OS using the individual patient data from ZUMA-3 (23rd July 2021 cut-off, mITT, n=78 for overall population and Ph+ subgroup and n=61 for Ph- subgroup).

For the comparators, the following models were selected for the company's base case: spline models for inotuzumab fitted to data from the INO-VATE study, using a 1-knot hazard spline for EFS and 2-knot normal spline for OS; generalised gamma models for FLAG-IDA fitted to data pooled from INO-VATE and TOWER for both EFS and OS; log-normal models for ponatinib using data from the PACE study for both EFS and OS. For blinatumomab, a matched population from SCHOLAR-3 was used with a 1-knot hazard spline selected for EFS, and a log-normal model for OS.

Table 37: Summary of survival distributions and datasets applied in the company's base case naïve comparisons

	Treatment	Dataset for model fitting	N	RFS/EFS/ PFS model	OS model	Comparisons used for
1	KTE-X19	ZUMA-3 mITT Phases 1+2 combined	78	Log-normal to RFS data	Log-normal	Inotuzumab, for overall population and Ph+ subgroup
						FLAG-IDA, for overall population and Ph+ subgroup
						Ponatinib, for Ph+ subgroup
		ZUMA-3 mITT Phases 1+2 combined, Ph- subgroup	61	Log-normal to RFS data	Log-normal	Inotuzumab, for Ph- subgroup
						FLAG-IDA, for Ph- subgroup
						Blinatumomab, for Ph- subgroup
2	Inotuzumab	AD from INO-VATE ITT intervention arm	164	1-knot hazard spline to EFS data	2-knot normal spline	KTE-X19, for overall population and Ph+, Ph- subgroups
3	FLAG-IDA	AD from pooled INO-VATE and TOWER ITT comparator arms	162+134	Generalised gamma to aggregated EFS data	Generalised gamma	KTE-X19, for overall population and Ph+, Ph- subgroups
4	Blinatumomab	SCHOLAR-3 SCA-3	[redacted]	1-knot hazard spline to EFS data	Log-normal	KTE-X19, for Ph- subgroup
5	Ponatinib	AD from PACE	32	Log-normal to PFS data	Log-normal	KTE-X19, for Ph+ subgroup

AD - aggregate data, mITT - modified intention to treat, Ph - Philadelphia chromosome, ITT - intention to treat, EFS - event-free survival, PFS - progression-free survival, RFS - relapse-free survival

The EFS/PFS and OS curves in the model are based on naïve indirect comparisons between ZUMA-3 and the studies informing the comparators. The MAIC analyses, which adjust ZUMA-3 data to match the characteristics of the comparator studies at baseline (see Section 3.4), were used for scenario analysis for inotuzumab and FLAG-IDA. The company justified their choice of naïve comparison for the base case because "*the target population in the MAICs is different to that of KTE-X19*". For blinatumomab, the SCHOLAR-3 selected cohort was considered by the company to be more generalisable to the UK population than TOWER and rendered similar point estimates for relative efficacy of KTE-X19 compared with the naïve comparisons of KTE-X19 data from ZUMA-3 versus blinatumomab data from TOWER.

Figure 11 and

Figure 12 show the naïve Kaplan-Meier curves for OS and EFS/PFS, respectively, for KTE-X19 and its comparators and the company's base case extrapolations. The extrapolations are presented up to three years, after which the cure assumption is applied; beyond this timepoint, the model applies a mortality hazard from the general population together with an SMR of 1.09.

In the model, KTE-X19 EFS and OS parametric extrapolations were fitted to the mITT ZUMA-3 population (that is, patients who actually received the infusion). These curves were then down-weighted to account for patients who do not receive the infusion and received alternative treatments. Combining the mITT KM and the non-responders KM provides the ITT KM (see Figure 13).

Figure 11: OS KM curves and the company's base case extrapolations for KTE-X19 and comparators

Figure 12: EFS/PFS KM curves and the company's base case extrapolations for KTE-X19 and comparators

Figure 13: ZUMA-3 KM OS plots for mITT and ITT populations versus fitted parametric curves

The company stated that *"goodness of fit"* of the fitted models was assessed using: (i) the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), whereby smaller AIC/BIC values indicate a better statistical fit; (ii) visual inspection against the observed KM functions; (iii) for the comparators, consistency of estimated cure fractions with the proportion of patients reported to have survived following receipt of an allo-SCT; (iv) clinical plausibility of long-term extrapolations beyond the trial period based on clinical experts' opinion and relevant published external data where available. The ERG notes that only (i) and (ii) relate to goodness of fit with (iii) and (iv) potentially providing additional external data for model selection. In fact, the company only used criteria (i) and (ii) to justify the selection of parametric survival models (see CS, Sections B.3.3.3.2 to B3.3.3.4). During the clarification process, the ERG asked the company if external evidence was used to inform survival model selection (see clarification response, question B9). In terms of the comparator data for OS, the company's response presented a comparison of their economic model's predicted proportion of patients cured at 3 years to the proportion cured at 3 years as derived from the comparator studies. The ERG notes that this is an *a posteriori* validation rather than *a priori* survival model selection criteria. For the ZUMA-3 OS data, the company stated that the 3-year survival probability of 46% reported from the 23/7/21 data cut-off is a model selection criterion which can be used to exclude the otherwise well-fitting (in terms of AIC/BIC and visual fit prior to the tail of the KM function) Weibull model which predicts 39% survival. The ERG notes that the 46% survival probability was presented in Table 12 of the CS, along with a 95% confidence interval of 33.0-58.2%. It is unclear to the ERG how advisable it is to use, in isolation, a point estimate of survival from the later data cut-off, to select models for the earlier data cut-off. With respect to model selection for all EFS models, the company stated that the economic model is largely insensitive to the choice of survival model.

The ERG notes that for the MAIC scenario explored in the cost effectiveness results (CS, B.3.8.3), the company uses the same ZUMA-3 model choices that were selected in the company's base case naïve comparison. The ERG would have preferred that a separate model selection exercise for the MAIC-adjusted ZUMA-3 population was conducted. In response to clarification question B6, the company presented the fitted parametric models, MCM, and spline models in addition to the AIC and BIC values for each of the three matched populations (i.e. ZUMA-3 matched on INO-VATE, ZUMA-3 matched on TOWER, and ZUMA-3 matched on INO-VATE salvage chemotherapy). However, no further analysis was carried out to select the most appropriate model fit and extrapolation.

The company found that cure fractions varied widely amongst the fitted MCMs and noted that this was likely to be due to the immaturity of the data. For this reason, MCMs were not considered to be useful for the economic analysis. However, MCMs were included in a scenario analysis. In response to clarification question B10, the company stated that "*The scenario analysis using the MCMs can be considered purely exploratory in order to establish the impact on the ICER of assuming negligible cure*

fractions. In all populations and both EFS and OS, the log-normal MCM was the model used for KTE-X19, inotuzumab, blinatumomab and ponatinib, and the generalised gamma was the model used for FLAG-IDA. Note that these were not necessarily the best fitting MCM models according to AIC and BIC criteria." However, the response does not provide any further information to explain why the stated mixture-cure models were chosen for this scenario analysis.

In response to clarification question B3, the company confirmed that

Table 37, summarised its base case data and modelling choices. The ERG notes two points in particular:

(i) For the blinatumomab comparison in the Ph- subgroup, the matched SCHOLAR-3 SCA-3 synthetic control arm was used for blinatumomab, but the overall Phases 1 and 2 Ph- subgroup was used from ZUMA-3 (and not the Phase 2 Ph- subset that was matched in SCHOLAR-3). In response to clarification question B21, the company confirmed that the larger ZUMA-3 dataset was preferred for the comparison because of its increased size, longer follow-up, and for consistency with other comparisons.

(ii) For the ponatinib comparison in the Ph+ subgroup, the overall mITT population from Phases 1 and 2 was used. In response to clarification question B20, the company stated that "*the sample size of Ph+ subgroup was considered too small to inform KTE-X19 EFS and OS data*".

The ERG understands these modelling choices but notes that they may introduce bias into the results.

To assess the company's choice of base case survival models and the alternative models included for scenario analyses, the ERG considered the AIC and BIC statistics, visual goodness of fit together with the smoothed hazard plots provided in response to clarification question B8. The ERG also took into account the clinical advice provided by its clinical experts that for both EFS and OS events, the hazard would tend to decrease over time. The ERG believes that the company has made reasonable choices for the base case survival models. The only exception was for OS survival in the PACE dataset for ponatinib where the ERG preferred the Gompertz model to the log-normal distribution. The reasons for this are:

(i) The hazard function predicted by the Gompertz model is more in keeping with the trend of the smoothed observed hazard as shown in Figure 14 which suggests that it will continue at a lower level than all the model predicted hazards.

(ii) The visual fit of the Gompertz function to the observed KM data is very good and is in keeping with the clear plateau from 25 months onwards as seen in Figure 15.

(iii) AIC and BIC values (188.9 and 191.8 for Gompertz compared to 189.7 and 192.6 for log-normal; see CS Appendix B, Table 160) show that the two models are comparable in terms of statistical fit.

The ERG notes that many of the survival models gave a similar statistical and visual fit to the observed data but with extrapolations that result in varying survival proportions at 3 years. In the absence of other clear *a priori* external data, the ERG considered that it was important to fully investigate the resulting uncertainty arising from plausible models. The ERG notes that the company's selection of models for scenario analyses from the plausible models is often the most optimistic choice from its perspective in terms of survival advantage for KTE-X19. In the case of the generalised gamma model for EFS and Ph-OS in the overall KTE-X19 population, the ERG considered that the model choice was unjustifiably optimistic in terms of the predicted hazard and survival extrapolation. The ERG's view is that the

following scenario analyses should be performed in addition to those chosen by the company: (i) Weibull for KTE-X19 overall EFS and OS; (ii) Weibull for KTE-X19 Ph- OS; (iii) log-normal MCM for FLAG-IDA OS; (iv) Weibull MCM and log-logistic for blinatumomab (SCHOLAR-3) EFS.

Figure 14: Smoothed observed hazard for OS for ponatinib from the PACE study with predicted hazards from the parametric survival models overlaid (reproduced from company's response to clarification questions Appendix, Figure 46)

Figure 15: OS for ponatinib from the PACE study. KM plot with parametric model survival functions overlaid (reproduced from company's response to clarification question Appendix, Figure 112)

4.2.4.3 Health-related quality of life

4.2.4.3.1 Health-related quality of life associated with model health states

The company conducted an SLR for HRQoL evidence in adult patients with R/R ALL (see CS Appendix H). This systematic review originally identified ten studies and its update included an additional conference abstract; the latter reported EQ-5D values from ZUMA-3.[23] Nine of the ten studies identified in the original SLR related to the HRQoL estimates of blinatumomab and inotuzumab and SoC in the TOWER and INO-VATE studies. However, the company opted to use HRQoL data collected in ZUMA-3 in the model as "*these utility values were collected prospectively from the trial population and this was therefore deemed the most appropriate source*."

Table 38 summarises the utility values associated with health states used in the company's base case model. EQ-5D-5L scores were collected for mITT Phase 2 ZUMA-3 cohort at screening, day 0, day 28, month 3, and then every 3 months until month 15. These intervals were categorised into three main time periods (pre-injection including screening and day 0 visit, post-injection pre-relapse, and post-injection post-relapse). The collected EQ-5D-5L values were then mapped to the 3L version using the algorithm reported by van Hout.[70] The company's base case analysis aggregated cases where there was more than one observation for an individual within a time period by taking the mean of values in the time period in order to avoid bias towards individuals with multiple observations. The company then fitted four

mixed models for repeated measures (MMRM), one per each time period. These models each had two discrete covariates: model-based time-period and presence of grade 3 or 4 treatment emergent adverse event and their outputs are shown in CS Table 44.

Table 38: The different sets of utility values included in the company's economic model

Health state	Value (95% CI)	Source
Event-free survival	[redacted]	ZUMA-3 cross-walked EQ-5D-3L values MMRM model, intercept value plus post-injection, pre-relapse parameter value
Progressed disease	[redacted]	ZUMA-3 cross-walked EQ-5D-3L values MMRM model, intercept value plus post-injection, post-relapse parameter value
Alive patients after 3 years	Age- and sex-matched general population	Ara and Brazier[59]

After 3 years from the start of the model, patients who remain alive (regardless of their progression status) are assumed to have EQ-5D-3L utility values equal to that of an age- and sex-matched general population.[59] This is equivalent to assuming that surviving patients are fully cured in terms of their HRQoL. Age-related utility decrements for the EFS and PD health states were estimated from the regression model reported by Ara and Brazier.

4.2.4.3.2 Health related quality of life associated with adverse events

Utility decrements associated with AEs were incorporated as one-off values in the first model cycle. In line with TA554,[52] a utility decrement of 0.42 related to pre-treatment hospitalisation associated with blinatumomab or FLAG-IDA was applied for 9 and 21 days respectively. The company updated the model in response to clarification question B69 to account for AEs related to conditioning chemotherapy given prior to KTE-X19 infusion, with a one-off disutility value of 0.039 in line with TA677.[55]

The frequency of AEs for individual treatments included in the model are presented in Table 42 of the CS, and was informed by the appropriate clinical trials for each treatment. For KTE-X19 and blinatumomab, the model only included Grade 3 or 4 AEs occurring in ≥5% of the mITT ZUMA-3 phases 1 and 2 combined and TOWER populations, respectively. However, the INO-VATE study reported serious AEs occurring in ≥2% of patients on inotuzumab. The ERG asked the company to run a sensitivity analysis using the 2% threshold for KTE-X19 (clarification question B35). Instead, the company presented a scenario where all AEs were removed from the model and commented that "*the*

model is not very sensitive to the inclusion of AEs". The ERG notes that this scenario increased the ICER of KTE-X19 versus inotuzumab by around £3,000 per QALY gained.

Utility decrements associated with adverse events included in the model alongside the assumed duration per event are presented in the CS Table 46. Adverse event durations were sourced from ZUMA-3 study.

In addition, the ERG notes that the disutility value (0.208) associated with VOD was an over-estimate of the impact of the AE due to the unavailability of defibrotide injections to treat all trial patients as discussed in TA541.[71] At the time, the company applied both the high disutility value and defibrotide injection costs to produce a unfavourable ICER estimate for inotuzumab.

Table 39 presents the QALY loss due to AEs associated with each of the technologies included in the economic model. The ERG questioned the large difference between the KTE-X19-associated loss estimated in this STA versus that estimated for KTE-X19 in the mantle cell lymphoma appraisal TA677 ([redacted] in the original model versus 0.0713 in TA677) (clarification question B69). The company replied that AE durations were higher with TA677 because data were not available and assumptions had to be made. They added that the number of AEs in TA677 considered in the model was higher compared with this STA (35 versus 20). However, the ERG notes that the modelled QALY loss is also lower than -[redacted], the AE disutility estimated via the MMRM model fitted to QoL data collected in ZUMA-3 Phase 2.

Table 39: QALY loss due to AEs for different technologies in the economic model

Technology	Associated QALY loss
KTE-X19	[redacted]
Blinatumomab	0.09
Inotuzumab	0.28
Ponatinib	0.27
FLAG-IDA	0.16

†This differs from the previously reported value of [redacted] as the company amended mistakes in its original calculation.

4.2.4.4 Resources and costs

The resource use and costs included: pre-treatment costs, treatment acquisition costs, administration costs, health state unit costs and resource use, subsequent treatment costs including allo-SCT, AE unit costs and resource use, and terminal care costs.

The company's SLR of cost and resource studies (CS Appendix I) initially identified 12 publications reporting on health care resource utilisation, with only one study reporting UK data.[72] However, the reported estimates in this study were informed by clinicians' opinion; hence, the company chose to apply resource use estimates sourced from previous NICE STAs of treatments for R/R ALL.[52, 53, 71]

The ERG highlights that the company carried separate costing for each resource used for patients on KTE-X19, however the ERG is aware that there is a tariff across England for delivering a CAR-T therapy which could be used as an estimate of the combined costs of leukapheresis and any resources used both during and directly after infusion delivery (i.e. hospital stay, administration costs, AEs occurring post-infusion). The clinical lead for NHS England Cancer Drugs Fund advised the ERG that the tariff across England is on average, approximately [redacted] per patient for CAR-T treatment delivery, which includes leukapheresis, administration costs and subsequent care, and a market force factor.

4.2.4.4.1 KTE-X19 pre-treatment costs

The costs associated with KTE-X19 pre-treatment incorporated those associated with leukapheresis, conditioning therapy (to prepare patients to receive treatment), and bridging chemotherapy (to stabilise disease while waiting for infusion). A summary of all KTE-X19 pre-treatment costs is provided in Table 40. All costs were applied once-only at the start of the first model cycle. As described in Section 4.2.3, cost multipliers were used to account for patients who did not have KTE-X19 but who had leukapheresis or conditioning/bridging chemotherapies.

Table 40: Summary of all KTE-X19 pre-treatment costs in the company's model

Cost item	Cost per patient	Adjusted cost in the model	Source/assumption
Leukapheresis	£1,953.38	£2,479.29	NHS Reference Costs 2019/20,[62] weighted average of HRGs for stem cell and bone marrow harvest (currency codes SA34Z, SA18Z), as per NICE TA559[73] Adjusted cost estimated using a multiplier of 1.27 applied to reflect the 21 patients (out of 78) who underwent leukapheresis, but not KTE-X19 infusion
Conditioning chemotherapy	Hospital admission and administration costs £2,820.54	£3,205.51	Hospital admission: • NHS Reference Costs 2019/20,[62] weighted average of Acute Lymphoblastic Leukaemia with CC score 0-5+ SA24G-J, Day case • Hospital stay was 7 days for 65% of patients in line with TA554[52]

	Chemotherapy acquisition £228.60		• The remaining 35% received 3 consecutive days of chemotherapy in outpatient setting (see Section 4.2.4.4.3 for IV administration costs) Chemotherapy acquisition: • 3 infusions of fludarabine 25 mg/m^2 and one infusion of cyclophosphamide 900 mg/m^2 • Source of unit costs: electronic Market Information Tool (eMIT)[63] • BSA percentile from ZUMA-3, used to estimate dose and vial combination. Assumed drug wastage. Adjusted cost estimates using a multiplier of 1.05 to reflect the 4 patients (out of 82) who underwent conditioning therapy, but not KTE-X19 infusion
Bridging chemotherapy	Administration costs £1,087.48 Chemotherapy acquisition £201.73	£1,607.10	Hospital admission: • Duration of bridging therapy was 10 days to be received in outpatient setting[52] • Oral and IV administration costs were applied as described in Section 4.2.4.4.3 Chemotherapy acquisition: • Regimens were assumed based on distributions observed in mITT ZUMA-3 Phases 1 and 2 combined and reported in CS Table 52 • Source of unit costs: eMIT[63] • BSA percentile from ZUMA-3, used to estimate dose and vial combination. Assumed drug wastage. Adjusted cost estimates using a multiplier of 1.25 to reflect the 18 patients (out of 91) who underwent bridging therapy, but not KTE-X19 infusion

4.2.4.4.2 Treatment costs

4.2.4.4.2.1 KTE-X19

Infusion and administration costs of KTE-X19 including intensive care unit (ICU) and hospital stay are presented in CS Table 53. The proportion of patients who received the infusion were 78.79% of the ITT ZUMA-3 population. Table 41 summarises the treatment costs for KTE-X19.

Table 41: KTE-X19 overall treatment costs in the company's model

Cost category	Cost per patient	Proportion of KTE-X19 cohort arm to which cost is applied
Pre-treatment costs	£7292	100%

KTE-X19 infusion cost (including PAS)	[redacted]	78.79%
KTE-X19 administration cost (including ICU and hospital stay)	£14,765	78.79%

PAS - Patient Access Scheme

The remaining 21.21% who failed to receive the infusion went on to take one of the other comparators as shown by the distribution presented in Table 40 of the CS. In summary, 11.1% receive FLAG-IDA, 5% receive inotuzumab, whereas the remaining 5% receive either blinatumomab (Ph- status) or ponatinib (Ph+ status).

4.2.4.4.2.2 Inotuzumab

The unit cost of a 1mg vial of inotuzumab is £8048 as per NHS Drug Tariff.[64] Section 4.2.2 presents the dosing schedule of inotuzumab, whilst Table 42 updates Table 54 of the CS. In the updated model, the company linked vial calculations to BSA distribution, and considered reductions for the first dose of cycles 2 and 3 for responders. Administration costs including hospital stays are presented in Table 55 of the CS. All treatment costs related to inotuzumab were included as a once-only cost in the first model cycle.

Table 42: Inotuzumab drug acquisition costs

Cycle	day number	Recommended dose	% patients receiving regimen	Number of vials required	Acquisition cost per patient
Cycle 1 – 21 days	Day 1	0.8 mg/m^2	100%	2.01	£16,177
	Day 8	0.5 mg/m^2	100%	1.28	£10,341
	Day 15	0.5 mg/m^2	100%	1.28	£10,341
Cycle 2 onwards – 28 days	Day 1	0.8 mg/m^2	26.2%	0.53	£4242
	Day 1	0.5 mg/m^2	73.8%	0.95	£7629
	Day 8	0.5 mg/m^2	100%	1.28	£10,341
	Day 15	0.5 mg/m^2	100%	1.28	£10,341

4.2.4.4.2.3 Blinatumomab

Acquisition costs for blinatumomab were based on the list price to the NHS[66] (£2017 per 38.5µg vial, of which 28µg was useable). The drug regimen for blinatumomab used in the model was based on the dosing schedule as per protocol in TOWER and as discussed in Section 4.2.2, no vial sharing was

assumed. Blinatumomab acquisition and administration costs are presented in Table 56 and Table 57 of the CS. Administration costs include hospital stay for an average of 10 days of cycle 1, daily pump set-up cost, and outpatient administration cost.

In response to clarification question B71, the company changed the currency code for outpatient administration cost to reflect delivering subsequent elements of chemotherapy (currency code SB15Z: £253.77) rather than delivery at first attendance (currency code SB13Z: £302.53); this is in line with the approach used in TA450.[53] Table 23 summarises the acquisition and administration costs for blinatumomab. The weighted average number of cycles per patient was 1.45. Costs were applied once every six weeks in the first week of the cycle (4 weeks on treatment plus 2 weeks off treatment).

Table 43: Blinatumomab drug acquisition and administration costs applied in the model

Cycle	Dose per day (µg)	Administration cost components	% patients receiving regimen	Acquisition costs per patient	Administration costs per patient
Cycle 1 (days 1-7)	9	Hospital stay	96%	£13,554	£5,281
Cycle 1 (days 8-10)	28			£40,663	
Cycle 1 (days 11-28)		Pump daily set-up costs, bag change every three days, and IV administration costs			£1,534
Cycle 2	28		31%	£17,508	£666
Cycle 3	28		10%	£5,648	£215
Cycle 4	28		4%	£2,259	£86
Cycle 5	28		4%	£2,259	£86

4.2.4.4.2.4 Ponatinib

The unit price for ponatinib is £5050 per pack of 30 tablets of 45 mg ponatinib.[67] In the model, patients continue to receive ponatinib provided they remain event-free (used as a proxy for time on treatment) for a maximum of three months. Oral administration costs were assumed for ponatinib every 30 days in addition to treatment costs of FLAG-IDA, based on expert opinion, despite FLAG-IDA not being in used in the PACE study.

4.2.4.4.2.5 FLAG-IDA

FLAG-IDA treatment costs are summarised in Table 59, Table 60, and Table 61 of the CS. In response to clarification question B72, the company amended the drug acquisition cost per single administration to be £50 (the price of one vial) instead of £251 (the price of a pack of 5 vials) which resulted in total treatment costs of £1,836 per cycle (instead of £3,642). Costs were applied once every four weeks in the first week of the cycle.

4.2.4.4.3 Drug administration costs

The itemised drug administration costs applied in the model are presented in Table 49 of the CS.

Table 44 summarises the administration costs of KTE-X19 and the four comparators included in the model.

Table 44: Administration costs applied in the model

Intervention	Administration cost assumptions and calculations	Total administration cost
KTE-X19 – Conditioning chemotherapy	65% are inpatients and accrue the cost of hospital stay (£550) for 7 days. The remaining 35% receive IV chemotherapy for 3 days (3 * £303)	£2821 (£2965 after applying a cost multiplier of 1.05)
KTE-X19 – Bridging chemotherapy	Weekly dosing schedules were multiplied by 10/7 to estimate the costs of 10 days (duration of bridging therapy), oral administration costs were only assumed when a new pack is needed. For each IV treatment component, the number of administrations per 10 days was multiplied by IV administration cost (£303)	£1087 (£1356 after applying a cost multiplier of 1.25)
Inotuzumab	Patients receive the first two doses of the first cycle in an inpatient setting for 9.5 days with the third dose accruing IV administration costs (£303) For subsequent cycles, the three doses were multiplied by £303	£5528 for cycle 1, and £908 for subsequent cycles
Blinatumomab	10 days of hospital stay in cycle 1 (see Table 43). Afterwards, a daily pump cost of £3.89 was applied in addition to the IV administration cost (£254) twice weekly	£7099 for cycle 1, and £2147 for subsequent cycles
Ponatinib	A new pack is needed every 30 days for an oral administration cost of £211	£49 per week
FLAG-IDA	The treatments are administered over a course of 16.8 days per cycle in an inpatient setting[53]	£9241 per cycle

4.2.4.4.4 Medical resource use associated with health state

Health care resource use was assumed to depend on the patient's health state (pre- or post-progression), and time from starting treatment for R/R ALL. Associated costs comprised outpatient consultant visits, clinical tests and procedures with frequency based on TA554.[52] These are described in detail in Table 62, Table 63 and Table 64 of the CS. Unit costs for each were obtained from NHS Reference Costs.[62] A summary of the total costs by health state and by follow-up year, for each treatment arm, is presented in

Table 45. The increased costs associated with KTE-X19 treatment in year 1 is due to the increased frequency of consultant visits in the first year.

Table 45: Summary of health state resource use costs per week

Health state and year	KTE-X19	Comparators
EF (year 1)	£138.44	£72.97
EF (year 2)	£31.18	£30.99
EF (year 3)	£15.64	£15.50
EF (cured patients)	£7.70	£7.70
PD	£66.67	£66.67

EF - event-free, PD - progressive disease

4.2.4.4.5 Subsequent treatment costs for relapsed patients

Following disease progression, patients were assumed to receive subsequent treatments although not the therapy initially received. Subsequent treatment regimens included: inotuzumab in combination with ponatinib; inotuzumab alone; cyclophosphamide in combination with dexamethasone; and blinatumomab. The distribution of subsequent treatments for patients on KTE-X19 was sourced from the mITT ZUMA-3 Phases 1 and 2 combined dataset; this distribution was also assumed for patients initially treated with FLAG-IDA. However, for patients who started on inotuzumab, ponatinib, or blinatumomab, the distribution was re-weighted to exclude the initial treatment for R/R disease. Table 65 of the CS presents the distributions used for the different interventions in the economic model.

Subsequent treatment costs were applied as a once-only cost at the point of progression assuming the same treatment durations as when used pre-relapse. In response to clarification question B73, the company amended the costs of inotuzumab to include cycle-specific administration costs, and of blinatumomab to avoid double counting of pump and IV administration costs. Table 46 updates Table 66 of the CS based on the company's updated model.

Table 46: Subsequent therapy one-off costs

Initial regimen	Weighted acquisition cost for subsequent therapy	Weighted administration cost for subsequent therapy
KTE-X19	£25,225	£2051
Blinatumomab	£25,087	£1812
Inotuzumab	£9324	£1197
Ponatinib	£19,316	£1844
FLAG-IDA	£25,225	£2051

A proportion of patients in the model are assumed to receive an allo-SCT, with rates sourced from the relevant clinical trial evidence for each intervention (Table 47). Although 14 out of 78 patients (18%)

constituting mITT ZUMA-3 Phase 1+2 went on to receive allo-SCT, the company assumed in its base case that no patients in the model will receive SCT after KTE-X19. The reasons for this are provided in Section 4.2.3.

Table 47: Subsequent allo-SCT distribution

Initial regimen	Proportion receiving allo-SCT	Source
KTE-X19	0.0%	Assumption
Blinatumomab	13.21%	SCHOLAR-3 SCA-3
Inotuzumab	48.20%	INO-VATE
Ponatinib	46.88%	PACE
FLAG-IDA	22.93%	Pooled standard of care arm INO-VATE and TOWER*

SCA - synthetic control arm, SCT - stem cell transplant

The costs associated with allo-SCT were comprised of the following components: stem cell harvesting, the cost of the procedure, and the cost of long-term follow-up (up to 24 months). The total cost of allo-SCT was estimated as £117,751 and was applied as a one-off cost in the first cycle of the model.

The cost of stem cell harvesting and the allo-SCT procedure were obtained from NHS Reference Costs.[62] The cost of follow-up was obtained from a UK Stem Cell Strategy Oversight Committee Report published in 2014.[74] The costs over the follow-up period were weighted for the proportion surviving after the procedure to estimate the total mean follow-up cost per procedure (as illustrated in Table 69 in the CS), and were inflated to 2020 costs using the Hospital and Community Health Services (HCHS) index.[50]

4.2.4.4.6 AE costs

The model incorporated a weighted total AE cost, which was estimated from the unit cost of each event and the proportion of patients estimated to experience that event over the course of first-line treatment. The costs associated with the treatment of each AE were derived from NHS Reference Costs 2019–2020.[62] Where an AE was not associated with a specific unit cost in NHS Reference Costs, the company assumed equivalence to a similar event. The costs of AEs were applied as a once-only cost in the first model cycle. Table 42 in the CS reports the AE rates applied in the economic model, whereas CS Table 72 details the corresponding unit cost of AEs alongside the sources/assumptions used.

The cost of CRS accounted for treatment with tocilizumab and duration in an ICU for patients with Grade 3 or 4 symptoms ([redacted]%). Tocilizumab treatment costs were derived from the proportion of patients who had Grade 3 or 4 symptoms and the NHS Reference Costs,[62] assuming one administration

of tocilizumab was required for each patient. The ERG notes that this proportion differs from the value reported in the CSR for patients requiring tocilizumab for CRS.[36] The ICU stay was assumed to comprise 4.3 days and was costed using NHS Reference Costs.[62] The ERG notes that this was the median value reported for ICU stay for mITT ZUMA-3 Phases 1 and 2 combined and not a mean. CRS AE cost is reported in CS Table 70.

VOD costs were associated mainly with inotuzumab were calculated in line with the submission for inotuzumab in NICE TA541.[71] The cost per day (£1879) of excess hospital stay due to severe VOD was inflated using the HCHS index.[50]

In response to clarification question B69, the company identified an implementation error with how AE costs were calculated in their original model. The updated once-only AE costs applied for each treatment group are presented in Table 48. The costs of AEs associated with inotuzumab is largely driven by VOD events.

Table 48: Total once-only cost for AEs in the model

Treatment	Total once-only cost for AEs
KTE-X19	[redacted]
Blinatumomab	£775.06
Inotuzumab	£18,140.98
Ponatinib	£567.76
FLAG-IDA	£2,543.46

4.2.4.4.7 Terminal care costs

The model includes the costs of terminal care to all patients; this is applied to the incident number of deaths in each model cycle. The cost of terminal care was assumed to be £8,437, based on the 2014 report by Georghiou and Bardsley[69] where costs were inflated using the HCHS index.[50]

4.2.5 Model validation and face validity check

The CS reports that the assumptions and parameter values used in the model were validated by clinical experts, and that a technical review of the cost-effectiveness model was conducted by an independent modeller (CS, Section B.3.10). The ERG undertook further validation checks and identified minor errors which were fixed in the company's response to clarification questions.

4.2.6 Methods for model evaluation

The CS presents the results of the economic evaluation in terms of the incremental cost per QALY gained for KTE-X19 versus inotuzumab, FLAG-IDA, blinatumomab, and ponatinib. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSAs are presented in the form of a tornado diagram (reported in terms of ICERs for KTE-X19 versus each comparator). The distributions applied in the company's PSA are summarised in CS, Appendix M.

Three separate sets of results were presented for overall R/R ALL population, Ph- subgroup and Ph+ subgroup. The three groups differed by the comparators used, KTE-X19 clinical efficacy data as outlined in

Table 37, and post-relapse subsequent treatments as detailed in Section 4.2.4.4.5. In the post-clarification presentation of results, the company added a fully incremental analyses at the ERG's request.

4.2.7 Cost effectiveness results

The ERG noted that the updated model had limitations in its PSA and DSA in that the uncertainty in all costs were excluded (see response to clarification question B28), and some PSA iterations lacked face validity, for example, the utility in PD could be higher than for EFS, and the utility for EFS could be greater than that of the age- and sex-matched population (clarification question B42). The ERG's critique focusses solely on the deterministic base case; however, the ERG has amended the probabilistic model to address the perceived limitations, noting that this has no substantial impact on the results. The first change included the uncertainty on all costs except list prices; the second change was to reduce the higher utility in a pair of utilities to that of the lower pair if they were deemed to lack face validity.

All results presented in this section include the company's agreed PAS ([redacted] simple price discount). The results of the company's analyses based on the confidential PAS for blinatumomab, inotuzumab, ponatinib, and tocilizumab are presented in a separate addendum.

Central estimates of cost-effectiveness

The company's base case cost-effectiveness results for the Ph- and Ph+ groups are presented in Table 49. For the Ph- subgroup, the probabilistic version of the model suggests that KTE-X19 therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared to FLAG-IDA resulting in an ICER of £37,713 per QALY gained whilst inotuzumab and blinatumomab are extendedly dominated. The ICERs for KTE-X19 compared to inotuzumab and blinatumomab were £20,017 and £36,289 respectively.

For Ph+ patients, the probabilistic version of the model suggests that KTE-X19 therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient compared to FLAG-IDA resulting in an ICER of £35,395 per QALY gained whilst inotuzumab and ponatinib are extendedly dominated. The ICERs for KTE-X19 compared to inotuzumab and ponatinib were £18,140 and £31,123 respectively.

The deterministic version of the model produces slightly lower ICERs for KTE-X19 versus the other comparators, however the model appears relatively linear based on the similarity of the deterministic and probabilistic estimates.

Table 49: The company's base case results (fully incremental analysis)

Technology	Total life years accrued	QALYs accrued	Total costs incurred	Incremental			ICER
				Life years	QALYs	Costs	
Ph- population							
Probabilistic model (run by the ERG after adaptation)							
FLAG-IDA	3.63	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.02	[redacted]	[redacted]				ED
Inotuzumab	7.64	[redacted]	[redacted]				
KTE-X19	14.10	[redacted]	[redacted]	10.47	[redacted]	[redacted]	£37,713
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £20,017 and £36,289 respectively.							
Deterministic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,380
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £18,108 and £34,753 respectively.							
Ph+ population							
Probabilistic model (run by the ERG after adaptation)							
FLAG-IDA	3.65	[redacted]	[redacted]	-	-	-	
Ponatinib	5.76	[redacted]	[redacted]				ED
Inotuzumab	7.62	[redacted]	[redacted]				
KTE-X19	14.84	[redacted]	[redacted]	11.19	[redacted]	[redacted]	£35,397
ICERs of KTE-X19 versus inotuzumab and ponatinib are £18,140 and £31,123 respectively.							
Deterministic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£33,972
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,396 and £29,508 respectively.							

ED - extendedly dominated, QALYs - Quality-adjusted life years, ICER - Incremental cost-effectiveness ratio, Ph - Philadelphia chromosome

The company presents disaggregated outcomes, costs incurred, QALYs and life years accrued by different elements or states in the deterministic model, these results are presented in Table 50 and

Table 51 for the Ph- and Ph+ populations, respectively. The differences in costs are primarily associated with the acquisition cost of technologies whilst most of the additional QALY gain is a consequence of the higher proportion of 3-year survivors in the KTE-X19 group, although it is [redacted].

Table 50: Base case disaggregated outcomes (Ph- population)

Description	KTE-X19	Inotuzumab	Blinatumomab	FLAG-IDA
Disaggregated costs (discounted)				
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT costs	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)				
EFS health state	[redacted]	[redacted]	[redacted]	[redacted]
PD health state	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

QALYs - quality-adjusted life years; AE - adverse event; SCT - stem cell transplant; EFS - event-free survival; PD - progressed disease

Table 51: Base case disaggregated outcomes (Ph+ population)

Description	KTE-X19	Inotuzumab	Ponatinib	FLAG-IDA
Disaggregated costs (discounted)				
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]	[redacted]
Allo-SCT costs	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)				
EFS health state	[redacted]	[redacted]	[redacted]	[redacted]
PD health state	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

QALYs - quality-adjusted life years; AE - adverse event; SCT - stem cell transplant; EFS - event-free survival; PD - progressed disease

4.2.8 Company's PSA

Table 49 shows the ERG's probabilistic estimates of the company's base case. The company also presented the results of the PSA using cost-effectiveness planes and CEACs for KTE-X19 compared with the other comparators. The company's PSA suggests the probability that KTE-X19 generates more net monetary benefit than other comparators at a willingness-to-pay (WTP) threshold of £30,000 per QALY gained is [redacted] and [redacted] for the Ph- and Ph+ populations, respectively. Assuming a WTP threshold of £50,000 per QALY gained, the probability that KTE-X19 generates more net benefit is [redacted] and [redacted] for the Ph- and Ph+ populations, respectively. Figure 16 and Figure 17 presents the company's base case PSA scatterplots for KTE-X19 versus comparators, whereas Figure 18 and Figure 19 shows the CEAC for the four technologies per each population, for the Ph- and Ph+ subgroups respectively.

Figure 16: Company's base case PSA scatterplots. KTE-X19 versus other technologies (run by the ERG after adaptation) - Ph- subgroup

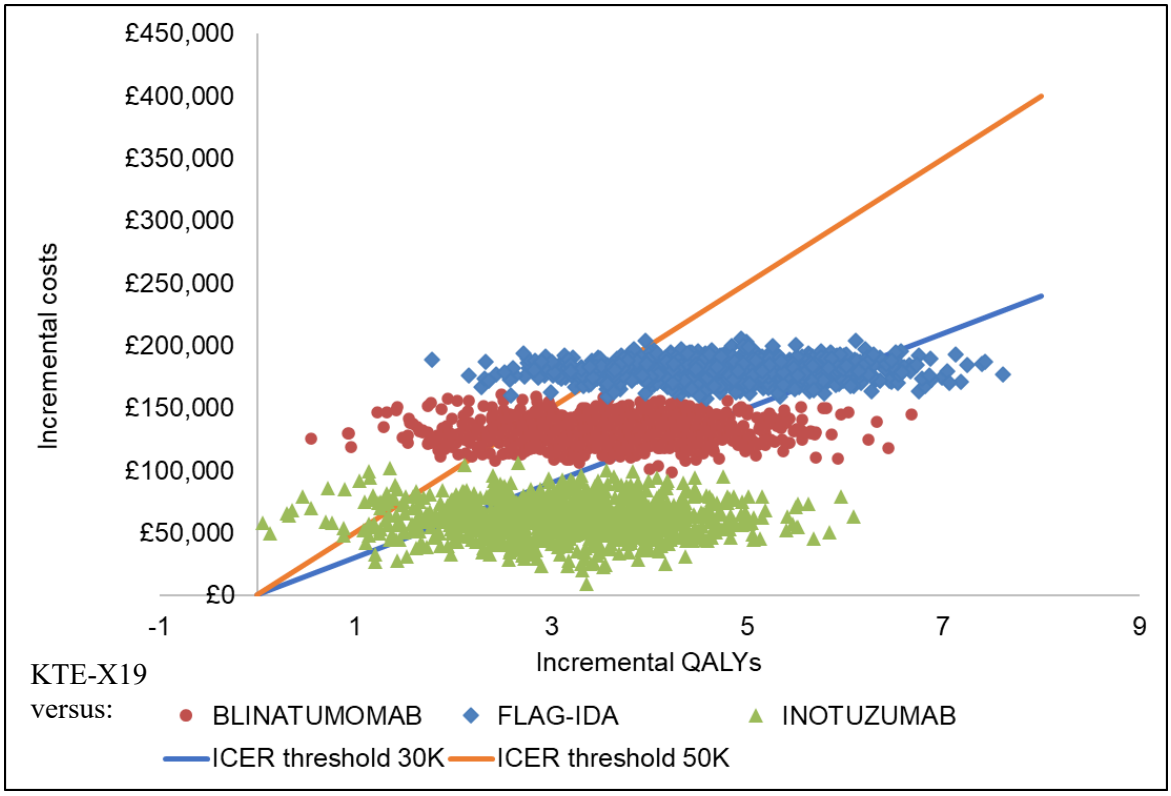


Figure 17: Company's base case PSA scatterplots. KTE-X19 versus other technologies (run by the ERG after adaptation) – Ph+ subgroup

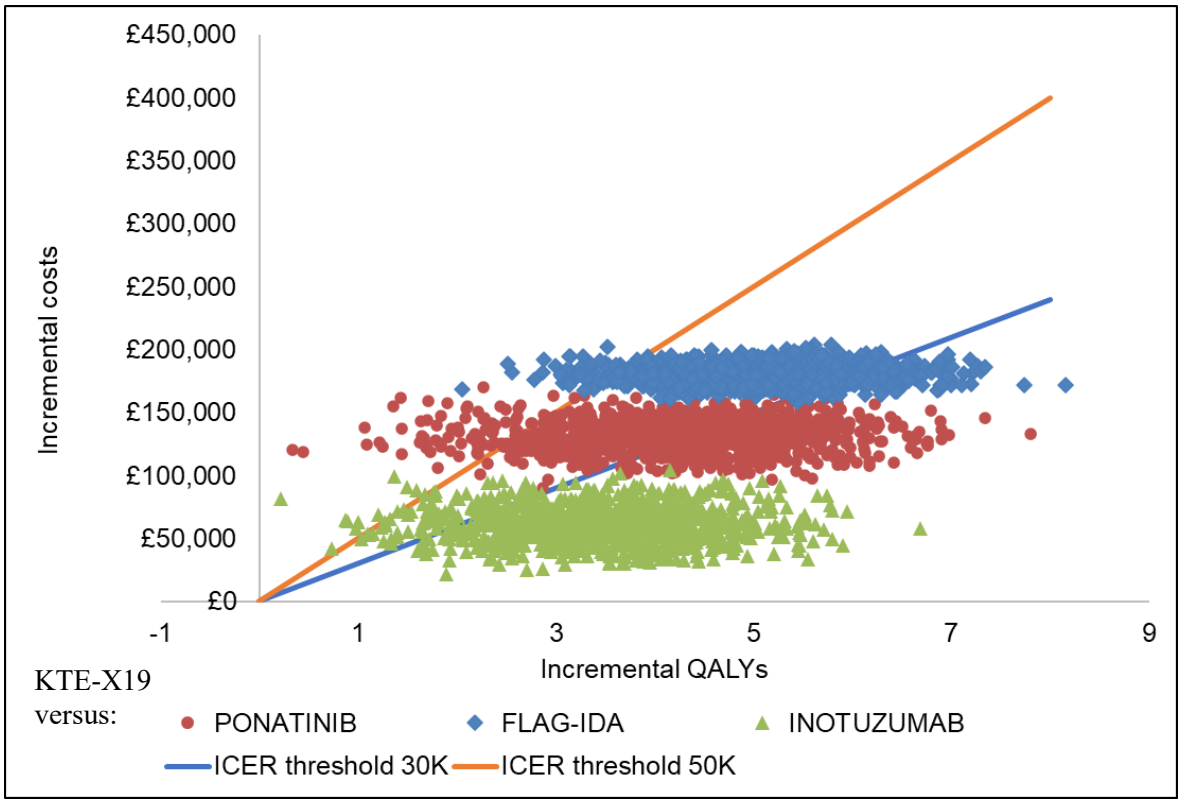


Figure 18: **Company's base case CEACs. KTE-X19 versus other technologies (run by the ERG after adaptation) - Ph- subgroup**

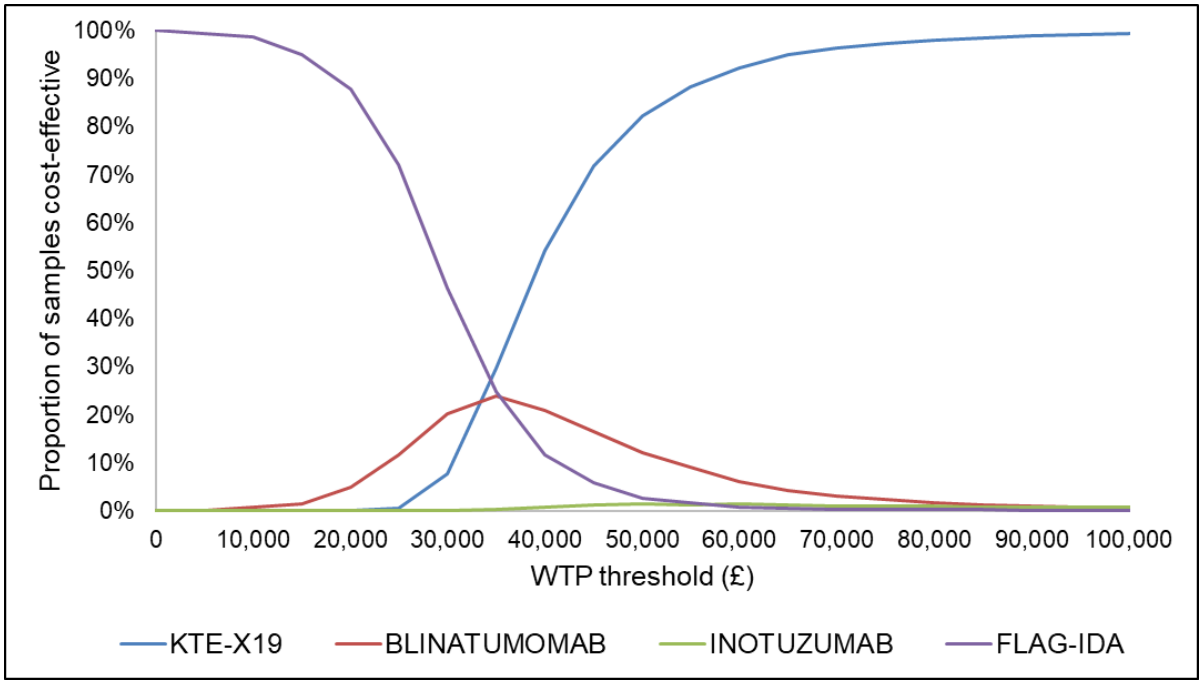
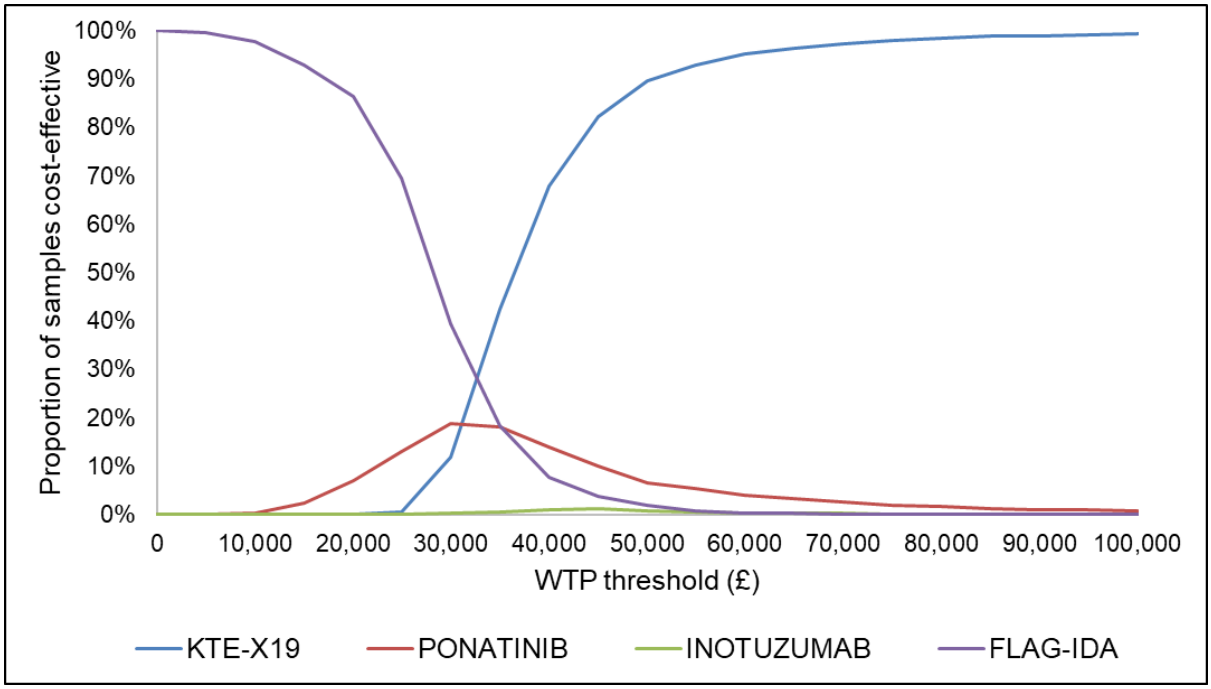


Figure 19: **Company's base case CEACs. KTE-X19 versus other technologies (run by the ERG after adaptation) - Ph- followed by Ph+ subgroup**



4.2.9 Company's DSA

DSAs are presented for KTE-X19 compared with relevant technologies using tornado plots. Most of these analyses are performed by assuming that the limit was set as +/- 20% of the mean, thus using 80% of the parameter value as a lower bound and 120% of a parameter value as an upper bound. The exceptions were: the cohort characteristics where standard error around the mean was calculated from the standard deviations reported in ZUMA-3, and the time horizon, discount rates, and acquisition costs of drugs which were not included in the DSA.

Following the clarification process, the ERG re-ran the DSA adopting the changes mentioned at Section 4.2.7; results are presented in

Figure 20 to Figure 23. The top 10 parameters with the most impact on the ICER are included in these tornado plot. For brevity, KTE-X19 versus ponatinib is the only pairwise comparison shown for Ph+ subgroup as the other comparisons would show similar conclusions to those in Ph- subgroup. For all comparators, the biggest impact was the change in the proportions of patients receiving allo-SCT, followed by the uncertainty in the proportions receiving different subsequent treatments, and the length and cost of hospital stay. For inotuzumab, the rate of VOD also affected the ICER.

Figure 20: Tornado plot of pairwise comparison of KTE-X19 versus inotuzumab (Ph- subgroup)

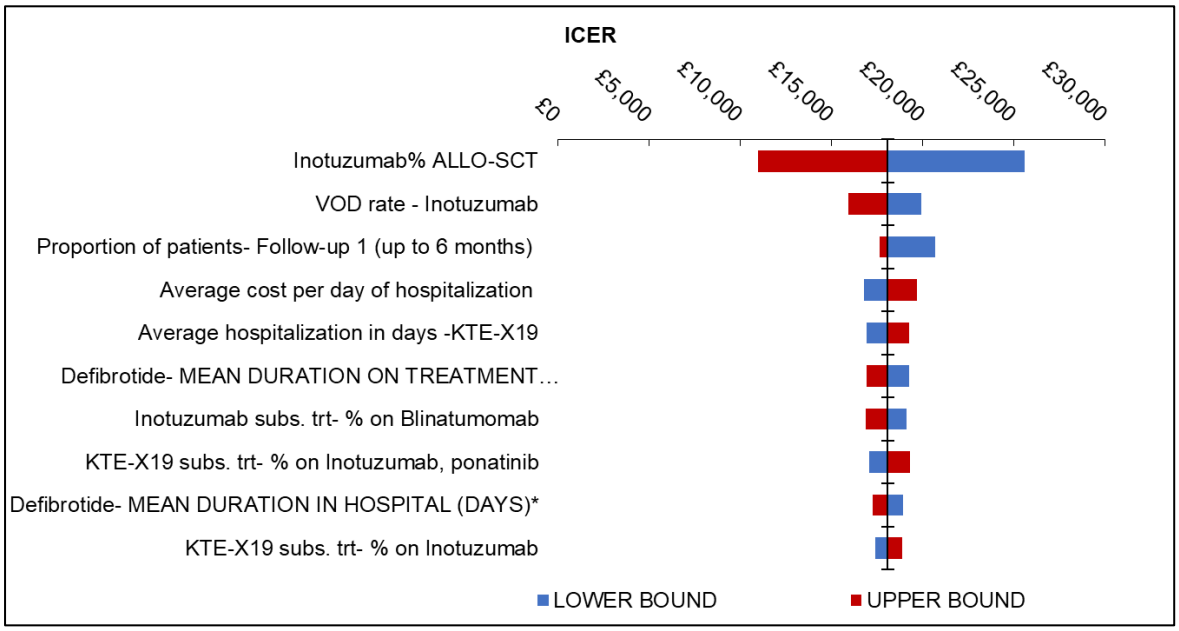


Figure 21: Tornado plot of pairwise comparison of KTE-X19 versus blinatumomab (Ph- subgroup)

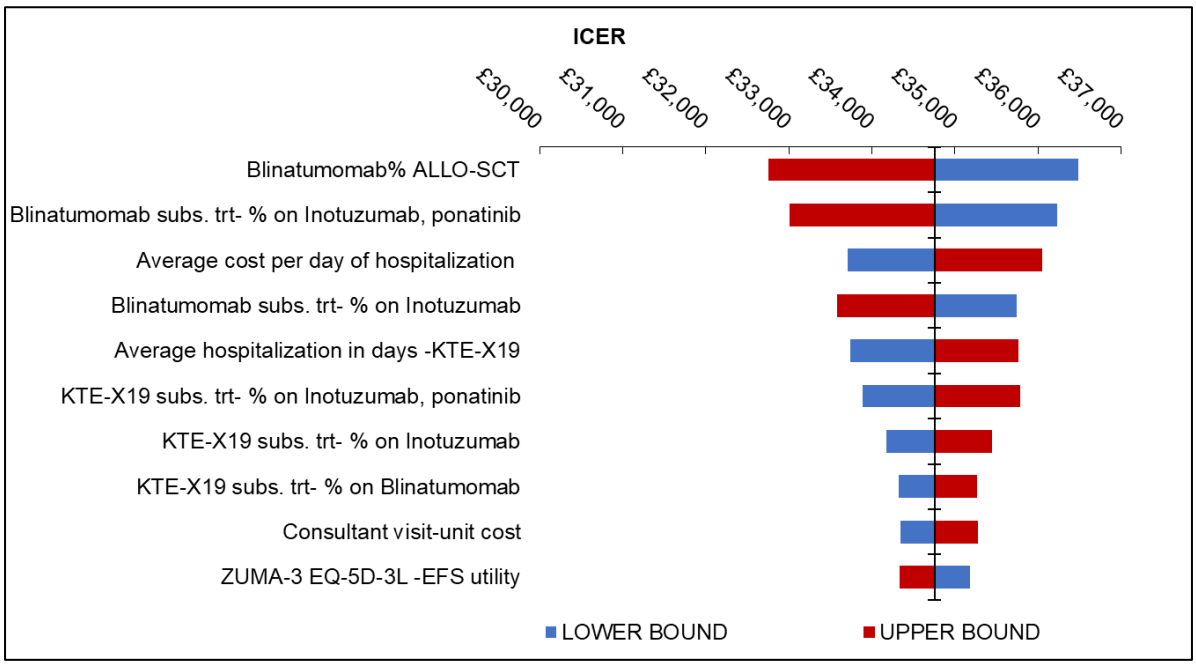


Figure 22: Tornado plot of pairwise comparison of KTE-X19 versus ponatinib (Ph+ subgroup)

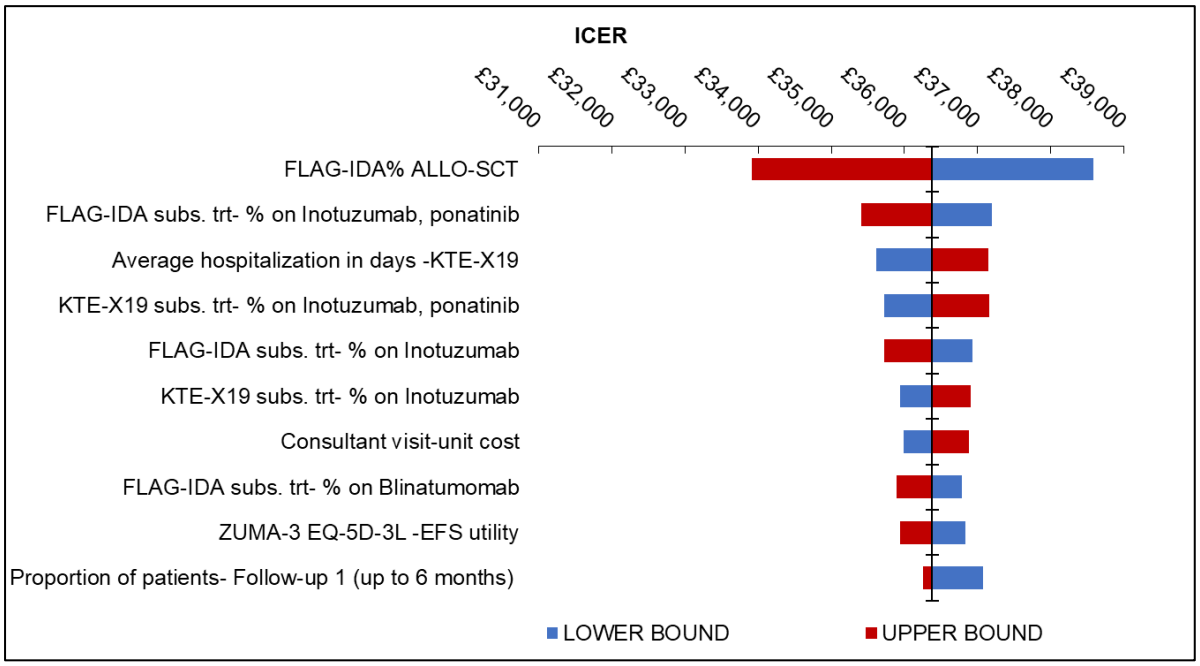
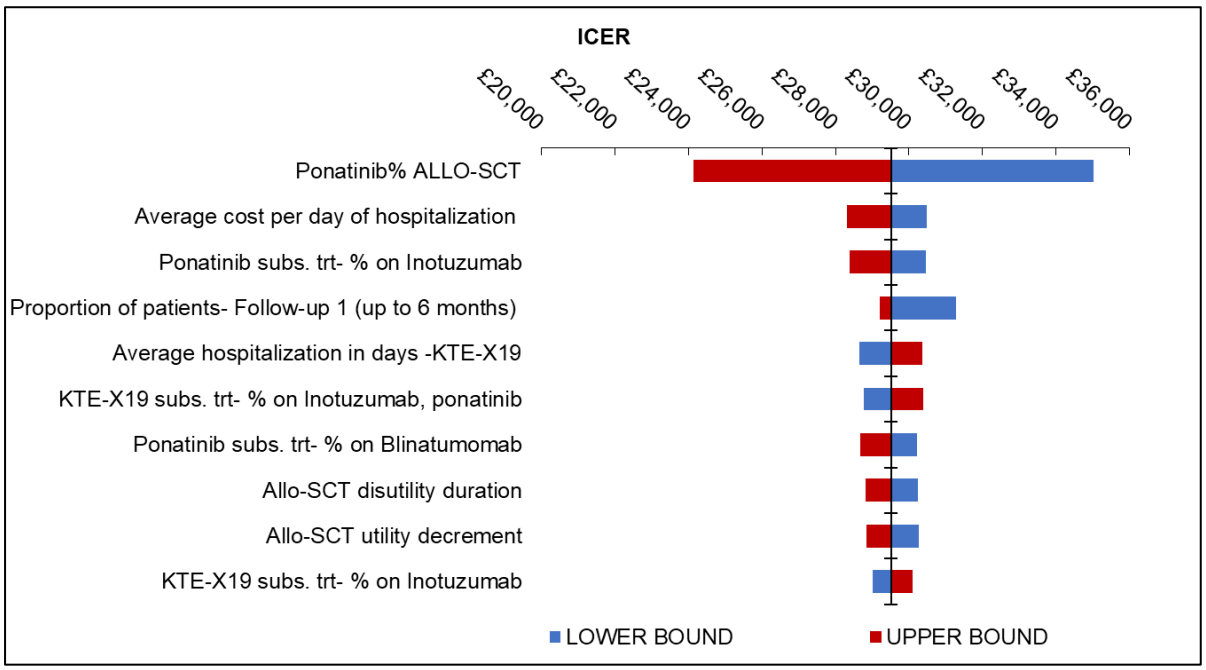


Figure 23: Tornado plot of pairwise comparison of KTE-X19 versus FLAG-IDA (Ph-subgroup)



4.2.10 Company's scenario analyses

The company carried out several scenario analyses that were updated post-clarification in addition to other scenario analyses requested by the ERG. For both subgroups, the scenario with the biggest impact was using MCMs for EFS and OS parameterisation and extrapolation, instead of parametric fits and spline models, increasing the ICERs by ~£20,000 to £30,000 per QALY gained. Decreasing the modelled time horizon from 57 to 20 years increased ICERs by £6,000-£14,000, whereas decreasing the discount rate from 3.5% to 1.5% decreased ICERs by ~£4,000-£9,000.

Using ITT data from ZUMA-3 (base case: mITT ZUMA-3), an SMR of 2.5 for cured patients (base case: 1.09), and utility of 0.76 from TA541 for cured patients (base case: general population values from Ara and Brazier) resulted in the ICER increasing by £2500 to £5000. A similar impact was observed when the cure point was assumed at 4 years (base case: 3 years) and allo-SCT costs were included for KTE-X19 in line with the observed use in ZUMA-3.

The ICER versus blinatumomab increased by ~£22,000 when the log-normal and generalised Gamma functions were selected for parameterising blinatumomab EFS and OS respectively (base case: 1-knot hazard spline and log-normal models respectively). For the KTE-X19 OS extrapolations, the use of the exponential and Weibull functions increased the ICERs by £4000 to £7000 (base case: log-normal model).

The ERG notes also that the ICER versus inotuzumab increased by ~£4,000 when AE-related costs were excluded.

The following scenarios had less impact on the ICER compared to the above mentioned scenarios; using data from Phase 2 ZUMA-3 (base case: Phase 1+2 combined), assuming different distributions of technologies for patients failing to receive KTE-X19 infusion, using external evidence for PD utility value, excluding AE-related costs (for ICERs versus blinatumomab, ponatinib, and FLAG-IDA), assuming different models for EFS extrapolations, removal of terminal care costs for cured patients, and excluding FLAG-IDA costs for patients on ponatinib.

4.3 Critique of company's submitted economic evaluation by the ERG

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS using the company's executable model.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 *Model verification*

The ERG believes the company's updated version of the model to be generally well programmed and free from major errors, and that the model structure and parameter values used are appropriate for the decision problem. The programming of the company's PSA was amended slightly by ERG as explained in Section 4.2.6, but the ERG does not believe this affects the model's ability to inform decision making. The ERG identified a small number of programming and implementation errors which impact the deterministic base case; these are explained in Section 4.3.3.

4.3.2 *Adherence of the company's model to the NICE reference case*

The company's economic analysis of KTE-X19 therapy in R/R ALL is generally in line with the NICE Reference Case. The ERG's summary of the adherence of the company's model to the NICE Reference Case is provided in Table 52.

Table 52: Adherence of the company's economic analyses to the NICE Reference Case[75]

Element	Reference case	ERG comments (a ✔ denotes the company's analyses are in line with the reference case)
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✔
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✔
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✔
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	✔
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	✔
Perspective on costs	NHS and PSS	✔
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✔
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✔
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✔

4.3.3 *ERG Critique of the modelling performed by the company*

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses.

Box 1: Summary of the main issues identified within the company's health economic model

(1) Presence of programming and implementation errors
(2) Uncertainty around the appropriateness of the company's ITC approach
(3) Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data
(4) Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19
(5) Concerns with life expectancy of cured patients compared to general population
(6) Issues with cured patients having the same utility values as general population
(7) Concerns around quantifying AE-related costs and QALY loss for KTE-X19 and inotuzumab
(8) Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA
(9) Uncertainty of the costs associated with delivering KTE-X19 infusion
(10) Issues with dosing regimens used for FLAG-IDA and ponatinib

4.3.3.1 Presence of programming and implementation errors

In the company's updated post-clarification model, the following issues were identified:

(a) Assumption of vial sharing

The vial sharing option was enabled within the company's economic model, and updated results presented were based on this assumption which means that there is no drug wastage. The company stated that vial wastage was assumed (CS, Section B.3.5.1.3) and it is possible that disabling the option may have been unintentional. The ERG contacted Professor Peter Clark (NHS England Cancer Drugs Fund Clinical Lead) for advice on the most appropriate vial-sharing base case for blinatumomab, inotuzumab and tozilizumab. His advice was that vial sharing should not be assumed and this has been incorporated in the ERG base case.

(b) BSA calculations were only enabled for vial sharing scenario

The company included the calculation of cyclophosphamide, FLAG-IDA, and inotuzumab based on the average BSA of ZUMA-3 patients. However, this could only be selected when vial sharing is included. The ERG notes that these calculations should only apply when vial sharing is excluded.

(c) Implementation error regarding cyclophosphamide acquisition cost calculation

Cyclophosphamide dosing used for KTE-X19 conditioning therapy was calculated based on the dose of 300 mg/m^2 (sheet 'Background-Dosing calc' cell BN11). However, the correct dose is 900 mg/m^2. In addition, the cost per dose calculation (sheet 'CAR-T pre-treatment costs' cell H32) erroneously

multiplies the unit cost of the 1000 mg vial by the number of 2000 mg vials needed and the cost of the 2000 mg vial by the number of 1000 mg vials needed.

(d) Fludarabine dosing and cost calculation issues

The acquisition cost of fludarabine used for KTE-X19 conditioning therapy appears to have been included twice in the model (sheet 'CAR-T pre-treatment costs' cell H35). Additionally, the current calculation is using the incorrect dose of 30 mg/ m^2 used for bridging therapy rather than the correct dose of 25 mg/m^2.

(e) Blinatumomab administration cost issues

In response to clarification question B73, the company removed one instance of double counted administration costs of blinatumomab as a subsequent treatment. The ERG notes however that there are still double counting issues for pump costs and another IV administration cost.

(f) Inotuzumab spline selections are not properly linked

Inotuzumab spline selections (sheet 'Background-Survival Comp' columns JJ and JU) are linked to FLAG drop down lists. This means that when the user selects spline models for inotuzumab, it does not impact on the model results, whereas selecting spline models for FLAG-IDA impacts both on inotuzumab and FLAG-IDA.

4.3.3.2 Uncertainty around the appropriateness of the company's ITC approach

The company's model uses relative treatment effect estimates from the naïve indirect comparisons in preference to those obtained from the MAICs for the comparison of KTE-X19 against each of inotuzumab, FLAG-IDA, and a synthetic control arm matched to the ZUMA-3 population for comparison with blinatumomab. The ERG believes that, of these two approaches, the MAIC analysis should be preferred. The reasons for this are as follows:

(i) Whilst the substantial reductions in ESS in the MAIC-adjusted ZUMA-3 populations resulted in greater uncertainty in the adjusted estimates, it nevertheless shows that there is substantial mismatch in the populations which should therefore be adjusted for;

(ii) Clinical advice provided to the ERG suggested that based on ECOG scores, the ZUMA-3 population may be a healthier population than those in TOWER and INO-VATE, therefore a naïve comparison without adjustment may be biased in favour of KTE-X19. Adjusting the ZUMA-3 population brings the HRs closer to unity, reducing the treatment advantage of KTE-X19. This is in keeping with the ERG clinicians' expectations, that the ZUMA-3 population is healthier than those included in the comparator studies and suggests that the MAIC is adjusting correctly;

(iii) The company stated that the ZUMA-3 population is representative of the target population for KTE-X19. However, clinical advice to the ERG was that the target population will be closer to that of the comparator populations. As an example, clinical advice to the ERG suggested that approximately 10% of patients would be expected to have an ECOG PS of 2 and there were no patients with an ECOG PS of 2 in the ZUMA-3 population.

For the blinatumomab comparison, the company has adjusted for bias by using the SCHOLAR-3 SCA-3 population which is matched to that of ZUMA-3. The ERG notes that this approach is preferable to an unadjusted comparison. However, as previously noted, the ZUMA-3 population may not be the most representative of the target population and for consistency with the other comparator ITCs, the ERG would have liked to have seen the results of a MAIC for the comparison with blinatumomab presented by the company.

The ERG accepts that a MAIC may not be feasible for the comparison with the small ponatinib population and accepts that there may be no alternative than to accept the naïve comparison. However, the ERG notes that there is significant possibility of bias associated with this approach.

4.3.3.3 Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data

The ERG believes that that the company has made reasonable choices for the base case survival models in their naïve comparisons. The only exception was for OS survival in the PACE dataset for ponatinib where the ERG preferred the Gompertz model to the log-normal distribution, as previously discussed in Section 4.2.4.2. The ERG would have preferred a separate model selection exercise to be presented for ZUMA-3 survival data adjusted by MAICs.

The ERG highlights again that these survival curves are only used up to the three-year timepoint, after which the general population mortality rate adjusted with an SMR is used.

4.3.3.4 Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19

In ZUMA-3, 14 of the 78 patients who received the infusion went on to receive subsequent allo-SCT. However, the company's model does not include either the costs or QALY impacts related to allo-SCT for the KTE-X19 arm. The CS mentions two main reasons for the exclusion. First, according to the company's clinical experts, "*no patients would receive a second allo-SCT and allo-SCT is not expected to be given as consolidation following a CAR T-cell therapy*". In response to clarification question A2, the company mentioned that 12 of the 14 patients who received subsequent allo-SCT, had CR/CRi following KTE-X19. Second, the company conducted a sensitivity analysis of the median OS stratified by censoring of allo-SCT which showed that "*survival appeared to be independent of subsequent SCT*".

As discussed in Section 3.2.6 and Section 3.5, the ERG has concerns over the ability of KTE-X19 to offer a standalone curative persistent therapy for R/R ALL patients. Clinical advice received by the ERG suggests that having a CR/CRi status does not rule out the possibility of MRD detection which would trigger the initiation of subsequent therapy. Moreover, the fact that allo-SCT was delivered to some ZUMA-3 patients means that they may have benefitted from it, costs were incurred, and patients' HRQoL was affected. Furthermore, the company's clarification response noted that their sensitivity analysis was not sufficiently powered, and the ERG remains uncertain of the imbalance in baseline characteristics between patients who received allo-SCT versus those who did not.

4.3.3.5 Concerns with life expectancy of cured patients compared to general population

The company's base-case applies an SMR of 1.09 to model the mortality risk of patients considered cured (that is, those patients alive after 3 years) compared to that of the age- and sex-matched UK general population. The ERG has concerns that the SMR applied to the background mortality may not appropriately reflect the excess mortality risk of long-term survivors with R/R ALL compared to the general population. The company states that this SMR "*was used by the company in the most recent NICE appraisal for KTE-X19 in mantle cell lymphoma (TA677) and was the ERG's preferred SMR in TA567 (Tisagenlecleucel in R/R DLBCL).*"

The applied SMR was obtained from a study in DLBCL patients,[54] hence it was preferred by the ERG in TA567 when the disease area was R/R DLBCL. However, the ERG for TA677 (KTE-X19 in R/R MCL) did not consider the DLBCL study to be of relevance in a different disease site.

The ERG explored evidence used in previous NICE STAs of R/R ALL. The CS for TA554 (tisagenlecleucel for R/R ALL in patients aged up to 25 years) applied an SMR value of 9.05 for 5-year survivors post-SCT with a wide range of values for scenario analyses.[52] For TA541 (inotuzumab for R/R ALL), the ERG used a '*conservative*' SMR value of 4 for 5-year surviving patients after receiving SCT,[71] whilst TA450 (blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia) assumed an SMR of 1. The ERG considers the 1.09 used by the company to be an underestimate, as clinical advice suggests that patients who have had R/R ALL are more likely to die than an age- and sex-matched population, although there remains uncertainty in the correct value to use.

4.3.3.6 Issues with cured patients have the same utility values as general population

The company's base-case assumes that the HRQoL of cured patients corresponds to the HRQoL of the age- and sex-matched UK general population, regardless of the health state prior to the cure timepoint. This means that after 3 years, all surviving patients are assumed to have no residual disease- or

treatment-related HRQoL decrement (that is, they are assumed to be functionally cured). However, the assumption was insufficiently justified, and the ERG clinical advisors noted that it is uncertain whether this assumption is reasonable. The advisors highlighted that this group of patients had received at least two therapies prior to receiving KTE-X19 and subsequent therapies, and that cumulative drug toxicity on its own – let alone the disease itself – would impact the quality of their remaining lives. Additionally, the assumption that patients are cured without residual comorbidities would not appear consistent with the assumption that patients have an increased risk of death compared to the age- and sex-matched population.

4.3.3.7 Concerns around quantifying AE-related costs and QALY loss for KTE-X19 and inotuzumab

The company estimates mean costs per patient related to AEs at [redacted] for KTE-X19. Clinical advisors to the ERG have concerns that this figure does not capture the full financial impact of drug toxicity. For instance, CRS cost calculation was based 4.3 days' worth of ICU stays in addition of one dose of tocilizumab. The ERG notes that this is inaccurate. In response to clarification question B62, the company assumed that the duration of ICU stay represents the median value for Phase 1+2 combined. However, the mean values reported in ZUMA-3 CSR (Table 14.3.18.1.1 and Table 14.3.18.1.2) were [redacted] days and [redacted] days for Phase 2 and Phase 1 respectively, for which the weighted average is more than [redacted] days.

Clinical advice provided to the ERG stated that vasopressors received by 30-40% of ZUMA-3 population are administered in ICU, and that neurological AEs experienced by at least 25% of the population need hospital readmission and stay supervised for a minimum of two weeks. Furthermore, a US economic study sponsored by the company estimated costs related to AE management following KTE-X19 infusion for R/R mantle cell lymphoma patients at $72,297 although the ERG acknowledges the difference between the US and English healthcare systems.[76]

The ERG believes these aspects have been missed in the cost estimation for AEs related to KTE-X19, and as a result ICER results for KTE-X19 against its comparators are underestimated. The ERG highlights that there is a tariff for delivering CAR-T therapy, and this is discussed at Section 4.3.3.9. The ERG assumes the tariff to cover AE costs related to KTE-X19.

With respect to AEs related to inotuzumab, the ERG illustrated in Section 4.2.4.3.2 that the assumptions used for estimating the AE impact on costs and QALYs include a degree of double counting. The ERG believes that if the costs of defibrotide injections are included; this would be associated with a decrease in the disutility caused by VOD.

4.3.3.8 Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA

The administration costs included for blinatumomab and FLAG-IDA in the company's base case capture inpatient and outpatient care and hospitalisation costs. The model used to inform TA450 explicitly excluded costs associated with AEs and states that "*since blinatumomab is administered initially in hospital, the treatment of AEs is likely to be provided during the hospital stay and therefore included in the hospitalisation cost. As patients are assumed to visit outpatient infusion centres every 4 days when receiving the drug out of hospital, it is likely AEs could be managed during these scheduled visits. For FLAG-IDA, patients are assumed to be hospitalised for 16.8 days each cycle. As with blinatumomab, the treatment of AEs is likely to be provided during the hospital stay*" which was endorsed by the ERG for that STA.[53] The ERG highlights that the duration of hospital stay for FLAG-IDA administration in the company's model for this appraisal (16.8 days), is markedly longer than the administration of the last treatment regimen in a cycle (filgrastim for days 0-9) and thus AEs are likely to be managed during the inpatient stay.

4.3.3.9 Uncertainty of the costs associated with delivering KTE-X19 infusion

The company's model includes costs for an average ICU stay of [redacted] days for delivering KTE-X19 infusion. Table 53 of the CS states that this was sourced from mITT ZUMA-3 Phases 1 and 2 combined. The ERG could not check the value in the CSR. Instead, the ZUMA-3 Phase 2 publication supplementary appendix states that "*median duration of hospitalization that occurred after infusion was 22 days (IQR, 17–35) and median duration of intensive care unit stays was 5 days (IQR, 4–10)*."[19] The ERG notes that the published IQR does not include the average value used in the model, hence believes that the value used in the model may not be accurate.

Clinical advice presented to the ERG highlighted that CRS represents a common adverse event of patients receiving KTE-X19, and that treatment requires a stay in ICU. The ERG is therefore concerned that the provision of KTE-X19 specialist centres may require that ICU beds are left vacant during the period that a patient is considered at risk of CRS to ensure availability. This may lead to additional costs which have not been included in the company's base-case model. The ERG notes that in the previous appraisal of KTE-X19 (TA677) an NHS Tariff was used to estimate the cost of administering KTE-X19 incurred by the NHS in a scenario analysis, although this figure was redacted. The clinical lead for NHS England Cancer Drugs Fund advised the ERG that the tariff across England is approximately [redacted] per patient for CAR-T treatment delivery.

4.3.3.10 Issues with dosing regimens used for FLAG-IDA and ponatinib

In the company's base case, FLAG-IDA was administered for a maximum of four 28-day cycles. Clinical advice received by the ERG indicated that for R/R ALL patients with at least two prior lines of

therapy, where it may be possible to bridge to allo-SCT, a maximum of two cycles would be given. For patients not eligible for allo-SCT, it is expected that less FLAG-IDA would be given. Furthermore, in both trials (INO-VATE and TOWER) patients received a median of one treatment cycle with only 22% receiving two or more cycles in INO-VATE.[11, 34]

For ponatinib, the company's base case included FLAG-IDA costs (including inpatient costs) in addition to ponatinib acquisition and administration costs. This contributes to 72% [redacted] out of the [redacted]) of ponatinib overall cost. The ERG highlights that the PACE study used to derive ponatinib efficacy did not include FLAG-IDA in the received dosing regimen.

4.4 Exploratory analyses undertaken by the ERG

4.4.1 *Overview of ERG's exploratory analyses*

The exploratory analyses performed by the ERG are provided in Section 4.4.2. Where quantitative analyses could not be provided, qualitative conclusions are provided. The ERG considers that the ICERs produced in the company's base case are suitable only for the comparisons of KTE-X19 in a similar population to ZUMA-3 (i.e., where some patients went on to receive subsequent allo-SCT and no patients have an ECOG PS of 2). The ERG's scenario analyses that use the results from the MAIC to adjust the ZUMA-3 population to those of the pivotal comparator studies explore the impact on the ICER of assuming a potentially more severe population with a proportion of patients still receiving allo-SCT subsequently. Neither population reflects the population in which the company want to position KTE-X19 (see Section 2.3.1).

4.4.2 *ERG's exploratory analyses - methods*

4.4.2.1 Correcting programming and implementation errors in the company's economic model

The ERG corrected the identified errors listed under Section 4.3.3.1 as follows:

(a) Assumption of vial sharing

The ERG assumes no vial sharing for its base case. This means that for any IV administered treatment, after a patient gets the recommended dose from a vial the remaining drug, if any, is wasted. Vial sharing is explored in a scenario analysis.

(b) BSA calculations were only enabled for vial sharing scenario

The ERG added IF statements and changed the order of CHOOSE function choices in order to apply calculations based on individual BSA whenever the vial sharing option is disabled. This applied to costs for cyclophosphamide and fludarabine used for conditioning chemotherapy sheet (sheet 'CAR-T pre-treatment costs' cell H32 and H35). This was also applied for inotuzumab and FLAG-IDA dosing calculations.

(c) Implementation error regarding cyclophosphamide acquisition cost calculation

The ERG corrected the cyclophosphamide dose to be 900 mg/m^2 (sheet 'Background-Dosing calc' cell BN11). The calculations have also been amended so that the unit cost of a vial is linked to the appropriate vial size.

(d) Fludarabine dosing and cost calculation issues

The ERG removed half of the 'double-counted' cost per dose used for fludarabine indicated for conditioning therapy, and adjusted the dose to 25 mg/m^2 (sheet 'Background-Dosing calc' cell AU11).

(e) Blinatumomab administration cost issues

The ERG removed the 'double-counted' pump costs and IV administration cost for the first treatment cycle of blinatumomab when used as a subsequent therapy (sheet 'Subsequent Tx' cell F40).

(f) Inotuzumab spline selections are not properly linked

The ERG linked the inotuzumab spline selections (sheet 'Background-Survival Comp' columns JJ and JU) to inotuzumab drop down selection lists (sheet 'Controls' cells H173 and H188).

4.4.2.2 Matching patient populations of ZUMA-3 and comparators

The ERG prefers the MAIC approach as it adjusts for the difference between study populations. The MAICs conducted by the company adjust the ZUMA-3 population to that of the comparator studies, however, if it is assumed that the HRs are transportable, an estimate can be made of the efficacy of the comparators in the ZUMA-3 population. The ERG wanted to compare ICERs from the MAIC using the comparator populations and the approach assuming transportable hazards, however the latter approach did not generate ICERs in the company's model.

For blinatumomab, the ERG explored both approaches; matching patients on blinatumomab back to ZUMA-3 (using SCHOLAR-3 SCA-3), and the MAIC conducted using the TOWER population. For ponatinib, the ERG had no choice but to accept the naïve comparison as it agreed that a MAIC was not feasible.

4.4.2.3 Using alternative survival curves to fit survival data

The ERG's base case assumes the same model fits selected for ZUMA-3 at the naïve comparisons to be also the best fits for ZUMA-3 population adjusted by MAICs. In addition, the Gompertz model is assumed to best fit ponatinib OS data.

In Section 4.2.4.2, the ERG noted that it would have liked the company to have explored the impact of different survival models fitted to time-to-event data. The ERG did not conduct these analyses as it was aware that a new data cut will be provided at TE, meaning that these exploratory analyses would become redundant.

4.4.2.4 Including allo-SCT associated costs and QALY loss for the KTE-X19 patients

The ERG's base case accounts for the 18% who received KTE-X19 infusion in ZUMA-3 and went on to receive allo-SCT. This involves adding an extra cost of £21,135 for the modelled KTE-X19 population and a disutility of -0.1.

4.4.2.5 Using alternative adjustments to the general population mortality for cured patients

The ERG assumes a higher SMR value for its base case. The ERG adopts the *'conservative'* estimate of 4 assumed by the ERG of TA541 for patients surviving after 5 years from allo-SCT, however acknowledges the uncertainty around the figure.

4.4.2.6 Assuming cured patients have lower HRQoL than the general population

The ERG assumes a multiplier (0.92) applied to general population utility values to adjust for lower HRQoL for cured patients after 3 years. This was calculated using the ratio between the utility value for post-infusion pre-relapse (0.82) and that for general population of similar age (0.89).

4.4.2.7 Exploring different cost assumptions for VOD and KTE-X19 and QALY loss assumptions associated with VOD

The ERG's base case removes half the costs (£73,197) and QALY loss (0.104) associated with VOD as these were thought to be an overestimate in TA541.[71] It also assumes AE-related costs for KTE-X19 are equal to that for inotuzumab as a conservative assumption. In the ERG's preferred naïve ICER the AE-related costs are assumed to be included in the tariff associated with providing CAR-T infusions (see Section 4.4.2.9)

4.4.2.8 Removing costs of AE management for blinatumomab and FLAG-IDA

The ERG's base case removes costs associated with AE management for blinatumomab and FLAG-IDA as it is expected that these costs are accounted for during hospital stay for drug administration.

4.4.2.9 Using the tariff associated with delivering CAR-T infusions

In its base case, the ERG uses the tariff for delivering a CAR-T infusion. Since the tariff is inclusive of all healthcare resource use aspects except the acquisition costs for KTE-X19, the ERG discards costs associated with leukapheresis, conditioning and bridging chemotherapies, administration costs, and management of AEs from the KTE analysis. Personal Communication with Professor Peter Clark suggested that assuming a value of [redacted] per patient receiving an infusion would be appropriate

4.4.2.10 Adjusting FLAG-IDA and ponatinib dosing regimens to reflect clinical practice

The ERG's base case applies a maximum of two cycles of FLAG-IDA. In addition, no adjunctive chemotherapy is assumed for patients on ponatinib.

4.4.3 *ERG's exploratory analyses – results*

4.4.3.1 Quantitative changes to the company's base case

4.4.3.1.1 Quantitative changes to the company's base case for the Ph- subgroup

Table 53 presents the results of the ERG's adjustments to the naïve comparison analyses for the Ph- subgroup, however, the ERG stresses that this approach has many limitations and that the MAIC-approach is preferred as it explicitly attempts to adjust for differences in key characteristics in study populations. The answers based on a MAIC-approach are provided in Section 4.4.3.2.

After correcting errors in the company's deterministic model, the ICER for KTE-X19 versus FLAG-IDA is estimated to be £36,566 per QALY gained, with both inotuzumab and blinatumomab being extendedly dominated. The largest change in the ICER is caused by using the tariff associated with delivering a CAR-T infusion, which increases the ICER to £48,443 and £50,681 versus FLAG-IDA and blinatumomab respectively.

Using an SMR of 4 applied to an age- and sex-matched general population mortality risk for cured patients (instead of 1.09) increased the ICER by over £7000; including allo-SCT costs and QALY losses for patients who received KTE-X19 increased the ICER by over £4000; and assuming cured patients have lower HRQoL than the general population (using a multiplier of 0.92), increased the ICER by over £2400. The ICER was relatively insensitive to the other exploratory analyses.

When including all the changes preferred by the ERG for the naïve comparison, the deterministic ICER increases to £70,545 for KTE-X19 versus FLAG-IDA (probabilistic ICER = £71,638). The deterministic ICERs of KTE-X19 versus inotuzumab and blinatumomab were £58,132 and £70,689 respectively (probabilistic ICERs are £58,454 and £71,382 respectively). Assuming vial sharing

increased the ICER for KTE-X19 against inotuzumab and blinatumomab by £8,000 and £3,000 respectively.

Table 53: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph- subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,380
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £18,108 and £34,753 respectively.							
ERG exploratory analysis 1: Correcting programming and implementation errors in the company's economic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.54	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,566
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £17,797 and £32,460 respectively.							
ERG exploratory analysis 2: Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population							
Blinatumomab	5.07	[redacted]	[redacted]				
KTE-X19	14.03	[redacted]	[redacted]	8.96	[redacted]	[redacted]	£31,690
ERG exploratory analysis 3: Not applicable as ponatinib is not used for the Ph- subgroup							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£40,717
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £24,209 and £40,473 respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]				ED
Inotuzumab	5.46	[redacted]	[redacted]				
KTE-X19	10.06	[redacted]	[redacted]	7.39	[redacted]	[redacted]	£43,829
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £21,649 and £42,046 respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£39,021
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £19,357 and £37,322 respectively.							
ERG exploratory analysis 7: Exploring different cost assumptions for VOD and KTE-X19 and QALY loss assumptions associated with VOD							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£37,168
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £21,747 and £35,554 respectively.							
ERG exploratory analysis 8: Removing costs of AE management for blinatumomab and FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£36,827
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £18,009 and £34,881 respectively.							
ERG exploratory analysis 9: Using the tariff associated with delivering KTE-X19 infusion							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]	2.45	[redacted]	[redacted]	£41,457
Inotuzumab	7.52	[redacted]	[redacted]				ED
KTE-X19	14.08	[redacted]	[redacted]	8.08	[redacted]	[redacted]	£50,681
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £36,578 and £48,443 respectively.							
ERG exploratory analysis 10: Assuming maximum of 2 cycles for FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.00	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.08	[redacted]	[redacted]	10.52	[redacted]	[redacted]	£37,184
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £17,627 and £34,338 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 4-10) – deterministic results							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£70,121
Inotuzumab	5.47	[redacted]	[redacted]				ED

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
KTE-X19	10.06	[redacted]	[redacted]	5.67	[redacted]	[redacted]	£70,689
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £58,132 and £70,545 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 4-10) – probabilistic results							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.42	[redacted]	[redacted]				ED
Inotuzumab	5.49	[redacted]	[redacted]				
KTE-X19	10.06	[redacted]	[redacted]	7.30	[redacted]	[redacted]	£71,638
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £58,454 and £71,382 respectively.							
ERG scenario analysis 1 (combining ERG preferred naïve comparison + allowing for vial sharing)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.40	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£59,777
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.06	[redacted]	[redacted]	5.67	[redacted]	[redacted]	£73,796
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £66,590 and £70,247 respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate, VOD - veno-occlusive disease

4.4.3.1.2 Quantitative changes to the company's base case for the Ph+ subgroup

Table 54 presents the results of the ERG's preferred naïve comparison analyses for the Ph+ subgroup. As shown, after correcting errors, the company's deterministic model produced an ICER for KTE-X19 versus FLAG-IDA of £34,052, with both inotuzumab and ponatinib being extendedly dominated. The largest change in the ICER is caused by using the tariff associated with delivering KTE-X19 infusion, which increases the ICER to £45,210.

Using an SMR of 4 applied to an age- and sex-matched general population mortality risk for cured patients (instead of 1.09) increased the ICER by over £6800; including allo-SCT costs and QALY losses for patients who received KTE-X19 increased the ICER by over £3900; and assuming cured patients have lower HRQoL than the general population (using a multiplier of 0.92), increased the ICER by over £2300. The ICER was relatively insensitive to the other exploratory analyses.

When including all the changes preferred by the ERG for the naïve comparison, the probabilistic ICERs of KTE-X19 increases to £52,348 versus inotuzumab, £65,936 versus FLAG-IDA, and £74,576 versus ponatinib QALY gained (deterministic ICERs are £51,962, £65,494 and £73,316 respectively).

Assuming vial sharing increased the ICER for KTE-X19 against inotuzumab by £8,000 per QALY gained.

Table 54: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph+ subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic)							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£33,972
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,396 and £29,508 respectively.							
ERG exploratory analysis 1: Correcting programming and implementation errors in the company's economic model							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.54	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,052
ICERs of KTE-X19 versus inotuzumab and ponatinib are £15,974 and £29,681 respectively.							
ERG exploratory analysis 2: Not applicable as blinatumomab is not used for the Ph+ subgroup							
ERG exploratory analysis 3: Using Gompertz curve to fit ponatinib OS data							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.99	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.89	[redacted]	[redacted]	11.33	[redacted]	[redacted]	£33,926
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,363 and £30,457 respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£37,958
ICERs of KTE-X19 versus inotuzumab and ponatinib are £21,811 and £34,183 respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.17	[redacted]	[redacted]				ED
Inotuzumab	5.46	[redacted]	[redacted]				

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
KTE-X19	10.62	[redacted]	[redacted]	7.95	[redacted]	[redacted]	£40,927
ICERs of KTE-X19 versus inotuzumab and ponatinib are £19,615 and £35,467 respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£36,440
ICERs of KTE-X19 versus inotuzumab and ponatinib are £17,534 and £31,613 respectively.							
ERG exploratory analysis 7: Exploring different cost assumptions for VOD and KTE-X19 and QALY loss assumptions associated with VOD							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,706
ICERs of KTE-X19 versus inotuzumab and ponatinib are £19,667 and £30,183 respectively.							
ERG exploratory analysis 8: Removing costs of AE management for FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£34,396
ICERs of KTE-X19 versus inotuzumab and ponatinib are £16,318 and £29,445 respectively.							
ERG exploratory analysis 9: Using the tariff associated with delivering KTE-X19 infusion							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]				ED
Inotuzumab	7.52	[redacted]	[redacted]				
KTE-X19	14.87	[redacted]	[redacted]	11.31	[redacted]	[redacted]	£45,210
ICERs of KTE-X19 versus inotuzumab and ponatinib are £33,000 and £42,943 respectively.							
ERG exploratory analysis 10: Assuming maximum of 2 cycles for FLAG-IDA and no chemotherapy with ponatinib							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
Ponatinib	5.65	[redacted]	[redacted]	2.09	[redacted]	[redacted]	£23,919
Inotuzumab	7.52	[redacted]	[redacted]				ED
KTE-X19	14.87	[redacted]	[redacted]	9.22	[redacted]	[redacted]	£36,818
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £15,946 and £34,709 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 3-10) – deterministic results							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.39	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£31,687
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.64	[redacted]	[redacted]	6.24	[redacted]	[redacted]	£73,316
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £51,962 and £65,494 respectively.							
ERG preferred naïve comparison (Exploratory analyses 1, 3-10) – probabilistic results							
FLAG-IDA	2.72	[redacted]	[redacted]	-	-	-	
Ponatinib	4.51	[redacted]	[redacted]	1.78	[redacted]	[redacted]	£30,418
Inotuzumab	5.50	[redacted]	[redacted]				ED
KTE-X19	10.67	[redacted]	[redacted]	6.16	[redacted]	[redacted]	£74,576
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £52,348 and £65,936 respectively.							
ERG scenario analysis 1 (combining ERG preferred naïve comparison + allowing for vial sharing)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
Ponatinib	4.39	[redacted]	[redacted]	1.72	[redacted]	[redacted]	£33,815
Inotuzumab	5.47	[redacted]	[redacted]				ED
KTE-X19	10.64	[redacted]	[redacted]	6.24	[redacted]	[redacted]	£72,647
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £59,726 and £65,350 respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate, VOD - veno-occlusive disease

4.4.3.2 Quantitative changes to the company's base case to show impact of using MAICs to adjust for differences among populations

The ERG could not explore the MAIC analyses for the subgroups. Hence, the overall population was used to show the impact on ICERs of using MAIC adjusted populations in combination with the other ERG preferred analyses. The ERG highlights that only inotuzumab and FLAG-IDA are used as comparators for the overall population.

Table 55 presents the results for the company's base case using MAICs, and then applying the changes explored by the ERG. The MAIC increased the ICER of KTE-X19 in the company's base case by over £18,000 versus FLAG-IDA, and £9800 versus inotuzumab; MAICs were not conducted for comparisons with other interventions. When applying the ERG preferred changes, the ICERs increase by over £64,000 for both comparators compared to the company's naïve comparison base case.

Table 55: Results of the ERG's deterministic MAIC exploratory analyses – overall population

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
KTE-X19	14.96	[redacted]	[redacted]	11.41	[redacted]	[redacted]	£34,378
ERG preferred analyses (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
KTE-X19	10.69	[redacted]	[redacted]	8.02	[redacted]	[redacted]	£65,857
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population							
FLAG-IDA	3.56	[redacted]	[redacted]	-	-	-	
KTE-X19	10.89	[redacted]	[redacted]	7.33	[redacted]	[redacted]	£52,380
ERG preferred analyses – MAIC-adjusted ZUMA-3 to FLAG-IDA population (deterministic results)							
FLAG-IDA	2.67	[redacted]	[redacted]	-	-	-	
KTE-X19	7.87	[redacted]	[redacted]	5.19	[redacted]	[redacted]	£100,143
ERG preferred analyses – MAIC-adjusted ZUMA-3 to FLAG-IDA population (probabilistic results)							
FLAG-IDA	2.75	[redacted]	[redacted]	-	-	-	
KTE-X19	7.92	[redacted]	[redacted]	5.18	[redacted]	[redacted]	£100,982
Company base case (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	7.52	[redacted]	[redacted]	-	-	-	
KTE-X19	14.96	[redacted]	[redacted]	7.44	[redacted]	[redacted]	£17,203
ERG preferred analyses (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	5.47	[redacted]	[redacted]	-	-	-	
KTE-X19	10.69	[redacted]	[redacted]	5.22	[redacted]	[redacted]	£52,637
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population							
Inotuzumab	7.52	[redacted]	[redacted]	-	-	-	
KTE-X19	12.09	[redacted]	[redacted]	4.56	[redacted]	[redacted]	£27,097
ERG preferred analyses – MAIC-adjusted ZUMA-3 to inotuzumab population (deterministic results)							
Inotuzumab	5.47	[redacted]	[redacted]	-	-	-	
KTE-X19	8.70	[redacted]	[redacted]	3.23	[redacted]	[redacted]	£81,978
ERG preferred analyses – MAIC-adjusted ZUMA-3 to inotuzumab population (probabilistic results)							
Inotuzumab	5.51	[redacted]	[redacted]	-	-	-	
KTE-X19	8.77	[redacted]	[redacted]	3.25	[redacted]	[redacted]	£82,321

4.4.4 *The ERG's estimate of the ICER*

The exploratory analyses conducted by the ERG at Section 4.4.3, indicate that there are plausible changes to parameter values which would increase the company's estimate of the ICER but where the most appropriate value remains uncertain. Such parameters include: the appropriate adjustment to differences in study populations; whether there is a reduced HRQoL for cured patients; and the magnitude by which the risk of mortality is increased.

The exploratory analysis which has the largest impact on the ICER is the use of MAICs to adjust the ZUMA-3 population to the trial populations of either FLAG-IDA or inotuzumab. The ERG would have explored also the effect of adjusting the populations of the other comparators to that of ZUMA-3 using HR values calculated from the MAIC, however, the model was not programmed to conduct the analyses. Furthermore, the analyses were only available for the overall population, and for the two mentioned comparators. The ERG accepts the unfeasibility of conducting a MAIC for ponatinib, but would have wished to explore results for blinatumomab using MAIC adjustment towards the TOWER study population.

In addition, the MAIC scenarios use the same distributions that fitted the survival data for the naïve comparisons, though a separate model selection exercise would have been more appropriate for the adjusted population.

As shown at Section 4.4.3.2, the ERG estimates that ICERs for KTE-X19 against the other comparators are higher by around £65,000 per QALY gained when compared to the company's base case naïve comparison when applying the ERG's preferred analyses.

4.5 Discussion

The model submitted by the company was implemented to a good standard. However, the ERG believes that the base case ICER is likely to be higher than that estimated by the company and prefers an ICER of approximately £100,143 for KTE-X19 against FLAG-IDA in the overall population (probabilistic ICER £100,982). The ERG-adjusted results from the naïve comparison suggested that KTE-X19 has a deterministic ICER in Ph- patients of £70,545 compared with FLAG-IDA (probabilistic ICER £71,638), and a deterministic ICER in Ph+ patients of £73,316 compared with ponatinib with inotuzumab being extendedly dominated (probabilistic ICER £74,576). Based on the relationship between the naïve comparison and the MAIC analyses, it is likely that these ICERs will change if a MAIC was applied.

The largest component in increasing the ICER is the use of MAICs to adjust for differences in population characteristics in key clinical studies, although other uncertainties remain (see Section 4.4.4). The ERG has been informed that additional data are going to be provided in the TE process, and

the ERG wishes these uncertainties to be explored by the company if possible, particularly in relation to analyses where HRs are assumed transportable to the ZUMA-3 population.

5 END OF LIFE

In Table 34 of the CS the company puts forward the case that KTE-X19 meets the NICE End of Life criteria. These criteria are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company used median OS data from previous trials to support meeting the first criterion, which were 5.3, 5.3, 6.9, 7.3 months for patients receiving FLAG-IDA, inotuzumab, blinatumomab, and ponatinib respectively (CS, Table 34). However, the company's base case model estimates mean life years to be 3.6, 5.8, 6.0, 7.5 years for patients receiving FLAG-IDA, ponatinib, blinatumomab, and inotuzumab respectively. All values are greater than 24 months and thus it is uncertain if the short life expectancy criterion is met. This conclusion did not change in the ERG exploratory analyses.

The estimated extension of life associated with KTE-X19 treatment is more than four years compared with all comparators. These values are in excess of the three-month period specified in the end-of-life criterion. This conclusion did not change in the ERG exploratory analyses.

The ERG highlights that reason for the large difference between mean and median survival values is attributed to the 3-year cure assumption applied in the model, where the proportions remaining alive at 3 years accrue most of the survival gain. Table 56 presents the alive proportions at 1 year, 2, 3 and 5 years for all involved technologies as per the company's base case economic model.

Table 56: Comparisons of modelled alive cohort at different time points

Technology	Proportion alive at			
	1 year	2 years	3 years	5 years
KTE-X19	59%	45%	37%	37%
Inotuzumab	35%	22%	18%	18%
Blinatumomab	35%	21%	14%	14%
Ponatinib	37%	20%	13%	13%
FLAG-IDA	27%	13%	8%	8%

6 OVERALL CONCLUSIONS

The key evidence for clinical effectiveness within the CS comprised one single-arm study (ZUMA-3) of KTE-X19 and four other studies informing comparators (TOWER for blinatumomab and FLAG-IDA, INO-VATE for inotuzumab and FLAG-IDA, SCHOLAR-3 SCA-3 for blinatumomab, and PACE for ponatinib). In the absence of a common comparator arm between KTE-X19 and any of the comparators, the company used a naïve comparison for its base case. The company also carried out a MAIC to explicitly minimise the differences between the ZUMA-3 population and the populations in the comparator studies, however this was only reported as a scenario analysis. In response to the clarification process, the company provided the HRs estimated from the MAICs; the ERG asked that these be used within the ZUMA-3 population to generate ICERs, however this was not undertaken.

The ERG has seen a later data cut-off for ZUMA-3, which shows that [redacted]. It would not be anticipated that there would be lengthy survival in patients who had relapsed and the ERG hypothesises that this may be the result of treatment benefit provided by allo-SCT and other subsequent therapies. The company presented post hoc analysis for OS based on allo-SCT status which showed no difference between the groups. However, the ERG notes that this evidence was neither pre-planned nor powered to detect a difference and the data within the analysis may be confounded.

The model submitted by the company was implemented to a good standard, although the ERG explored alternative assumptions to those used by the company. When considering all the possible amendments the ERG's preferred deterministic ICER was £70,545 in Ph- patients compared with FLAG-IDA (probabilistic ICER £71,638), and a deterministic ICER in Ph+ patients of £73,316 compared with ponatinib with inotuzumab being extendedly dominated (probabilistic ICER £74,576). Based on the relationship between the naïve comparison and the MAIC analyses, it is likely that these ICERs will increase if a MAIC was applied. The ERG would have liked to generate illustrative ICERs for the Ph subgroups when using MAICs and also to have generated ICERs using the ZUMA-3 population and assuming that the HRs estimated from MAICs were transportable; however, this functionality was not contained in the company's model.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults [ID1494

'Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 18 March** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Tariff cost

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Sections 4.3.3 (page 121) and 4.4.2.9 (131), The ERG notes that 'in the previous appraisal of KTE-X19 (TA677) an NHS Tariff was used to estimate the cost of administering KTE-X19 incurred by the NHS'. This is inaccurate, as this tariff was only used in a scenario analysis by the ERG and was not incorporated into the committee's preferred ICERs. During TA677 technical engagement, it was explained that this NHS tariff was based on prospective data collection, before the use of CAR-T became routine practice. Additionally, the ERG inconsistently states that the tariff is exactly [redacted] on pages, 17 and 131, whilst only approximately £100,000 on pages 102 and 127.	The ERG should specify that the tariff was only included as a scenario analysis in TA677 and was not included in the committee's preferred estimates. The ERG should further clarify the nature of their proposed tariff, whether it is based on prospective or retrospective data collection and whether it is exactly or approximately [redacted].	Inaccurate interpretation of evidence from previous STA and unclarity as to the source of data.	'In a scenario analysis' is now added to section 4.3.3.9 for clarity. The ERG highlights that this figure was included in the base case as the company did not accurately capture the administration costs associated with KTE-X19 delivery as described in Section 4.3.3.9 On p132 'assuming' has been added to clarify what has been assumed. The estimated cost figure was based on communication with Professor Peter Clark who advised that 'on average, the tariff across England is [redacted] patient' including 'a market force factor'. Further details have been added on page 103.

Issue 2 Cost effectiveness results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.7, page 111, Central estimates of cost-effectiveness, the ERG refers to the probabilistic results from the company's model, however the figures stated in the text do not match those stated in table 49.	The figures should be updated in line with the values reported in table 49.	Incorrect reporting of model results.	Table 49 is now updated to exclude the extendedly dominated comparators from the incremental analysis.

Issue 3 Positioning of allogeneic stem cell transplant

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 2.2 (page 26), the ERG states 'Allo-SCT is reserved for eligible patients who fail to respond to either blinatumomab, inotuzumab, ponatinib, or salvage chemotherapy. Afterwards, patients may be cured or	We propose that the text should be amended to the following: Allo-SCT is dependent on the attainment of complete remission with blinatumomab, inotuzumab, ponatinib, or salvage chemotherapy treatment. Aftermallo-SCT, patients may be cured or relapse and require further treatment. After relapse	As described in the CS, median OS in the pivotal trials of blinatumomab, inotuzumab, and ponatinib ranged from 7.7 - 8 months. As a result, feedback received from UK clinical experts was that none of these options are considered curative,	The paragraph is now amended to read "Allo-SCT is reserved for eligible patients as a consolidation treatment following complete remission with blinatumomab, inotuzumab, ponatinib, or

relapse and require further treatment.' This is inaccurate. SCT is primarily used for consolidation of treatment following attainment of remission in transplant-eligible patients.	following allo-SCT, survival expectations remain poor, with median OS 5.5 months, and estimated 5 year survival post-relapse 8%.	and that long-term outcomes for blinatumomab, inotuzumab, and ponatinib in UK clinical practice are largely contingent on subsequent SCT. For example, SMC even restrict the use of inotuzumab to patients for whom the intent is to proceed to SCT. Therefore, the claim that SCT is reserved for failure of these treatments, when SCT itself requires a patient to be in remission, is not supported by either clinical data or experts. Furthermore, 'patients may be cured or relapse and require further treatment'. In the EBMT analysis of 465 patients who relapsed post SCT at their centres, median survival post-relapse was 5.5 months, and the estimated post-relapse 5-year survival rate was only 8%. It should therefore be acknowledged that mortality post-relapse is a significant possibility.	salvage chemotherapy. After allo-SCT, patients may be cured or relapse and require further treatment." As this section is about current service provision, we have not provided outcomes which has been mentioned in Section 2.1.

Issue 4 Enrolled vs treated

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In Section 3.2 (page 39), the ERG states: 'Phase 2 was designed to evaluate the efficacy and safety of KTE-X19 at the target dose. In Phase 2, a different cohort of 71 adult patients with R/R ALL who met the criteria listed in Table 16 were enrolled and treated with KTE-X19.'	We propose that the text should be amended to the following: 'Phase 2 was designed to evaluate the efficacy and safety of KTE-X19 at the target dose. In Phase 2, a different cohort of 71 adult patients with R/R ALL who met the criteria listed in Table 16 were enrolled, and 55 subjects were treated with KTE-X19.'	Whilst 71 subjects were enrolled in ZUMA-3 (ITT), 55 were treated with KTE-X19 (mITT).	This is now amended to read "In Phase 2, a different cohort of 71 adult patients with R/R ALL who met the criteria listed in Table 16 were enrolled, of which 55 patients received KTE-X19 infusion."

Issue 5 ERG preference of MAIC over naïve comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.2, page 123, the ERG state that 'The ZUMA-3 population had better baseline health than the TOWER and INO-VATE populations, therefore a naïve comparison without adjustment is likely to be biased in favour of KTE-X19'	We propose rephrasing this to: 'on the basis of ECOG scores, the ZUMA-3 population had better baseline health than the TOWER and INO-VATE populations.'	This will clarify that the ERG has made this statement on the basis of ECOG score alone, while ignoring other known prognostic factors in R/R-ALL that were likely to bias against KTE-X19 (e.g. relapse following allo-SCT, >2 prior lines of therapy and Ph+ disease).	The text has been amended to show that it was the clinicians' impression that the ZUMA-3 population was healthier primarily based on ECOG score.

Issue 6 Standardised mortality ratio (SMR)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.5, page 125, the ERG state: 'The ERG explored evidence used in previous NICE STAs. The CS for TA554 (tisagenlecleucel for R/R ALL in patients aged up to 25 years) applied an SMR value of 9.05 for 5-year survivors post-SCT with a wide range of values for scenario analyses. For TA541 (inotuzumab for R/R ALL), the ERG used a 'conservative' SMR value of 4 for 5-year surviving patients after receiving SCT'	Given that the ERG explored evidence used in previous STAs, those where less excess mortality was assumed should also be included for completeness. For example, in the Axicabtagene ciloleucel appraisal (TA559), general population mortality was assumed. In the blinatumomab (TA450) appraisal, no SMR was included, and general population mortality was added to a restricted Gompertrz distribution in which the 'hazard rates for OS….asymptotically approach zero'.	The ERG stated that evidence in previous STAs was explored, but they only appear to have reported the more pessimistic results. For balance, the ERG should report the broader results, including those TAs that used more favourable assumptions.	Reference has been made to TA450 and the text has been changed.

Issue 7 Utility for cured patients

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.3.3.6 page 125, the ERG state: 'The ERG considered approaches used in previous STAs, and notes that the CS for TA554 applied the EFS utility for long-term survivors (beyond 5 years	The ERG state that they considered approaches in previous STAs, however only 2 STAs are discussed and only one is a CAR-T therapy. The ERG should state	The ERG stated that they considered approaches used in previous STAs, but they only appear to have reported the more pessimistic results. For balance, the ERG should report the broader results, including	Given how many TAs could potential be referenced, we have decided it better to delete the paragraph and the point can be discussed

from starting treatment).[52] In TA541, a utility value of 0.76 was applied for patients surviving beyond 5 years after receiving SCT, which was lower than equivalent general population utility values based on similar age (0.86).'	which therapies the appraisals considered for clarity. The ERG states the utility value of 0.76 from TA541 but omits the value of 0.91 used in TA554. This value, plus the assumptions used for other CAR-T examples provided by the company at clarification (TA559, TA567, TA667) should be included in this section for completeness.	those TAs that used more favourable assumptions.	on its merit at the NICE Appraisal Committee.

Issue 8 Generalisability

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.1.1 Page 45, 'Clinical advice provided to the ERG suggested that the ZUMA-3 population, particularly those in Phase 1, is healthier compared with the patients likely to be eligible for KTE-X19 therapy in practice in the UK. The reasons for this were that no participants were designated as Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 2 although these patients would potentially be treated with this therapy in clinical practice in England and that	The ERG should provide a reference for the 36% Ph+ estimate and clarity as to whether it is in the R/R adult population. Should this not correspond to a R/R population then the 36% is almost certainly factually incorrect. For example, a 2007 MRC study found 20% Ph+ in R/R adult ALL (1). Given this is similar to ZUMA-3 it does not need to be included as a distinction. Conversely, the ERG states that the INO-VATE study may be more representative of the patients who could receive KTE-X19 in the UK without stating that this study only recruited 15% Ph+ subjects.	The statement regarding Ph+ proportions in the UK may not refer to the correct population and may thus be factually incorrect. For balance and consistency, the ERG should include comparison of <u>all relevant prognostic factors and across all the various studies</u> when considering those studies to be most generalisable to the patients who could receive KTE-X19. Such factors, in addition to Ph and ECOG status, include prior	Text removed as suggested. The following text is added to Section 3.5: "Whilst the ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status, the lack of Ph+ patients in TOWER, and lower percentage in INO-VATE compared to ZUMA-3 add uncertainty on which study best reflects the

the proportion of patients with Ph+ would likely be higher (36% in a Medical Research Council study of UK adult ALL patients vs 22% in ZUMA-3' Section 3.5 Page 82, 'The ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status and as such may reflect the population who could receive KTE-X19 in England more accurately ZUMA-3.'	Regarding ECOG 2 status, the ERG report would benefit from stating that the current panel eligibility criteria for CAR-T's require an ECOG PS of 0 or 1, though it is possible that small number with ECOG PS 2 would be treated with this therapy in clinical practice in England. In summary, the following text would be a more accurate statement: Section 3.5 Page 82, 'Whilst the ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status, the lack of Ph+ patients in TOWER, and lower percentage in INO-VATE compared to ZUMA-3 make it hard to draw conclusions on which study best reflects the population who could receive KTE-X19 in England'.	allo-SCT, primary refractory, relapse within the first year and number of prior therapies received.	population who could receive KTE-X19 in England"

Issue 9 Clarification of dose

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.5 Page 58, the ERG states 'others accessed subsequent anticancer therapies. In total, [redacted] patients out of the 78 who received a KTE-X19 infusion received such therapies'.	We propose that the text should be amended to the following: 'others accessed subsequent anticancer therapies. In total, [redacted] patients out of the 78 who received a KTE-X19 infusion at target dose received such therapies'	A total of 100 subjects received a KTE-X19 infusion, of which 78 subjects received a KTE-X19 infusion at target dose.	Text amended as suggested.

Issue 10 Correction of sample size

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.4 Page 69: 'The ERG is unclear whether that means the N=[redacted] for this dataset shown in Table 29 should in fact be N=[redacted]'	Removal of this sentence with sample size in Table 29 corrected to [redacted].	This is a correction on our side. The correct sample size should be xx, with this also reflected in Table 29.	Text and figures in Table 29 amended as suggested.

Issue 11 Reporting of patient deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG states the following: Section 3.2.4.4 Page 58: 'Two patients died from treatment-related AEs in each phase of ZUMA-3 (4/78 subjects).' Section 3.5 Page 82: 'and four treatment-related deaths were recorded across all patients in the two phases.'	We propose that the text should be amended to the following: 'Two patients died from treatment-related AEs in each phase of ZUMA-3, with two of these deaths occurring in doses not taken forward to Phase 2 (4/78 subjects).' 'and four treatment-related deaths were recorded across all patients in the two phases, including two treatment-related deaths at target dose.'	The dosage of KTE-X19 under review is 1 x 106 anti-CD19 CAR T-cells/kg body weight (referred to as target dose in the submission). The two reported deaths during Phase 1 occurred in patients who were not exposed to target dose.	Text amended as suggested

Issue 12 Presentation of safety summary

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.4.4 Page 58: the ERG states: KTE-X19 produces high frequencies of AEs among patients, with Grade 3 or higher AEs such as pyrexia, hypotension, hypoxia, aphasia and encephalopathy affecting up to 67% of patients in Phase 1 and 36% in Phase 2. Two patients died from treatment-related AEs in each phase of ZUMA-3 (4/78 subjects). Clinical advice received by the ERG suggested that the frequency of the most common CRS and neurological AEs was higher than might be expected for other CAR-T and comparator therapies, for example, the only SAE or Grade 3 or higher treatment-emergent AEs affecting >10% of patients for inotuzumab were febrile neutropenia (11.6%) and veno-occlusive disease (VOD) (11.6%) (INO-VATE FINAL34),	We would propose the following amendments: Presentation of ponatinib Grade 3 AEs based on Cortes et al (2018). G3 or higher: thrombocytopenia (19%), neutropenia (22%), anaemia (19%). Addition of 19.9% anaemia and 14.6% thrombocytopenia for blinatumomab safety profile. Addition of FLAG-IDA adverse events of Grade 3 or higher data, to provide balance for 'comparator therapies'. Addition of Grade 5 treatment-related deaths in comparator trials, to be consistent with data provided for KTE-X19.	Building on issue 13. We have a number of issues with the presented paragraph: Errors: 1) The ponatinib data is based on Cortes et al (2013) and should instead report the Cortes et al (2018) safety for consistency. 2) Blinatumomab AEs according to Table 35 of the EPAR include the two stated as well as 19.9% anaemia and 14.6% thrombocytopenia. For balance, all comparators in the scope should be included, and so FLAG-IDA safety data, which is currently omotted, should be included (based on TOWER, INO-VATE). This is particularly true given the positioning of KTE-X19, where salvage chemotherapy is a highly relevant comparator. The ERG present the Grade 3 or higher AEs and deaths for KTE-X19, but only the Grade 3 or higher AEs for	These are not factual errors. In addition, anaemia and thrombocytopenia were not reported as being >10% in the cited publications related to TOWER, and the ERG could not find these figures in the EPAR documents. For completeness, the following data are added to Section 3.2.4.4: 1) FLAG-IDA safety data. 2) Ponatinib safety data from Cortes 2018 highlighting that the median follow-up is 56.8 months compared to 18.1 months in ZUMA-3. 3) Fatal adverse event data for comparators.

and for blinatumomab were febrile neutropenia (21.3%) and neutropenia (17.6%) (TOWER Supp11). In the PACE study, the only Grade 3 or 4 AEs with an incidence of >10% were also neutropenia (12%) and anaemia (12%).21		comparators. For balance and consistency, either both should be included for all treatments, or only Grade 3 AEs should be presented for KTE-X19.	

Issue 13 Interpretation of RFS data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6 Page 142, 'The ERG has seen a later data cut-off for ZUMA-3, which shows that the [redacted].'	We propose that this text be replaced with text explaining that [redacted]	The statement made by the ERG is factually inaccurate and coud be highly misleading to readers, [redacted]	Text amended to read " … [redacted] …"

Issue 14 Ponatinib NICE recommendation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.2 Page 28: 'Blinatumomab is recommended for R/R Ph-precursor B-cell ALL in adults, whereas ponatinib, with or without chemotherapy, is recommended for R/R Ph-precursor B-cell ALL in adults	Removal of nilotinib (not relevant to ALL in the UK) & clarification that dasatinib is not recommended in the UK due to the company refusing to submit (terminated appraisal TA714). Change 'Ph-' to 'Ph+' for ponatinib.	This paragraph appears to switch between approved indication & NICE recommendation and is somewhat confusing. For ponatinib the ERG appear to have included the CML	Text amended to read "Blinatumomab is recommended for R/R Ph-precursor B-cell ALL in adults, whereas ponatinib, with or without chemotherapy, is recommended for R/R

when the disease is resistant to dasatinib or nilotinib, or dasatinib or nilotinib cannot be tolerated and where imatinib is not clinically appropriate, or the T315I gene mutation is present. Inotuzumab is recommended for R/R CD22-positive precursor B-cell ALL in adults, additionally, people with R/R Ph+ should have had received at least one tyrosine kinase inhibitor (TKI). The NICE recommendations for blinatumomab, ponatinib and inotuzumab are each subject to the companies providing these products according to confidential Patient Access Scheme (PAS) discounts.'		reimbursement criteria (e.g. nilotinib), which is not relevant. In addition, ponatinib is not recommended for R/R Ph- ALL, it is indicated for Ph+ disease.	Ph+ precursor B-cell ALL in adults when the disease is resistant to dasatinib, or dasatinib cannot be tolerated and where imatinib is not clinically appropriate, or the T315I gene mutation is present. The ERG notes that NICE was unable to make a recommendation on dasatinib for Ph+ ALL as the company did not provide an evidence submission (TA714)."

Issue 15 Imatinib positioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.3.3 Page 31: 'The ERG also notes that imatinib can be used as a subsequent treatment for patients who cannot tolerate dasatinib, and that ponatinib is only used if imatinib is not clinically appropriate.'	We propose changing this text to: 'The ERG also notes that imatinib is a first line treatment, and that ponatinib is only used if imatinib is not clinically appropriate.'	As the ERG notes in the decision problem, 'Dasatinib has no recommendation from NICE in ALL as the company did not make a submission'. Therefore imatinib use being contingent on intolerance to dasatinib is not a reality in UK clinical practice.	The following text added "The ERG notes that NICE was unable to make a recommendation on dasatinib for Ph+ ALL as the company did not provide an evidence submission (TA714)."

Issue 16 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12: the ERG refer to a 'medium follow-up time'	Medium should be corrected to median	Typographical error	Word corrected in Sections 1.4 and 3.5
Page 11: the ERG refer to 'Further, analyses'	Further should be Furthermore or remove comma	Typographical error	Word corrected to Furthermore
Page 11: the ERG refer to 'analyses...Appraisal Committee has'	Has should be changed to Have	Grammatical error	Word corrected
Page 12: the ERG refer to 'some circumstance'	Circumstance should be corrected to circumstances	Typographical error	Word corrected
Page 25: the ERG refer to 'pre-cursor'	Pre-cursor chould be corrected to precursor	Typographical error	Word corrected
Page 25: the ERG refer to 'subtype in adults is'	Is should be changed to involved	Grammatical error	The sentence has been rewritten for clarity.
Page 26: the ERG refer to 'five-year'	Five-year should be corrected to five years	Grammatical error	Error corrected
Page 28: the ERG refer to 'R/R B-cell ALL'	B-cell should be corrected to B-precursor	Terminology error	Change made
Page 36: the ERG refer to 'cytaribine responses'	Cytaribine should be corrected to cytarabine	Typographical error	Word corrected
Page 37: the ERG refer to 'data extracted'	Suggested correct to 'data was extracted'	Grammatical error	This is now corrected to 'Data were extracted'
Page 84 & 33: the ERG refer to the initial SLR as conducted in March 2019	Date needs to changed to June 2019	Typographical error	Change made.
Page 87: the ERG refer to inotuzumab when detailing the blinatumomab dosing, 'Blinatumomab dosing used in the model reflects the schedule	Intozumab should be changed to blinatumomab	Typographical error	Word corrected

used in the TOWER study where inotuzumab was IV-administered'			
Page 91: the ERG state: ‘incidence of grade 3 or 4 AEs occurring in ≥2% of the trial population for inotuzumab, and ≥5% of that for KTE-X19 and rest of comparators.’ This is not true for ponatinib.	The text should ammended to reflect what is stated in the CS, that is ‘incidence of grade 3 or 4 AEs occurring in ≥2% of the trial population for inotuzumab, ≥20% for ponatinib and ≥5% of that for KTE-X19 and rest of comparators.’	Typographical error	Text in Table 36 amended as suggested

Page 126: the ERG refer to ‘comordities’	Comordities should be corrected to comorbidities	Typographical error	Word corrected
Page 128: the ERG refer to ‘The ERG’s scenario analysis that use’	Analysis should be corrected to analyses	Typographical error	Word corrected
Page 128: the ERG refer to ‘patients still receiving’	Receiving should be corected to recieving	Typographical error	No change made.
Page 130: the ERG refer to ‘AEs related costs’	AEs should be corrected to AE	Typographical error	All instances changed to AE-related costs
Page 131: the ERG state ‘it is expected these costs’	Rephrase to ‘it is expected that these costs	Grammatical error	Word added
Page 131: the ERG states ‘the answers based on a MAIC-approach is provided’	‘Is’ should be changed to ‘are’	Grammatical error	Word corrected
Page 15: the ERG states ‘..went in to receive allo-SCT'	‘in’ should be corrected to ‘on’	Typographical error	Word corrected
Page 30: the ERG states: ‘This process is stated to eliminate the ‘the risk of premature..’	Delete one of the occurrences of the word ‘the’	Typographical error	Word deleted
Page 50: the ERG suggests efficacy of KTE-X19 may be ‘overstimated’	Correct to overestimated	Typographical error	Word corrected
Page 50: the ERG include a line break between ‘presented in’ and ‘table 21’, likely due to a cross-referencing issue.	Removal of line break	Cross-referencing error	Cross-referencing issue corrected
Page 59: the ERG states: ‘the most common interventions were inotouzumab..’	Correction of ‘inotouzumab’ to ‘inotuzumab’	Typographical error	Word corrected
Page 93 Table 37: ERG states: ‘1-knot hazard spline to EFS dara’	Correction of dara to data	Typographical error	Word corrected

Page 103, first row of table 40, the ERG states: 'as NICE TA559'	Propose changing to 'as per NICE TA559'	Grammatical error	Word added
Page 111, ERG states 'inotouzumab'	Inotouzumab should be corrected to inotuzumab	Typographical error	Word corrected

Issue 17 Unmarked confidential data

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 59	In addition to the 14 patients who received allo-SCT, others accessed subsequent anticancer therapies. In total, 32 patients out of the 78 who received a KTE-X19 infusion received such therapies with 9 (39%) in Phase 1 and 23 (42%) in Phase 2. The most common interventions were inotouzumab (14 patients), cyclophosphamide (9 patients), ponatinib (8 patients), dexamethasone (7 patients), and blinatumomab (6 patients). In addition, two patients were retreated by KTE-X19 in Phase 2 and had no response.	In addition to the 14 patients who received allo-SCT, others accessed subsequent anticancer therapies. In total, [redacted] patients out of the 78 who received a KTE-X19 infusion received such therapies with [redacted] ([redacted]%) in Phase 1 and [redacted] ([redacted]%) in Phase 2. The most common interventions were inotouzumab ([redacted] patients), cyclophosphamide ([redacted] patients), ponatinib ([redacted] patients), dexamethasone ([redacted] patients), and blinatumomab ([redacted] patients). In addition, [redacted] patients were retreated by KTE-X19 in Phase 2 and had no response.	Markings added as suggested

Page 82	The RFS KM (**Error! Reference source not found.**) reaches zero at month 26 indicating that all uncensored patients had relapsed or died, however there is only one observed death after this time point, with six patients surviving between month 26 and month 46 (**Error! Reference source not found.**).	The RFS KM (**Error! Reference source not found.**) [redacted] (**Error! Reference source not found.**).	Markings added as suggested
Figures 11-13, pages 95-96	The graphs in figures 11-13 contain unpublished KM curves from ZUMA-3.	The figures should be marked up as AIC.	Markings added as suggested
Page 126	However, the mean values reported in ZUMA-3 CSR (Table 14.3.18.1.1 and Table 14.3.18.1.2) were 11.9 days and 2.2 days for Phase 2 and Phase 1 respectively, for which the weighted average is more than 4.3 days.	However, the mean values reported in ZUMA-3 CSR (Table 14.3.18.1.1 and Table 14.3.18.1.2) were [redacted] days and [redacted] days for Phase 2 and Phase 1 respectively, for which the weighted average is more than [redacted] days.	Markings added as suggested
Page 142 ***but please note Issue 13***	The ERG has seen a later data cut-off for ZUMA-3, which shows that the RFS KM appears to be zero at month 26, indicating that all patients had relapsed or died; the ERG notes that this contrasts with the OS KM plot which plateaus.	The ERG has seen a later data cut-off for ZUMA-3, which shows that [redacted]	Markings added as suggested

References

1. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood [Internet]. 2007 Feb 1 [cited 2021 Jun 23];109(3):944–50. Available from: http://ashpublications.org/blood/article-pdf/109/3/944/1287586/zh800307000944.pdf

NICE National Institute for Health and Care Excellence

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **31st of August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults
ID1494

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Matthew Hudson
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Kite Pharma (a Gilead company)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Introduction

Gilead would like to thank the NICE technical team for reviewing the company submission for KTE-X19 in R/R adult ALL, preparing the technical report, and for providing us with the opportunity to engage in the technical engagement process.

Our response is split into three separate parts:

1) Our response to the key issues for engagement & additional issues

2) Details of the revised company base case

3) Additional supportive evidence

As noted during the technical engagement call and in our original CS, since submitting to NICE, a later database lock has become available, with data cut off 23rd July 2021, providing approximately an additional 9 months of efficacy data (median follow-up of 21 months compared to 12 months as presented in the original CS). In addition to this, CHMP positive opinion has been received for KTE-X19 for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)' (1). As such, the additional supportive evidence section comprises: (1) results from the latest database lock; and (2) post hoc subgroup analysis of ZUMA-3 aligned to the anticipated regulatory label.

Key issues for engagement

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Presence of programming and implementation errors in the company's economic model	No	Gilead thanks the ERG for identifying and correcting these programming and implementation errors. We are aligned with the ERG's approach to these corrections and thus accept these changes in addition to the assumption of no vial sharing.
Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach	No	**Gilead considers the SCHOLAR-3 study to be the most appropriate indirect treatment comparison (ITC) for blinatumomab, and the naïve comparison to be the most appropriate source for the other comparators.** The ERG prefers the matched adjusted indirect comparison (MAIC) vs. blinatumomab to SCHOLAR-3 (blinatumomab individual patient data [IPD] matched to KTE-X19 IPD) because they consider it 'debatable' whether the ZUMA-3 population reflects the population of patients who would be likely to be eligible for KTE-X19 in clinical practice in England. Specifically, the ERG queries the absence of ECOG performance status (PS) 2 patients in ZUMA-3 and a lower percentage of Philadelphia chromosome positive (Ph+) patients, although the latter point was conceded by the ERG during the factual accuracy check (FAC). The ERG also queried that SCHOLAR-3 matched only phase 2 patients from ZUMA-3 rather than the pooled phase 1 and 2 cohort used in the survival modelling, resulting in a smaller sample size. They also had concerns as to whether all eligible trials had been included in SCHOLAR-3.

		In the CS, Gilead justified the use of a naïve comparison for other comparators by pointing out that the hazard ratio (HR) for overall survival (OS) from the SCHOLAR-3 analysis was identical to that from the naïve comparison against blinatumomab [redacted], whereas that from the MAIC [redacted] diverged. This was despite SCHOLAR-3 including patients who were all blinatumomab or inotuzumab naïve, biasing against KTE-X19 ZUMA-3util patients (>50% had received prior blinatumomab or inotuzumab). According to the NICE Technical Support Document 18 (2) the MAIC can be considered a cruder method of adjustment than matched IPD, which delivered the higher HR preferred by the ERG. The ERG did not consider the similarity between the IPD-adjusted and naïve HR applicable to the other comparators and have not sufficiently justified their preference to deviate from the TSD guidance. In our response, we consider each of these ERG critiques in turn: **Generalisability of ZUMA-3 population to patients likely to receive KTE-X19 in clinical practice** Gilead would like to note that the ERG's stance on this point softened significantly during response to FAC, moving from: '*The ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status and as such may reflect the population who could receive KTE-X19 in England more accurately [than] ZUMA-3.'* (page 82, ERG report pre-FAC) to: *'Whilst the ERG notes that the comparative studies for blinatumomab and inotuzumab included patients with an ECOG 2 status, the lack of Ph+ patients in TOWER, and lower percentage in INO-VATE compared to ZUMA-3 add uncertainty on which study best reflects the population who could receive KTE-X19 in England*" (Page 89, ERG report)

		Based on a number of important prognostic factors, ZUMA-3 is the most generalisable population to patients likely to receive KTE-X19 in UK clinical practice: 1. The ERG question ZUMA-3's generalisability to patients likely to receive KTE-X19 in UK clinical practice based on ECOG PS alone. Whilst it is the case that ZUMA-3 did not include patients with an ECOG PS of 2, we consider this to be representative of patients likely to be offered KTE-X19 in UK clinical practice for the following reasons: • To be eligible for KTE-X19 treatment for mantle cell lymphoma (MCL) under the Cancer Drugs Fund (CDF), patients must have an ECOG PS 0 or 1. The only exception is if the patients ECOG PS moves to 2 between harvest and infusion (3) • In a UK real-world evidence study presented at the 2022 European Bone Marrow Transplantation (EBMT)-European Hematology Association(EHA) 4th European CAR-T meeting (4), the baseline characteristics of two cohorts approved for CAR-T treatment by a centralised UK national CAR-T Clinical Panel using uniform eligibility criteria were presented. The two CAR-T treatments were KTE-X19 for MCL and axicabtagene ciloleucel (axi-cel, Yescarta) for large B-cell lymphoma (LBCL). Only 1 of 29 patients (3.4%) treated with KTE-X19 and 1 of 74 patients (1.4%) treated with axi-cel had an ECOG PS 2.at the time of infusion. As such, when applying the CDF criteria to previous CAR-Ts, the percentage with an ECOG PS 2 is closer to ZUMA-3 than either TOWER or INO-VATE 2. We consider the ERG's second generalisability issue, the proportion of Ph+ patients in ZUMA-3, to have been resolved during the FAC as the ERG were unable to support their higher proportion with a publication. Furthermore, Gilead would like to re-emphasise that in a study of 609 adults with R/R ALL in the UK, Fielding *et al.*, (2007) observed 20% of patients with Ph+ disease (5). This is closest to – and in fact slightly lower than - that observed in the Ph 1+2

combined population in ZUMA-3 (22%) and notably higher than TOWER (0%) and INO-VATE (15%).

Generalisability of the SCHOLAR-3 study, which matched phase 2 ZUMA-3 patients only, to the pooled phase 1 and 2 data

Gilead disagrees that the use of phase 2 data only in the SCHOLAR-3 study compromises the results.

Focusing on the key prognostic factors, it is apparent from Table 2.1 below that the baseline characteristics of the two cohorts are in close alignment; key prognostic factors do not differ substantially between the Phase 2 cohort and the pooled Phase 1 + 2 cohort. Any results obtained by matching the phase 2 cohort are expected to be similar to those matching the pooled phase 1 and 2 cohorts to which the survival data used in the model are fitted. The smaller sample size in SCHOLAR-3 does not justify preference for a much cruder adjustment method such as the MAIC, which also adjusts to the wrong population.

Furthermore, while the ERG has concerns that relevant trials were excluded in SCHOLAR-3, it is notable that one of the included trials in SCHOLAR-3 was TOWER, the trial adjusted to in the MAIC. The SCHOLAR-3 study, with access to more trials than TOWER alone, therefore had a much larger pool of patients with appropriate baseline characteristics to match to.

Table 2.1: Comparison of key prognostic factors between ZUMA-3 phase 2 and pooled phase 1/2 patients

Prognostic factor	Phase 2 cohort (N = 55)	Phase 1 and 2 cohort (N = 78)
Mean age		
With prior SCT		

First relapse within 12 months		[redacted]			
Relapsed or refractory to 2nd or greater line of therapy					
ECOG status: 0 1					

Key: ECOG, Eastern Cooperative Oncology Group; SCT, stem-cell transplant.

Preference for naïve comparisons for other comparators

As stated previously, SCHOLAR-3 matched IPD from blinatumomab studies to ZUMA-3 IPD, a population that we have shown to be generalisable to UK clinical practice. The HR from the SCHOLAR-3 analysis, which was biased against KTE-X19 on the basis of prior treatment with blinatumomab and inotuzumab, produced an identical HR to the naïve comparison against blinatumomab. Gilead believes that this justifies using the naive HRs for other comparators, however the ERG is of a different opinion. We believe that two published MAICs and/or simulated treatment comparison (STCs) support the transferability of the blinatumomab results to FLAG-IDA and inotuzumab:

- Proskorovsky *et al.* (2019) matched IPD from the INO-VATE study (inotuzumab vs. FLAG-IDA) to aggregate data from TOWER (blinatumomab vs. FLAG-IDA) (6). Both MAIC and STC methods were employed. The adjusted OS HRs vs. blinatumomab using both methods were better than the naïve HR, implying bias against inotuzumab in the naïve comparison. However, differences were small and advantages non-significant.
- Song *et al.,* (2019) conversely matched IPD from TOWER to aggregate data from the INO-VATE study (7). The matched median OS for

		blinatumomab increased vs. the naïve OS, implying bias against blinatumomab in the naïve comparison. Once more, differences were small and advantages non-significant. Both studies had weaknesses arising from use of aggregate-level data e.g., the inability to match Ph status and/or number of prior therapies. Notably, both studies produced directionally opposite results, but differences between the naïve and adjusted comparisons remained small in both cases. These issues would be further compounded in any KTE-X19 MAIC, given that only aggregate data are available from both INO-VATE and TOWER. Considering the large shift in OS HR observed in our MAIC vs. blinatumomab [redacted] vs an HR of [redacted] that remains stable whether derived from a naïve comparison or IPD matched to the appropriate target population, we are surprised that the ERG considers the MAICs more robust than either the SCHOLAR-3 analysis or naïve comparisons for use in the economic modelling. In summary, Gilead firmly stands by its choice of the SCHOLAR-3 analysis vs. blinatumomab and naïve comparisons vs. inotuzumab and FLAG-IDA. Note: the HRs above refer to the overall population in the company submission critiqued by the ERG. Updated HRs for the regulatory subgroup >25 years can be found in the additional supportive evidence appendix document.
Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	No	**Gilead agrees with the ERG's preferred survival models** Upon further inspection of the survival curve data for ponatinib OS, we agree with the ERG that the Gompertz model aligns better with this data compared to the log-normal model that was applied in the original CS. We have therefore amended the cost-effectiveness model base-case to reflect this change.
Key issue 4: Exclusion of allo-SCT related costs and QALY	No	**Gilead asserts that KTE-X19 patients would not receive allo-SCT in clinical practice**

loss for patients on autologous auto-CD19-transduced CD3+.		The ERG queried the ability of KTE-X19 to offer a standalone curative therapy and chose to reinstate the costs of SCT that Gilead had removed. Gilead maintains that the most recent data cut supports a cured population, and that sensitivity analyses demonstrate this to be a standalone cure not dependent on SCT. Furthermore, UK clinicians have stated that they would not use SCT following a CAR-T. We expand on these issues below: **The latest data cut supports the previous observation of a cured fraction of patients** As described in the additional supportive evidence section, 21 months of follow-up data are now available for ZUMA-3. As shown in Figure 1, KM estimates of OS at 12, 18, and 24 months are [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. The KM median OS at the latest data cut is [redacted] months (95% CI: [redacted]). **Figure 1: KM Plot of OS (Phase 1 + 2 combined)**

		[redacted] Key: CI, confidence interval; NE, not estimable. **Source:** (8). **Allo-SCT in ZUMA-3 was either pre-planned due to poor prognostic indicators or administered to consolidate remission, and would not be used in UK clinical practice** • Use of allo-SCT in patients who received KTE-X19 in ZUMA-3 is not sufficient basis for assuming that allo-SCT would be a realistic treatment option for KTE-X19 patients within the model. • As described in our response to clarification question A2, [redacted]

		[redacted]
		• Clinical feedback received by Gilead as part of an advisory board was that in UK clinical practice, clinicians would not consolidate response with allo-SCT.
		• This is particularly true of the anticipated positioning of KTE-X19 in UK clinical practice, where patients are either:
		  ○ Relapsed post allo-SCT, where clinicians said that in UK clinical practice a second allo-SCT would not be performed.
		  ○ Contraindicated to allo-SCT.
		
		Lack of clinical benefit associated with allo-SCT in ZUMA-3
		
		• As part of our response to clarification question A2, we stated that [redacted] subjects that went on to receive allo-SCT had achieved CR/CRi per central assessment, [redacted] As such, allo-SCTs in ZUMA-3 were almost exclusively performed in patients who had achieved remission, rather than in response to worsening prognosis. When taking this into consideration, Gilead believes that the benefit of KTE-X19 occurs independently of allo-SCT.
		• Further support for this comes from a sensitivity analysis of median OS stratified by censoring at allo-SCT, in which survival in responders appeared to be independent of subsequent SCT. There was thus no survival benefit associated with allo-SCT in ZUMA-3 (Figure 2).

		Figure 2: KM Plot of OS for OCR subjects stratified by censoring at allo-SCT (Phase 1 + 2 combined)  Key: CI, confidence interval; NE, not estimable; OCR, overall complete remission; SCT, stem cell transplant. Source: (8). We retain our base-case assumptions, allo-SCT is not included as a subsequent treatment option for patients who receive KTE-X19.
Key issue 5: Concerns with life expectancy of cured patients compared to general population	No	**Gilead considers the SMR preferred by the ERG not relevant to the patient population nor to patients treated using a CAR-T**

		The company base-case applies an SMR of 1.09 to model the mortality risk of patients considered cured (that is, those patients alive after 3 years) compared to that of the age- and sex-matched UK general population. The ERG has concerns that the SMR applied to the background mortality may not appropriately reflect the excess mortality risk of long-term survivors with R/R ALL compared to the general population. However, the EAG also acknowledge that there is uncertainty with regards to the correct value to use to model the increase mortality risk of cured patients. **SMR proposed by the ERG relates to long-term survival following SCT and not treatment with a CAR-T** For cured patients (those still alive after a 3-year cure timepoint) the company base-case applies a standardised mortality ratio (SMR) of 1.09 to general population mortality. The SMR of 1.09 has been sourced from a study in DLBCL, Maurer *et al.*, 2014 and was the ERG's preferred SMR in TA567 (tisagenlecleucel in R/R DLBCL). The ERG state that they believe this to be an underestimate and instead preferred an SMR of 4, that was applied previously for 5-year survivors post-SCT in TA541 (inotuzumab for R/R ALL). The ERG substantially increased the SMR applied to long-term survivors in the economic model. However, this SMR reflects the survival of patients who have received an SCT, a treatment which is not only more burdensome than CAR-T but also has longer-term treatment requirements. The company believes that the SMR of 4 is not applicable to R/R ALL patients that had received KTE-X19 or any other CAR-T treatment. This SMR value is based on 5-year survival observed in patients who received SCT (Martin *et al.*, 2010). It is important to note that there are considerable differences for post-SCT patients vs. post-CAR-T patients. For instance, up to two-thirds of patients who receive allogeneic-SCT develop graft versus host disease (GVHD) which may require long-term treatment with immunosuppressants if chronic. Both GVHD and

		immunosuppressants are factor known to increase non-relapse mortality (9,10). Furthermore, only 16% of the patient population in Martin *et al.*, (2010) had ALL, and it is not reported whether any of these patients had R/R disease. Therefore, there are issues of generalisability due to the treatment (SCT vs. CAR-T) as well as the patient population. As stated by the ERG in their report, TA450 (blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia) assumed an SMR of 1. Given that the model results show greater efficacy of KTE-X19 vs. blinatumomab, we do not believe that the SMR of 1.09 is an underestimate, as lower SMR values have been accepted for less effective treatments. Gilead would also like to note that long-term cure with blinatumomab is contingent on consolidation with allo-SCT and is therefore more likely to be represented by the Martin *et al.*, (2010) study than KTE-X19.
Key issue 6: Concerns with cured patients having the same utility values as general population	No	**Gilead stands by its assertion that health-related quality of life (HRQoL) of cured patients would the same as or close to the general population** In the company base-case, patients alive at the 3-year time-point in the model are assumed to be cured and experience similar HRQoL to the general population. Utility for these patients were modelled using an age- and sex-matched population, using the approach detailed in Ara and Brazier, (2010) (11). The ERG is of the opinion that the cumulative drug toxicity and the impact of having R/R ALL at some point of their lives would mean that the utility for cured patients would be lower than the age- and sex-matched population. The ERG therefore applied a utility decrement (multiplier) equal to the difference between HRQoL in the event-free survival (EFS) health state and the equivalent age-and sex-adjusted general population. In doing so, the ERG inherently assumes that HRQoL of a patient who has been cured of ALL for years is the same as that in a patient who has recently undergone treatment for their R/R ALL and does not yet know their long-term outcome. This very clearly lacks face validity based on the emotional impact alone of recent diagnosis and treatment on the patient vs. knowing that they are cured.

		Secondly, it ignores the fact that patients will recover over time from their ALL and its treatment. The impact of going from limited treatment options to a long-term cure was captured in a patient interview by Leukaemia Care as part of their patient organisation submission in the technical engagement papers for this appraisal. Leukaemia Care, who disclosed no funding from Gilead, conducted an update to their 2017 patient survey for the purpose of this submission, as well as two patient interviews. One of these patients, who had received SCT, as well as a CAR-T post-SCT relapse, explained the impact of CAR-T at a time when they were told limited options were available: "*CAR-T means that I get a third chance at life. The doctors had said that I could continue with chemo but it would only be effective for a limited time so it's likely that I wouldn't be here without it [CAR T]. For me, it was 100 times easier than a transplant with less side effects and a quicker recovery time*" (Page 6, patient organisation submission). The evidence provided by Leukaemia Care highlights the substantial HRQoL gains likely to be achieved following CAR-T induced cure in this patient population. The ERG state that *'the assumption that patients are cured without residual comorbidities would not appear consistent with the assumption that patients have an increased risk of death compared to the age- and sex-matched population'* (Page 138, ERG report). We do not agree with this statement. The application of general population mortality does not indicate that cured patients have no comorbidity, but rather that this is within the limits of that experienced by others of the same age. Furthermore, increased mortality risk in cured patients does not necessarily mean that patients would score lower on self-reported HRQoL measures such as the EQ-5D compared to the general population. Quantity of life

		is not equal to quality of life, which is an important consideration given the context of the poor outcomes for R/R ALL patients. **HRQoL in CAR-T patients vs. allo-SCT recipients** Further support for Gilead's assumptions regarding the utility of cured patients comes from Leukaemia Care's patient organisation submission. As already described, Leukaemia Care undertook one-to-one conversations with two patients who had received CAR-T therapy after relapsing post-SCT, and as such can offer a personal perspective on the relative burden of each treatment. One of the key quotes taken from Page 6 of the patient organisation submission is presented below: 'The younger patient explained "*there is actually nothing really bad about CAR T, it was such a stark contrast to what I had already been through with my stem cell transplant*". This is due to the less severe, short-term and more manageable side effects this patient experienced after CAR T in comparison to SCT. After CAR T she says, "*everyone was asking me how I felt and it was the first time I was able to say that I actually felt better*."' This, in combination with the quote provided on the previous page that included ' *"For me, it was 100 times easier than a transplant with less side effects and a quicker recovery time*"' offers support for Gilead's position that SCT poses a considerably greater post-treatment burden than CAR-T, and as such is likely to adversely impact long-term QoL. As such, studies reporting long-term QoL in SCT-cured patients are not likely to be representative of long-term QoL in CAR-T cured patients. **HRQoL assumptions applied in previous appraisals**

The utility assumptions applied for cured patients are similar to those accepted at committee for other STAs of CAR-T infusions or treatments in R/R ALL. A summary of this is presented below.

Table 1.2: Utility assumptions applied for cured patients in previous appraisals of CAR-T or in R/R ALL

Appraisal	General population utility applied for cured patients?
Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (TA559)	Yes
Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years (TA554)	Yes
Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma (TA677)	The company base-case assumed that people who had treatment with autologous anti-CD19-transduced CD3+ cells whose disease has not progressed after 5 years of treatment have the same health-related quality of life as the general population. The committee concluded that it was not clear if long-term survivors would have the same health-related quality of life as people in the general population of the same age and sex.

		<table><tr><td>Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (TA541)</td><td>Committee concluded that utility values 5 years post-transplant are likely to be between those presented in Kurosawa *et al.,* (2016) (0.76) and the value for the general population (0.88).</td></tr><tr><td>Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia (TA450)</td><td>Yes</td></tr></table>
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ and inotuzumab	No	Gilead accept the ERG's base case change which removes half the costs (£73,197) and QALY loss (0.104) associated with veno-occlusive disease (VOD), given that these costs were thought to be an overestimate in TA541. The ERG's assumption that AE-related costs for KTE-X19 are equal to that for inotuzumab as a conservative assumption is not applied in the revised company base-case, due to reasons provided in the response to key issue 8. Namely, the revised company base-case only applies costs for AEs that incur an ICU stay, thus this assumption is not relevant. As discussed in the response to Key Issue 9, Gilead do not accept the tariff associated with providing CAR-T infusions that the ERG has applied in their preferred ICER, therefore AE-related costs are included in the company's updated base-case.
Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	No	**Adverse events that result in ICU stay are included accounted for** The ERG state that they believe there may be double-counting of the adverse event (AE) costs associated with blinatumomab and FLAG-IDA as these costs would be captured within the inpatient and outpatient administration costs included for these treatments. The ERG highlights that in NICE TA450 (blinatumomab),

		treatment-related AEs were assumed to be included within the cost of the initial hospital stay for both blinatumomab and FLAG-IDA. The length of stay (LOS) for both appraisals was informed by the key clinical trials underpinning the efficacy of these treatments in the population of interest. The ERG's rationale for excluding AE-related costs for blinatumomab and FLAG-IDA is also applicable to KTE-X19. LOS in the KTE-X19 arm is based on the observed LOS in ZUMA-3 and thus captures LOS associated with the management of AEs as well as that for treatment administration. On this basis, Gilead believe that all treatment-related AEs, aside from those resulting in an ICU stay, such as VOD or CRS, should be excluded. This is in line with the methodology applied in previous appraisals. Gilead have reviewed previous NICE appraisals of CAR-T infusions and other interventions in R/R ALL and found that adverse events are typically assumed to be covered within the treatment administration costs. However, costs of additional hospitalisation due to serious adverse events such as VOD and CRS are typically included as the management of these AEs would incur ICU stay costs, the costs of which are not captured within the NHS reference costs HRG codes for inpatient stay. In the updated company base-case model, only those AEs that require an ICU stay are included in the cost calculations, whilst all other treatment-related AEs are excluded.
Key issue 9: Uncertainty of the costs associated with delivering autologous auto-CD19-transduced CD3+ infusion	No	We are deeply concerned about the inclusion of the NHS England CAR-T delivery tariff, both in terms of the implications for a fair and transparent procedure in this appraisal and the ramifications this is likely to have for patient access to CAR-T therapies generally in England. In line with the Methods Guide NICE must consider what the *true cost* of the treatment is to the NHS.

		The cost analysis submitted by Gilead followed recommended NICE methods and the relevant hierarchy of evidence, Gilead's cost analysis therefore included our best estimate of the costs of delivering CAR-T therapy, using an approach which included systematic identification of evidence using published sources and clinical validation. However, in the ERG report and base case, an assumed tariff for delivering CAR-T therapy in England of [redacted] (the **NHS Tariff**) was raised. This is stated to be based on expert advice however no evidence of how this figure was calculated was provided in the ERG report despite the significant impact it has on the ICER. A similar 2022/23 tariff cost of £96,016 was raised during the committee meeting for axicabtagene ciloleucel for the treatment of refractory low-grade non-Hodgkin's lymphoma (ID1685) which led the Committee to conclude that Gilead's cost model may not be reflective of NHS practice, and ultimately not recommend that the product be made available to NHS patients. The Appraisal Committee recognised that there is a lack of transparency about what costs the NHS Tariff included, that greater transparency is required to explore potential issues of double counting and noted that the clinical experts as well as Gilead strongly disagreed with the figure used by NHS England. However, it nevertheless concluded that the NHS Tariff estimate represented the best available source to inform the cost that the NHS is paying currently. No explanation for this conclusion is provided, although we infer that the figure is used by NHS England in practice. In the absence of any transparency for the NHS Tariff figure, this approach is both procedurally unfair and unreasonable. Our position remains the same in this appraisal – in the absence of transparency and evidence – the ERG and Committee should not implement an assumed tariff of [redacted]. Since the Committee meeting for ID1685, we have used our best efforts to understand what the NHS Tariff includes and how it has been calculated, so that we can compare it to our cost analysis. Our understanding is that this tariff was established by NHS England in 2019 with the introduction of CAR-T therapies.

		After the Committee meeting, NHS England provided to us and to NICE the same high-level summary of what is included in the NHS Tariff. However, this summary does not give any detail on what specific elements comprise the NHS Tariff and does not provide sufficient transparency nor resolve the issues highlighted by the Committee in the appraisal consultation document. For example, it is not possible to explore potential issues of double counting. There remains no transparency on the methods used to calculate, nor on evidence used to substantiate, the value of the NHS Tariff. It remains unclear whether the NHS Tariff is reliable or includes costs which are not relevant to a NICE appraisal. In circumstances where the tariff value is central to this appraisal and to any consideration of CAR-T therapies, it is clearly essential that this is fully transparent and can be understood and tested by stakeholders. We therefore requested more specific information, including an itemised breakdown of the pathway costs reflecting resource utilisation across the patient pathway for patients meeting the standard care patient pathway and patients on the complex patient pathway, assumptions on the proportion of patients meeting the standard care pathway and the complex patient pathway and related validation. NHS England have assessed our request as a request under the Freedom of Information Act. Under that Act, NHS England have until 6 September 2022 to respond. Despite the apparent introduction of the NHS Tariff some years ago it has not been considered appropriate by NICE for inclusion in any other CAR-T guidance to date. This included the prior guidance for axicabtagene ciloleucel in 3L DLBCL in 2019 (TA559), and the appraisal of KTE-X19 in MCL in 2021 (TA677). While the NHS Tariff was noted in the ERG response in TA677 the value (£92,000 at that time) is redacted from public view and the ERG noted the lack of transparency in how the NHS Tariff was arrived at and the fact that the value was due to be re-evaluated following the appraisal (NHS England have confirmed that the NHS Tariff remains under review); ultimately the NHS Tariff was not included in the final decision. Any decision to adopt a different approach in the current appraisal should be justified by clear reasoning; this is currently absent.

		In order to carry out a general assessment of the NHS Tariff figure, we have obtained evidence from the Adelphi Real World DLBCL DSP™, a real-world point-in-time survey of haematologists, haem-oncologists, and medical oncologists and their patients with DLBCL in the UK, Germany, Spain, Italy, France and Canada in 2021. The analysis considered the 100 days following CAR-T administration. A total of [redacted] patients received CAR-T at 3rd line in the DSP UK sample; in European countries (UK, Germany, Spain, Italy and France), there were a total of [redacted] patients who received CAR-T at 3rd line. The analysis found that [redacted] of the [redacted] patients in the UK who received CAR-T were hospitalised as an inpatient for an average of [redacted] within the first 100 days of administration (within the European countries this value was [redacted] nights). Additionally, UK patients had an average of [redacted] outpatient visits (within European countries this value was [redacted] (SD: [redacted]) visits). Applying a daily hospitalisation cost of £550 per inpatient bed day (aligned with the cost-effectiveness model) and a cost of £217.00 per outpatient visit (NHS Reference Costs 2020/21; Outpatient Attendance; 370 (Medical Oncology)), this results in a cost of [redacted] for UK patients ([redacted] for European patients) which is a small fraction of the NHS Tariff figure. Whilst this data is taken from a different indication, it still applies to CAR-T, and the sheer magnitude of the difference in values obtained from utilisation of this data compared to the NHS tariff amplify Gilead's concerns relating to the lack of transparency around how this figure is derived. These findings also align with the [redacted] days of hospitalisation resulting in the [redacted] cost associated with CAR-T infusion included within the company cost-effectiveness model. Given the lack of transparency surrounding the NHS Tariff and the uncertainty in how the value was derived and its constituents, the real-world evidence and the approach followed in previous appraisals of CAR-T therapies, a recommendation based on the use of this NHS Tariff would clearly be procedurally unfair and, in the absence of reasoning appears arbitrary and unreasonable. Further, such a decision would lack credibility, conflicting with NICE's reputation for transparent,

		evidence based decision-making and for facilitating accelerated patient access to transformative therapies. If there is uncertainty around clinical costs, the only fair and reasonable conclusion the Committee can reach based on the evidence it has been provided with is to include the cost of treatment shown in our cost analysis, calculated using NICE recommended methods and based on evidence, in preference to the NHS Tariff figure until any uncertainty is resolved. If the Committee believes that the clinical costs associated with CAR-T therapy are uncertain, we would propose that as a potential solution the health care resource use following CAR-T infusion could be studied carefully, and accurately determined during a period of CDF access in order to help establish a methodical, evidence-based treatment cost for future NICE appraisals. CAR-T therapies have an extremely high manufacturing cost due to their innovative and personalised nature, which limits the level of discount which can be offered. If imposed across the CAR-T class, the NHS Tariff, which is wholly lacking in transparency and we believe to be substantially incorrect, will have the effect of Gilead's provision of CAR-T therapy almost certainly not being cost effective without a level of discount which will not be commercially viable. This will result in new patients, such as those with ALL, not gaining access to these innovative, life-saving therapies, but also existing patient groups losing access as currently available therapies exit the CDF. NHS England is known as a world leader in cell therapy and the potential loss of future and current access will be to the detriment of patient outcomes and to the reputation of the UK as an early adopter of transformative science. Given the potentially huge impact on patients we strongly urge the Committee to consider the consequences of this issue in full.
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	No	**FLAG-IDA dosing** In the original submitted company base-case, it was assumed that patients on FLAG-IDA would be treated until disease progression, or for a maximum of 4 28-day cycles. The ERG's preferred base-case assumes a maximum of 2 cycles of

		FLAG-IDA, based on clinical advice and the INO-VATE and TOWER studies. Based on further clinical expert opinion provided to Gilead, which aligned with that received by the ERG, we accept the ERG's preferred base-case assumption of a maximum of two cycles of FLAG-IDA. **Use of adjunctive chemotherapy alongside ponatinib** The ERG's preferred base-case assumes no adjunctive chemotherapy for patients receiving ponatinib. However, this is not aligned with clinical expert opinion received by Gilead or the NCRI-ACP-RCP-RCR professional organisation submission reported in technical engagement papers. On page 4 of the professional organisation submission, the group state 'for Philadelphia positive relapsed / refractory B ALL patients can be prescribed ponatinib. This is usually prescribed alongside a chemotherapy backbone.' Exclusion of chemotherapy costs for ponatinib patients in the ERG's base-case is thus a significant omission and does not reflect clinical practice in the UK. Whilst Gilead acknowledge that the assumption that all ponatinib patients receiving FLAG-IDA may be an overestimate, clinical feedback and supporting evidence also point towards the ERG's approach being an underestimate. Therefore, we propose a middle ground is likely to be most representative of clinical practice. To this end, the updated company base-case assumes that 15% of ponatinib patients receive adjunctive chemotherapy with FLAG-IDA.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: **End-of life criteria: short life expectancy**	Section 5, page 153	No	In the ERG's technical report (section 5, pp.153), they cite the mean life years in the model base case to pose uncertainty around whether the short life expectancy criterion for end-of-life (normally less than 24 months) is satisfied. Specifically, the ERG refers to mean life years predicted by the model, rather than median survival or proportion of patients alive after 2 years that were observed in clinical trials or the real-world setting. Median OS and 2-year OS are key survival measures and therefore are more appropriate barometers for considering the application of an end-of-life weighting; indeed NICE commonly uses these measures rather than the ERG's approach.

Gilead strongly maintains the position that KTE-X19 for R/R adult ALL qualifies for end-of-life.

Based on: (1) pivotal trials of comparators; (2) previous NICE TA's in the same indication; and (3) the committee deliberations for avelumab (TA788), Gilead strongly believe that KTE-X19 for r/r adult ALL meets both end-of-life criteria. These points will be discussed in turn.

Median OS for comparators in pivotal trials was 4.0-8.0 months, markedly lower than the 24-month threshold stipulated by NICE

Adult ALL has historically had a dismal prognosis; following relapse to front-line therapy, prognosis is especially dire, with most R/R adult ALL patients unlikely to live beyond a year (12). Whilst the introduction of new treatment options for R/R ALL has improved the prognosis, median OS in pivotal trials for the comparators was markedly lower than the 24-month threshold set out in NICE's end-of-life eligibility criteria (Table 3.1).

Table 2.1: Median OS in pivotal trials for R/R adult ALL comparators

Comparator	Trial	Median OS
Blinatumomab	TOWER (13)	7.7 months
Inotuzumab	INO-VATE (14)	7.7 months
Ponatinib	PACE (15)	8.0 months

FLAG-IDA	TOWER, INO-VATE (13,14)	4.0 months 6.7 months	

FLAG-IDA, fludarabine, cytarabine, idarubicin, granulocyte-colony stimulating factor.

In the context of the median OS of 4-8 months demonstrated in comparator clinical trials, we consider it wholly implausible that the indicated population for KTE-X19 has a life expectancy normally greater than 24 months.

Previously appraised treatments in R/R adult ALL have qualified for end-of-life criteria

As demonstrated in Table 2.1, improvements in median OS have been incremental with the introduction of new technologies. As such, we feel that despite SoC differing to varying degrees at the time of previous TAs in adult R/R ALL, decisions on end-of-life made by committees as part of previous appraisals are relevant to this appraisal.

As detailed below, committees have consistently agreed that adults with R/R ALL have a short life expectancy (normally less than 24 months). This conclusion has been based on median OS in pivotal trials for SoC, which if applied here would result in the same conclusion, that the short life expectancy criterion is met.

			• TA450 (blinatumomab): the committee noted that life expectancy was 4 months for standard of care chemotherapy in TOWER and concluded that the short life-expectancy criterion was met. (16) • TA541 (inotuzumab): the committee discussed whether life expectancy without inotuzumab ozogamicin would be less than 24 months. It noted that median overall survival was 6.7 months with standard care in INO-VATE and concluded that the short life expectancy criterion was met. (17) • TA451: The committee concluded that the end-of-life criteria were met for people with Ph+ ALL regardless of allogeneic stem cell transplantation suitability. (18) **Avelumab (TA788) committee agreed that the model and decision on usual life expectancy are standalone considerations** As part of an appeal in defence of avelumab's qualification for NICE end-of-life criteria in TA788, committee deliberations provide additional support for Gilead's position that the totality of evidence should be considered when assessing the short life expectancy criterion. Data from pivotal trials and previous TA's provide robust support for the short life expectancy criterion being met in R/R adult ALL.

			Furthermore, the appeal panel for TA788 concluded on page 23 of the Final Appraisal Document that '*NICE stakeholders would consider it unreasonable to state that life expectancy for this population was normally more than 24 months, given that the modelled mean life expectancy indicated that most people (65%) did not survive after 24 months'* (19). The modelled mean life expectancy in the CS base case indicates that a higher percentage (78-87% across comparators) of people did not survive after 24 months. As such, we feel that the same rationale from TA788 should apply to KTE-X19; the use of mean life years in the model is of limited relevance within the context of the totality of evidence presented. In conclusion, based on comparator pivotal trials demonstrating <8 months median OS, all previous appraisals for this indication meeting the short life expectancy criterion, and the pragmatic approach to deliberations for avelumab TA788 where use of mean life years was deemed unreasonable, Gilead is of the strong opinion that KTE-X19 for R/R adult ALL qualifies for both end-of-life criteria.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 1: Prescence of programming and implementation errors in the company's economic model	The original submitted cost-effectiveness model had some errors in the way it was programmed and implemented in terms of vial sharing, drug cost calculations based on body surface area (BSA), cyclophosphamide and fludarabine acquisition cost calculations, blinatumomab administration costs and the linkage of inotuzumab spline selection list to the rest of the model.	Gilead have accepted the EAG's corrections which are an assumption of no vial sharing, corrected calculations for how the vial consumption is calculated based on BSA, correction of the cyclophosphamide and fludarabine dose, removing remaining double counting for blinatumomab administration costs, and correcting the links for the spline selection list of inotuzumab.	£98

Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	The log-normal distribution was used to model overall survival (OS) for ponatinib	The Gompertz model is used to model OS for the ponatinib arm	-£1,006
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ and inotuzumab	The utility decrement applied for VOD was -0.208 and the cost for this AE was £153,767.	The utility decrement applied for VOD is -0.104 and the cost for this AE is £76,884.	-£2,277
Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	AE costs were included for all treatment-related AEs, for all treatments.	Only the costs for those AEs which result in an ICU stay i.e. VOD and CRS were included. The median number of ICU days for CRS was corrected from [redacted] to [redacted] days	-£74
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	It was assumed that patients on FLAG-IDA would be treated until disease progression, or for a maximum of 4 28-day cycles. All ponatinib patients in the model recieve adjunctive chemotherapy with FLAG-IDA.	Patients receive a maximum of 2 cycles of FLAG-IDA. 15% of ponatinib patients receive adjunctive chemotherapy with FLAG-IDA.	-£1,191

Non-ERG report related issue: restriction of age to >25 in line with the anticipated regulatory label.	The original cost-effectiveness model included data for all ZUMA-3 patients.	In line with the CHMP positive opinion received for KTE-X19 for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)', ZUMA-3 data have been restricted to a subgroup of patients >25.	£362

Sensitivity analyses around revised base case

The sensitivity analyses around the revised company base-case are provided in the supplementary appendix reporting the updated cost-effectiveness results.

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Technical engagement response form: additional supportive evidence

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Technical engagement response form

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **31st of August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults
ID1494

Additional supportive evidence

As described in our CS, and confirmed during the technical engagement call, a further database lock with cut off 23rd July 2021, providing an additional 9 months of follow up compared to the data cut off used in the CS (9th September 2020) is now available, providing longer-term evidence of the durability of effect with KTE-X19 in r/r adult ALL (1). In addition, in July 2022 Gilead received a positive opinion from the CHMP, for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)' (2). Notably, the inclusion of '26 years of age and above' deviates very slightly from the label that was anticipated in the CS, which was for all adults. As Gilead are following the Reliance route, this label is anticipated to be identical for MHRA. As such, our additional supportive evidence comprises:

1) Efficacy data for KTE-X19 – data from ZUMA-3 with an additional 9 months' follow-up (21 months compared to 12 months in the CS)

2) Post-hoc subgroup analysis of ZUMA-3 aligned to the anticipated regulatory label population

New evidence is provided for validation purposes. Additionally, the data introduced here have been incorporated into the cost-effectiveness model calculations, ensuring the model is representative of the most up-to-date data, as well as the appropriate population for decision-making.

Efficacy data for KTE-X19: 23/07/21 database lock

Follow-up analyses to the primary analyses for ZUMA-3 that have become available since the original CS provide further support for the initial conclusions that KTE-X19 provides an effective treatment option for adults with r/r ALL, with the potential for long-term survivorship in a population for whom current SoC is associated with median OS of less than 8 months (3–5).

At the time of follow-up analysis, the median follow-up from KTE-X19 infusion among the Phase 2 mITT was [redacted] months (range: [redacted] months). For subjects treated in Phase 1, the median follow-up from KTE-X19 infusion was [redacted] months (range: [redacted] months); all subjects treated in Phase 1 had at least [redacted] months of potential follow-up. Consistent with the CS, all data presented is for the combined Ph1+2 population, which consists of all patients treated at target dose in Phase 1 and all patients treated at Phase 2 (1).

Overall survival

OS for all subjects treated at target dose (Phase 1 + 2 combined) is summarised in Table 1, and a graphical display of the OS curve is shown in Figure 1.

KM estimates of OS at 12, 18, and 24 months were [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. The KM median OS was [redacted] months (95% CI: [redacted]), with a reverse KM median follow-up time for OS of [redacted] months (95% CI: [redacted] months).

Table 1: OS (Phase 1 + 2 combined)

OS	1e6 Dose Level (Phase 1 and Phase 2) (N = 78)		
Number of subjects, n		[redacted]	
Death, n (%)			
Censored, n (%)			
Alive on or after DCO, n (%)			
Full withdrawal of consent, n (%)			
Lost to follow-up, n (%)			
KM median (95% CI) OS (months)			
Min, Max OS (months)			
Survival free rates (%) (95% CI) by KM estimation at			
3 months			
6 months			
9 months			
12 months			
15 months			
18 months			
24 months			
30 months			
36 months			
42 months			
48 months			

54 months	[redacted]
Median (95% CI) follow-up time (months) (reverse KM approach)	[redacted]

Data cutoff date = 23Jul2021.
Abbreviations: CI, confidence interval; DCO, data cutoff date; KM, Kaplan-Meier; Max, maximum; Min, minimum; NE, not estimable; OS, overall survival.
Notes: 1e6 = 1 x 106 anti-CD19 CAR T cells/kg. OS for subjects treated with KTE-X19 is defined as the time from KTE-X19 infusion date to the date of death from any cause. Subjects who had not died by the analysis data cutoff date were censored at their last contact date prior to the data cutoff date, with the exception that subjects known to be alive or determined to have died after the data cutoff date were censored at the data cutoff date. '+' indicates censoring.
Source: ZUMA-3 CSR 21 month addendum (1).

Figure 1: KM plot of OS (Phase 1 + 2 combined)

Data cutoff date = 23Jul2021.
Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; OS, overall survival. Notes: 1e6 = 1 x 106 anti-CD19 CAR T cells/kg.
Source: ZUMA-3 CSR 21 month addendum (1).

Notably, in a sensitivity analysis of median OS stratified by subsequent allo-SCT, survival in responders appeared to be independent of subsequent SCT (Figure 2).

Figure 2: KM plot of OS for OCR subjects stratified by subsequent allogeneic SCT (Phase 1 + 2 combined)

Data cutoff date = 23Jul2021.
Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; OS, overall survival. Notes: 1e6 = 1 x 106 anti-CD19 CAR T cells/kg.
Source: ZUMA-3 CSR 21 month addendum (1).

Relapse-free survival

A graphical display of the KM RFS curve is shown in Figure 3. KM estimates of RFS rates at 6, 12, 18 months were [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively. The KM median RFS was [redacted] months (95% CI: [redacted] months), with a reverse KM median follow-up time for RFS of [redacted] months (95% CI: [redacted] months).

Figure 3: KM plot of RFS (Phase 1 + 2 combined)

Data cutoff date = 23Jul2021.

Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; KM, Kaplan-Meier; RFS, relapse-free survival. Notes: 1e6 = 1 x 10^6 anti-CD19 CAR T cells/kg.

Response rate & duration of remission

No further responses were observed to those achieved by the time of primary analyses. Among the 58 subjects who achieved a CR or CRi, the KM median DOR was [redacted] months (95% CI: [redacted] months), with a reverse KM median follow-up time for DOR of [redacted] months (95% CI: [redacted] months). Overall, [redacted] subjects were censored: [redacted] subjects were in ongoing remission as of the data cutoff date, [redacted] subjects had an allo-SCT, [redacted] subjects started new anticancer therapy, and [redacted] subject was lost to follow-up. [redacted] subjects relapsed, and [redacted] subjects died. The KM estimates of the proportion of responders who remained in remission at 6, 12, and 18 months from first response were [redacted] (95% CI: [redacted]), [redacted] (95% CI: [redacted]), and [redacted] (95% CI: [redacted]), respectively.

Figure 4: KM plot of DOR per investigator assessment (Phase 1+2 combined)

Data cutoff date = 23Jul2021.
Abbreviations: CAR, chimeric antigen receptor; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; KM, Kaplan-Meier; NE, not estimable.
Notes: 1e6 = $1x10^6$ anti-CD19 CAR T cells/kg.

Regulatory label subgroup analysis:

Baseline characteristics

In the pivotal ZUMA-3 study, [redacted] of 78 treated subjects in the Phase 1 + 2 combined analysis set were aligned with the anticipated regulatory label for KTE-X19 for the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor ALL. As presented in Table 2, baseline characteristics of the two cohorts are in close alignment, including on key prognostic factors such as ECOG status, prior SCT, ≥2 prior lines of therapy and duration of 1st remission ≤12 months.

Table 2: Baseline characteristics: comparison of ZUMA-3 CS population and population aligned to regulatory label

Characteristics	**Phase 1 + 2 combined (n=78)**	**Phase 1 + 2 combined >25 years (n=[redacted])**
Age category, n (%)		
< 65 years	[redacted]	
≥ 65 years		
Male, n (%)		
ECOG performance status, n (%)		
0		
1		
Philadelphia chromosome t(9:22) mutation, n (%)		
MLL translocation t(4:11) of Myc translocation t(8:14), n (%)		

Characteristics	Phase 1 + 2 combined (n=78)	Phase 1 + 2 combined >25 years (n=[redacted])
Complex karyotype (≥ 5 chromosomal abnormalities), n (%)		
Low hypodiploidy (30–39 chromosomes), n (%)		
Near triploidy (60–78 chromosomes), n (%)		
Number of lines of prior therapy, n (%)		
1		
2		
≥3		
Prior blinatumomab, n (%)		
Blinatumomab as the last prior therapy, n, (%)		
Prior inotuzumab ozogamicin, n (%)		
Prior allogenic SCT, n (%)		
Prior autologous SCT, n (%)		
Prior radiotherapy, n (%)		
Refractory, n (%)*		
Primary refractory		
R/R after ≥ 2 lines of therapy[a]		
R/R post-allo-SCT[b]		
First relapse with remission ≤ 12 months		
BM blasts at screening, median % (range)		

Characteristics	Phase 1 + 2 combined (n=78)	Phase 1 + 2 combined >25 years (n=[redacted])
BM blasts at baseline, median % (range)		
BM blasts after bridging chemotherapy, median % (range)		
BM blasts >25% at baseline, n (%)		
Extramedullary disease at screening, n (%)		
CNS disease at baseline, n (%)		
CNS-1		
CNS-2		

Data cutoff date = 23Jul2021.
Abbreviations: CNS, central nervous system; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; ECOG, Eastern Cooperative Oncology Group; LVD, longest vertical dimension; MLL, mixed lineage leukaemia; NR, no response; PD, progressive disease; PR, partial remission; SCT, stem cell transplant; SPD, sum of the products of diameters; STDEV, standard deviation.
Note: Excludes information collected after retreatment.
Baseline is defined as the last assessment prior to the start of conditioning chemotherapy.
a. Two subjects with relapsed or refractory disease to 2nd or greater lines of therapy were erroneously not marked in the eCRF as such.
b. One subject had prior autologous transplant but was erroneously marked in the eCRF as relapsed/refractory disease after allogeneic SCT.
Source: (6).

OCR

Table 3: Summary of Best Overall Response using Independent Review (Phase 1 + 2 combined, >25 years)

Response Category, n (%)	Phase 1, 1e6 Dose Level (N = [redacted])	Phase 2 (N = [redacted])	Combined (N = [redacted])
Number of OCR (CR + CRi)	[redacted]		
CR			
CRi			
CRh			
BFBM			
PR			
NR			
Unknown or not evaluable			

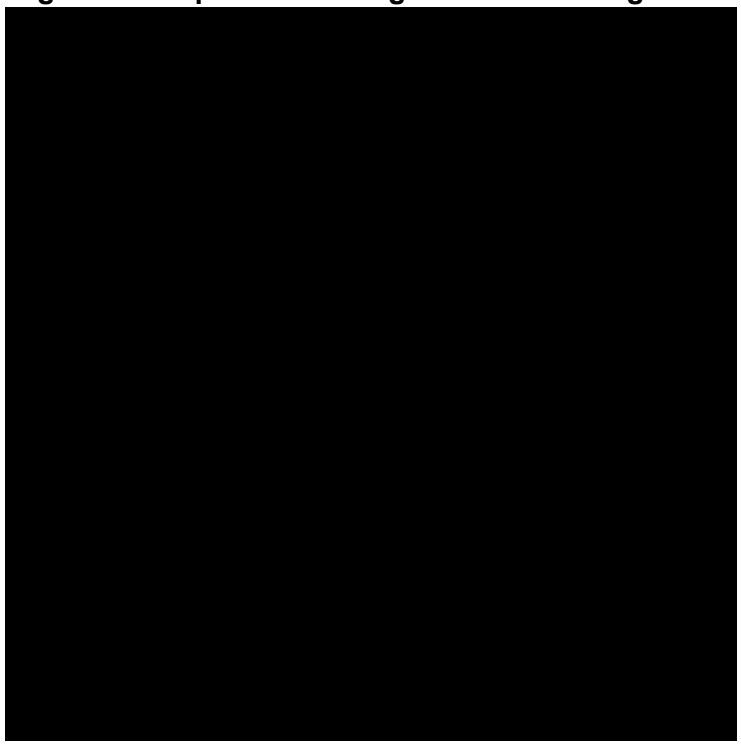
Data cutoff date = 23Jul2021.
Abbreviations: BFBM, blast-free hypoplastic or aplastic bone marrow; CR, complete remission; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; NR, no response; PR, partial response; OCR, overall complete remission.
All dosed subjects (EMA) is defined as all subjects treated with KTE-X19 who were 26 years old or older.
Source: (6).

Overall survival

Figure 5: KM plot of OS (Phase 1 + 2 combined, >25 yrs)

Data cutoff date = 23Jul2021.
Abbreviations: CI, confidence interval; NE, not evaluable.
1e6 = 1 × 10^6 anti-CD19 CAR T cells/kg.
Source: (6).

Figure 6: KM plot of OS: original vs censoring at allo-SCT



Abbreviations: alloSCT, allogeneic stem cell transplant.
Source: (6).

Relapse free survival

Figure 7: KM Plot of RFS using Independent Review (Phase 1 + 2 combined, >25yrs)

Data cutoff date = 23Jul2021.
Abbreviations: CI, confidence interval.
All dosed subjects (EMA) is defined as all subjects treated with KTE-X19 who were 26 years old or older.
Source: (6).

Indirect treatment comparison

The updated indirect treatment comparison results for the regulatory subgroup of the Phase 1 + 2 combined population are presented in Table 4 and Table 5.

Table 4: Summary of ITC results (OS)

		Previous			21 months, >25yrs		
Comparison	**ZUMA-3 analytical set**	**Naïve comparison HR**	**ESS***	**MAIC HR (CI) 3 salvage status***	**Naïve comparison HR**	**ESS***	**MAIC HR (CI) 3 salvage status***
X19 vs blinatumomab (TOWER)	Phase 1 + 2 combined	[redacted]					
X19 vs inotuzumab (INO-VATE)	Phase 1 + 2 combined						
X19 vs pooled chemo	Phase 1 + 2 combined						

Abbreviations: ESS, effective sample size; HR, hazard ration; X19, KTE-X19.
Source: updated MAIC report (7)

Table 5: Summary of ITC results (EFS)

		Previous			21 months, >25yrs		
Comparison	**ZUMA-3 analytical set**	**Naïve comparison HR**	**ESS***	**MAIC HR (CI) 3 salvage status***	**Naïve comparison HR**	**ESS***	**MAIC HR (CI) 3 salvage status***
X19 vs Blinatumomab (TOWER)	Phase 1 + 2 combined	[redacted]					
X19 vs Inotuzumab (INO-VATE)	Phase 1 + 2 combined						
KTE-X19 vs pooled chemo	Phase 1 + 2 combined						

Abbreviations: ESS, effective sample size; HR, hazard ration; X19, KTE-X19.
Source: updated MAIC report (7)

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6. Kite, a Gilead company data on file. Regulatory subgroup tables & figures. 2022;

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Table 1: Summary of changes to company base-case following technical engagement

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement
Key issue 1: Prescence of programming and implementation errors in the company's economic model	The original submitted cost-effectiveness model had some errors in the way it was programmed and implemented in terms of vial sharing, drug cost calculations based on body surface area (BSA), cyclophosphamide and fludarabine acquisition cost calculations, blinatumomab administration costs and the linkage of inotuzumab spline selection list to the rest of the model.	Gilead have accepted the EAG's corrections which are an assumption of no vial sharing, corrected calculations for how the vial consumption is calculated based on BSA, correction of the cyclophosphamide and fludarabine dose, removing remaining double counting for blinatumomab administration costs, and correcting the links for the spline selection list of inotuzumab.
Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	The log-normal distribution was used to model overall survival (OS) for ponatinib	The Gompertz model is used to model OS for the ponatinib arm
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ and inotuzumab	The utility decrement applied for VOD was -0.208 and the cost for this AE was £153,767.	The utility decrement applied for VOD is -0.104 and the cost for this AE is £76,884.
Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	AE costs were included for all treatment-related AEs, for all treatments.	Only the costs for those AEs which result in an ICU stay i.e. VOD and CRS were included. The median number of ICU days for CRS was corrected from [redacted] to [redacted] days
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	It was assumed that patients on FLAG-IDA would be treated until disease progression, or for a maximum of 4 28-day cycles. All ponatinib patients in the model receive adjunctive chemotherapy with FLAG-IDA.	Patients receive a maximum of 2 cycles of FLAG-IDA. 15% of ponatinib patients receive adjunctive chemotherapy with FLAG-IDA.

Non-ERG report related issue: restriction of age to >25 in line with the anticipated regulatory label.	The original cost-effectiveness model included data for all ZUMA-3 patients.	In line with the CHMP positive opinion received for KTE-X19 for 'the treatment of adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL)', ZUMA-3 data have been restricted to a subgroup of patients >25.

B.1.1 Base-case results

B.1.1.1 Overall population

Table 2: Base-case results (overall population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	13.686	[redacted]	-	-	-	-
Inotuzumab	[redacted]	6.752	[redacted]	[redacted]	6.934	[redacted]	£18,671
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	10.464	[redacted]	£36,591

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.1.1.2 Ph- population

Table 3: Base-case results (Ph- population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	12.649	[redacted]	-	-	-	-
Blinatumomab	[redacted]	4.740	[redacted]	[redacted]	7.910	[redacted]	£31,089
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	9.428	[redacted]	£39,806
Inotuzumab	[redacted]	6.752	[redacted]	[redacted]	5.898	[redacted]	£20,648

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.1.1.3 Ph+ population

Table 4: Base-case results (Ph+ population)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	13.614	[redacted]	-	-	-	-
Ponatinib	[redacted]	5.388	[redacted]	[redacted]	8.226	[redacted]	£37,608
FLAG-IDA	[redacted]	3.222	[redacted]	[redacted]	10.392	[redacted]	£36,166
Inotuzumab	[redacted]	6.752	[redacted]	[redacted]	6.862	[redacted]	£17,872

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

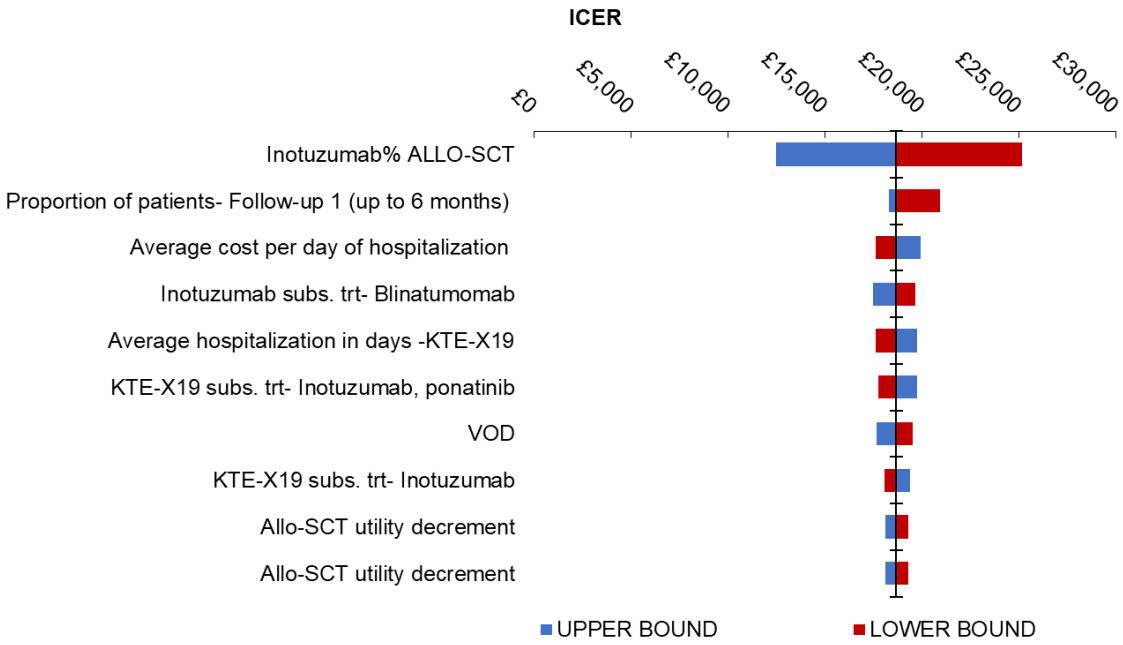
B.1.2 Sensitivity analyses

B.1.2.1 Deterministic sensitivity analysis

Table 5: OWSA results, overall population, inotuzumab

Parameter	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	£25,179	£12,470	£12,709
Proportion of patients- Follow-up 1 (up to 6 months)	£20,946	£18,275	£2,671
Average cost per day of hospitalization	£17,633	£19,947	£2,314
Inotuzumab subs. trt- Blinatumomab	£19,666	£17,495	£2,171
Average hospitalization in days - KTE-X19	£17,611	£19,730	£2,119
KTE-X19 subs. trt- Inotuzumab, ponatinib	£17,756	£19,758	£2,002
VOD incidence	£19,505	£17,682	£1,824
KTE-X19 subs. trt- Inotuzumab	£18,060	£19,401	£1,341
Allo-SCT utility decrement	£19,290	£18,126	£1,164

Figure 1: OWSA results, overall population, inotuzumab

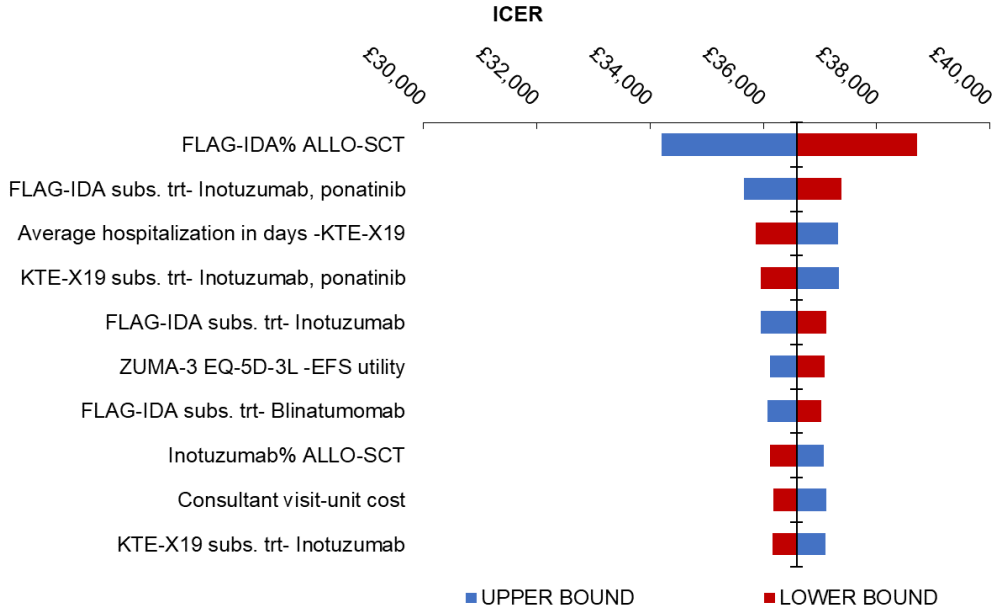


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant.

Table 6: OWSA results, overall population, FLAG-IDA

Parameter	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	£38,712	£34,205	£4,507
FLAG-IDA subs. trt- Inotuzumab, ponatinib	£37,379	£35,654	£1,725
Average hospitalization in days -KTE-X19	£35,859	£37,322	£1,463
KTE-X19 subs. trt- Inotuzumab, ponatinib	£35,959	£37,341	£1,382
FLAG-IDA subs. trt- Inotuzumab	£37,117	£35,962	£1,155
ZUMA-3 EQ-5D-3L -EFS utility	£37,082	£36,112	£969
FLAG-IDA subs. trt- Blinatumomab	£37,023	£36,074	£949
Inotuzumab% ALLO-SCT	£36,123	£37,065	£942
Consultant visit-unit cost	£36,176	£37,118	£942
KTE-X19 subs. trt- Inotuzumab	£36,169	£37,094	£925

Figure 2: OWSA results, overall population, FLAG-IDA

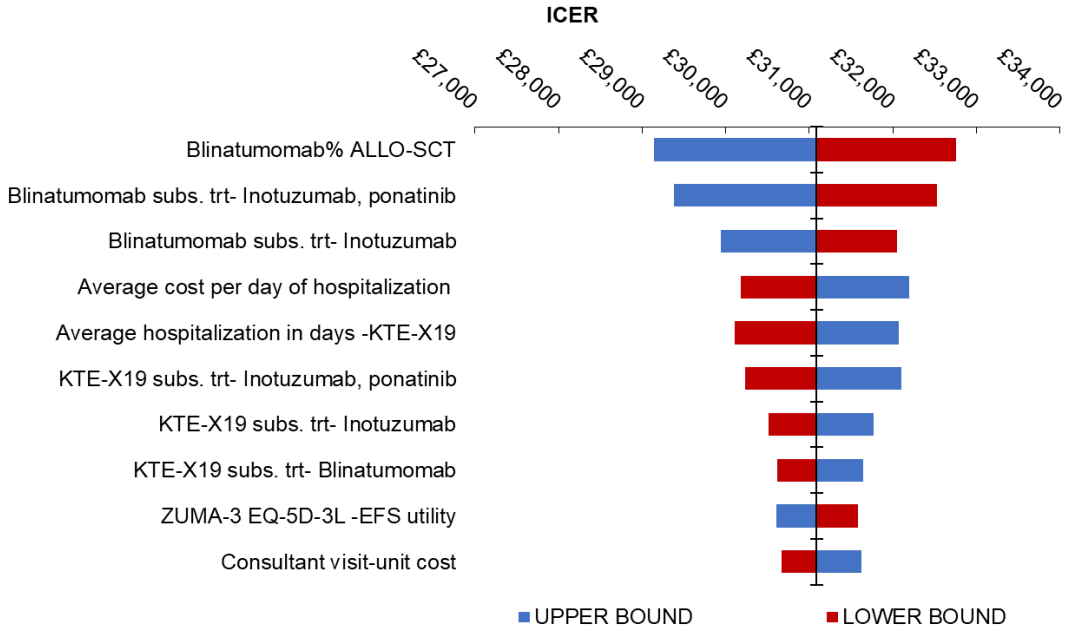


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; VOD, veno-occlusive disease; STC: stem cell transplant.

Table 7: OWSA results, Ph- population, blinatumomab

Parameter	Lower bound ICER	Upper bound ICER	Difference
Blinatumomab% ALLO-SCT	£32,762	£29,145	£3,617
Blinatumomab subs. trt- Inotuzumab, ponatinib	£32,534	£29,383	£3,151
Blinatumomab subs. trt- Inotuzumab	£32,052	£29,942	£2,111
Average cost per day of hospitalization	£30,186	£32,198	£2,012
Average hospitalization in days -KTE-X19	£30,105	£32,073	£1,968
KTE-X19 subs. trt- Inotuzumab, ponatinib	£30,233	£32,106	£1,873
KTE-X19 subs. trt- Inotuzumab	£30,517	£31,772	£1,254
KTE-X19 subs. trt- Blinatumomab	£30,620	£31,649	£1,030
ZUMA-3 EQ-5D-3L -EFS utility	£31,581	£30,611	£970
Consultant visit-unit cost	£30,671	£31,621	£950

Figure 3: OWSA results, Ph- population, blinatumomab

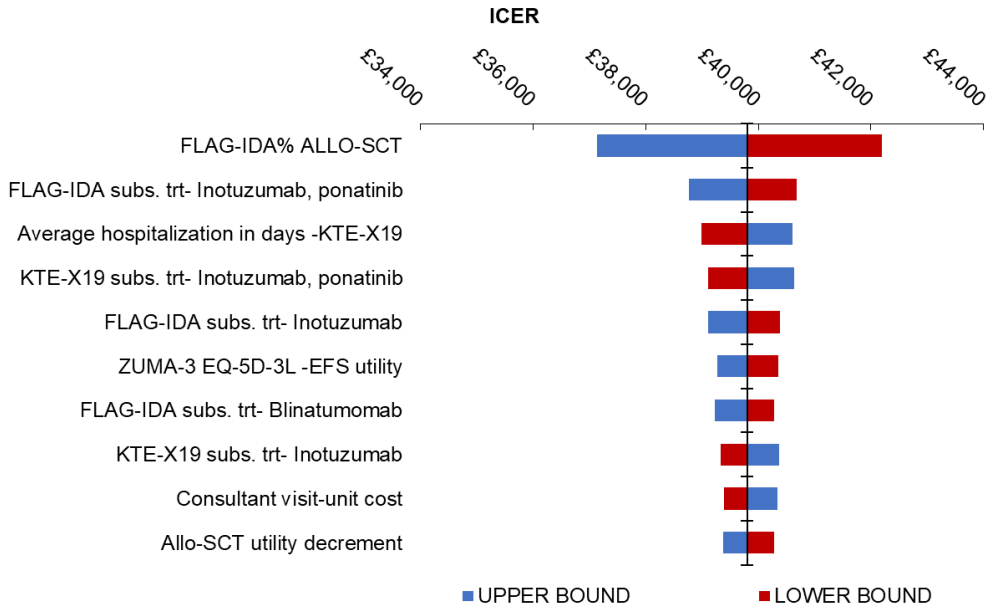


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant.

Table 8: OWSA results, Ph- population, FLAG-IDA

Parameter	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	£42,190	£37,129	£5,061
FLAG-IDA subs. trt- Inotuzumab, ponatinib	£40,678	£38,769	£1,909
Average hospitalization in days -KTE-X19	£38,996	£40,615	£1,619
KTE-X19 subs. trt- Inotuzumab, ponatinib	£39,102	£40,642	£1,541
FLAG-IDA subs. trt- Inotuzumab	£40,388	£39,109	£1,279
ZUMA-3 EQ-5D-3L -EFS utility	£40,360	£39,267	£1,093
FLAG-IDA subs. trt- Blinatumomab	£40,284	£39,234	£1,050
KTE-X19 subs. trt- Inotuzumab	£39,336	£40,367	£1,032
Consultant visit-unit cost	£39,389	£40,336	£947
Allo-SCT utility decrement	£40,276	£39,376	£911

Figure 4: OWSA results, Ph- population, FLAG-IDA

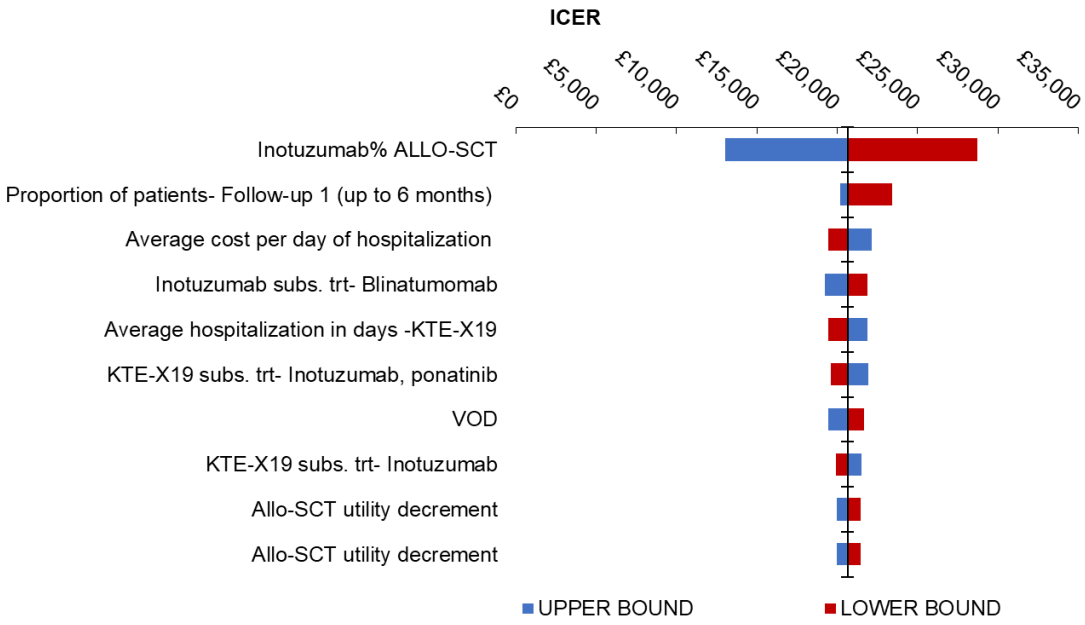


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant.

Table 9: OWSA results, Ph- population, inotuzumab

Parameter	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	£28,738	£13,018	£15,719
Proportion of patients- Follow-up 1 (up to 6 months)	£23,415	£20,167	£3,248
Average cost per day of hospitalization	£19,442	£22,131	£2,690
Inotuzumab subs. trt- Blinatumomab	£21,873	£19,200	£2,673
Average hospitalization in days - KTE-X19	£19,416	£21,880	£2,464
KTE-X19 subs. trt- Inotuzumab, ponatinib	£19,577	£21,921	£2,345
VOD	£21,676	£19,430	£2,246
KTE-X19 subs. trt- Inotuzumab	£19,933	£21,503	£1,570
Allo-SCT utility decrement	£21,449	£19,951	£1,515
Allo-SCT utility decrement	£21,449	£19,951	£1,498

Figure 5: OWSA results, Ph- population, inotuzumab

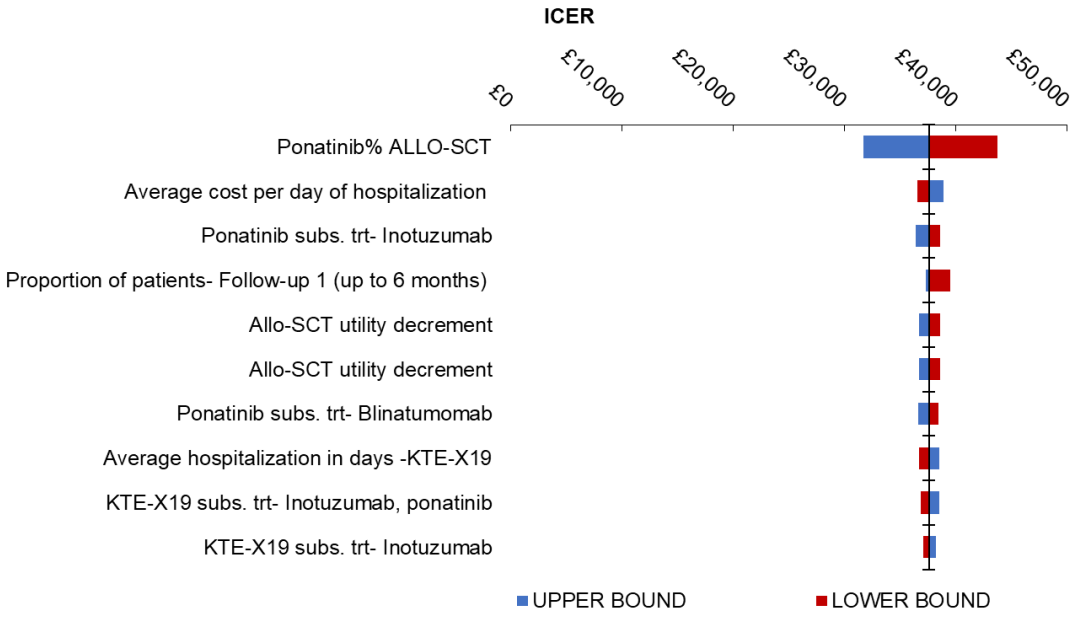


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant; VOD, veno-occlusive disease.

Table 10: OWSA results, Ph+ population, ponatinib

Parameter	Lower bound ICER	Upper bound ICER	Difference
Ponatinib% ALLO-SCT	£43,713	£31,670	£12,043
Average cost per day of hospitalization	£36,565	£38,891	£2,325
Ponatinib subs. trt- Inotuzumab	£38,622	£36,405	£2,218
Proportion of patients- Follow-up 1 (up to 6 months)	£39,481	£37,282	£2,199
Allo-SCT utility decrement	£38,633	£36,697	£1,959
Allo-SCT utility decrement	£38,633	£36,697	£1,936
Ponatinib subs. trt- Blinatumomab	£38,441	£36,620	£1,821
Average hospitalization in days -KTE-X19	£36,708	£38,508	£1,801
KTE-X19 subs. trt- Inotuzumab, ponatinib	£36,827	£38,536	£1,708
KTE-X19 subs. trt- Inotuzumab	£37,087	£38,231	£1,144

Figure 6: OWSA results, Ph+ population, ponatinib

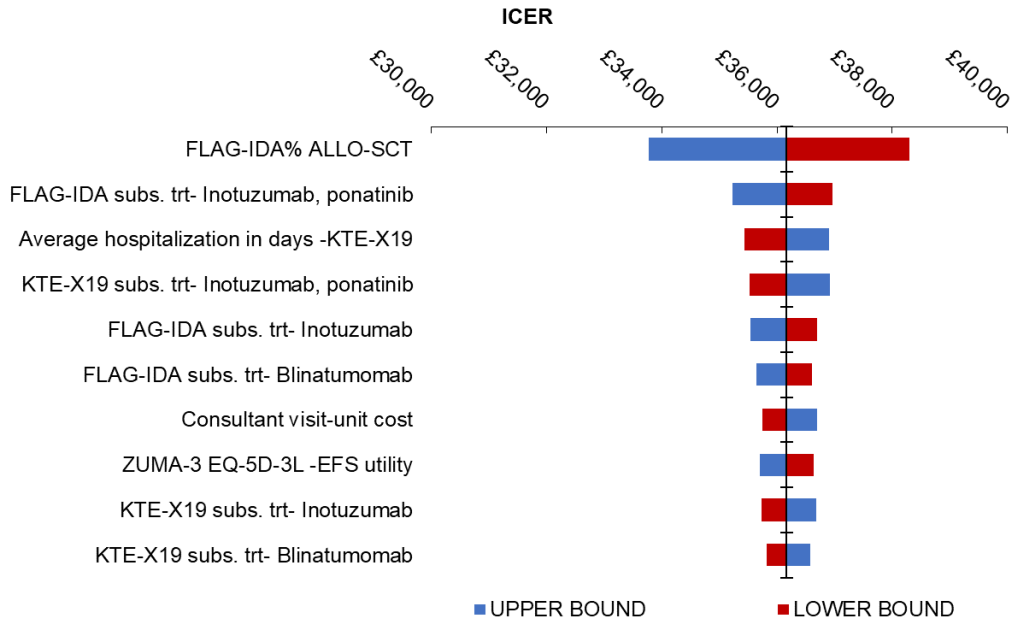


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant.

Table 11: OWSA results, Ph+ population, FLAG-IDA

Parameter	Lower bound ICER	Upper bound ICER	Difference
FLAG-IDA% ALLO-SCT	£38,298	£33,768	£4,529
FLAG-IDA subs. trt- Inotuzumab, ponatinib	£36,959	£35,223	£1,737
Average hospitalization in days -KTE-X19	£35,429	£36,902	£1,473
KTE-X19 subs. trt- Inotuzumab, ponatinib	£35,527	£36,925	£1,397
FLAG-IDA subs. trt- Inotuzumab	£36,696	£35,533	£1,163
FLAG-IDA subs. trt- Blinatumomab	£36,601	£35,646	£955
Consultant visit-unit cost	£35,751	£36,694	£943
ZUMA-3 EQ-5D-3L -EFS utility	£36,640	£35,703	£937
KTE-X19 subs. trt- Inotuzumab	£35,740	£36,675	£936
KTE-X19 subs. trt- Blinatumomab	£35,816	£36,584	£768

Figure 7: OWSA results, Ph+ population, FLAG-IDA

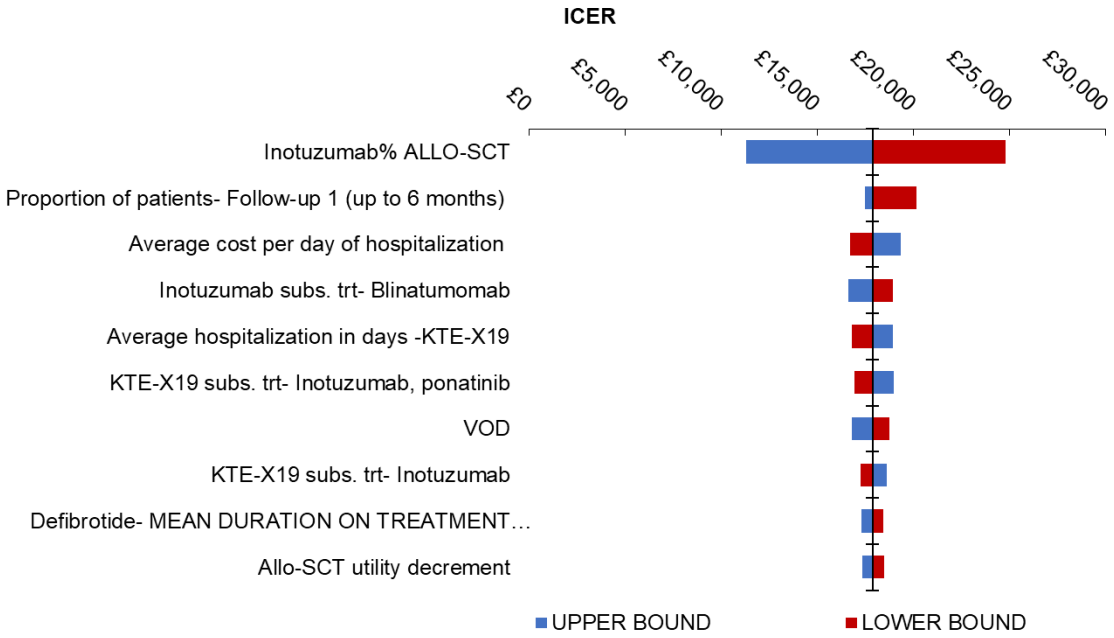


Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant.

Table 12: OWSA results, Ph+ population, inotuzumab

Parameter	Lower bound ICER	Upper bound ICER	Difference
Inotuzumab% ALLO-SCT	£24,776	£11,299	£13,477
Proportion of patients- Follow-up 1 (up to 6 months)	£20,175	£17,472	£2,703
Average cost per day of hospitalization	£16,687	£19,330	£2,644
Inotuzumab subs. trt- Blinatumomab	£18,937	£16,615	£2,322
Average hospitalization in days -KTE-X19	£16,802	£18,943	£2,141
KTE-X19 subs. trt- Inotuzumab, ponatinib	£16,944	£18,975	£2,031
VOD	£18,765	£16,815	£1,951
KTE-X19 subs. trt- Inotuzumab	£17,253	£18,613	£1,360
Defibrotide- MEAN DURATION ON TREATMENT (DAYS)	£18,452	£17,293	£1,159
Allo-SCT utility decrement	£18,472	£17,346	£1,139

Figure 8: OWSA results, Ph+ population, inotuzumab



Key: ICER, incremental cost-effectiveness ratio; PD, progressed disease; STC: stem cell transplant.

B.1.2.2 Probabilistic sensitivity analysis

Table 13: Probabilistic results - overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	13.706	[redacted]	-	-	-	-
Inotuzumab	[redacted]	6.800	[redacted]	[redacted]	6.906	[redacted]	£20,347
FLAG-IDA	[redacted]	3.295	[redacted]	[redacted]	10.411	[redacted]	£37,910

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 14: Probabilistic results - Ph- population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	12.668	[redacted]	-	-	-	-
Blinatumomab	[redacted]	4.852	[redacted]	[redacted]	7.816	[redacted]	£33,113
FLAG-IDA	[redacted]	3.323	[redacted]	[redacted]	9.346	[redacted]	£41,275
Inotuzumab	[redacted]	6.828	[redacted]	[redacted]	5.840	[redacted]	£22,661

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 15: Probabilistic results - Ph+ population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Pairwise ICER (£/QALY)
KTE-X19	[redacted]	13.649	[redacted]	-	-	-	-
Ponatinib	[redacted]	5.560	[redacted]	[redacted]	8.089	[redacted]	£39,252
FLAG-IDA	[redacted]	3.274	[redacted]	[redacted]	10.376	[redacted]	£37,325
Inotuzumab	[redacted]	6.825	[redacted]	[redacted]	6.824	[redacted]	£19,792

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 9:Scatter plot, overall population

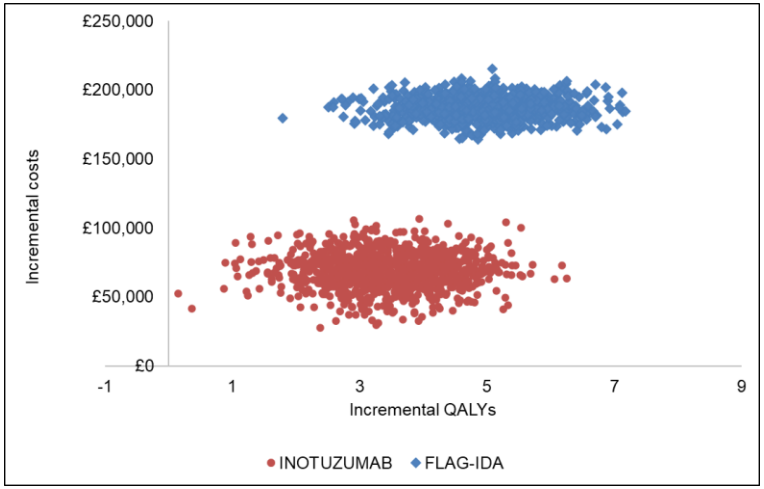


Figure 10: Scatter plot, Ph+ population

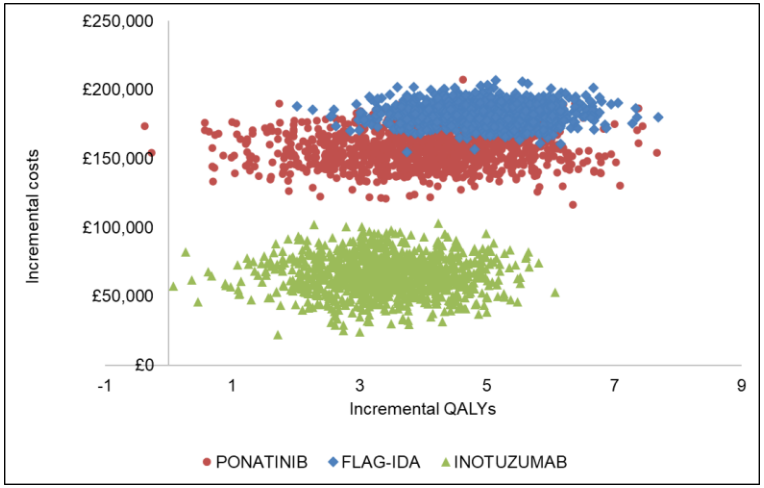


Figure 11: Scatter plot, Ph- population

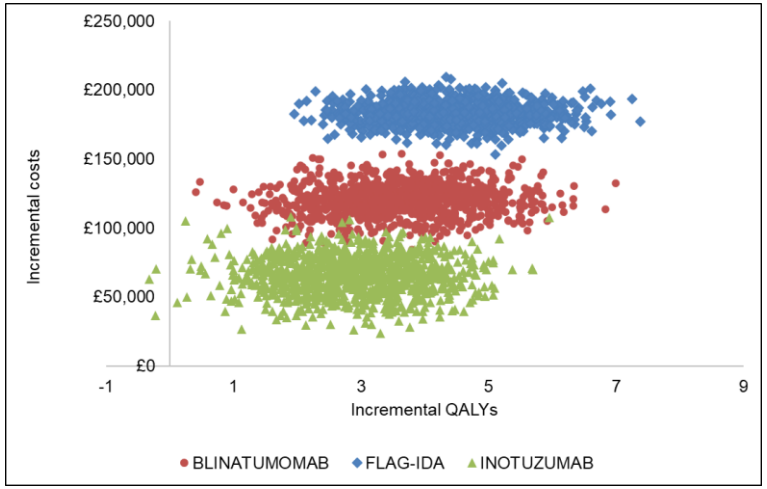


Figure 12: CEAC, overall population

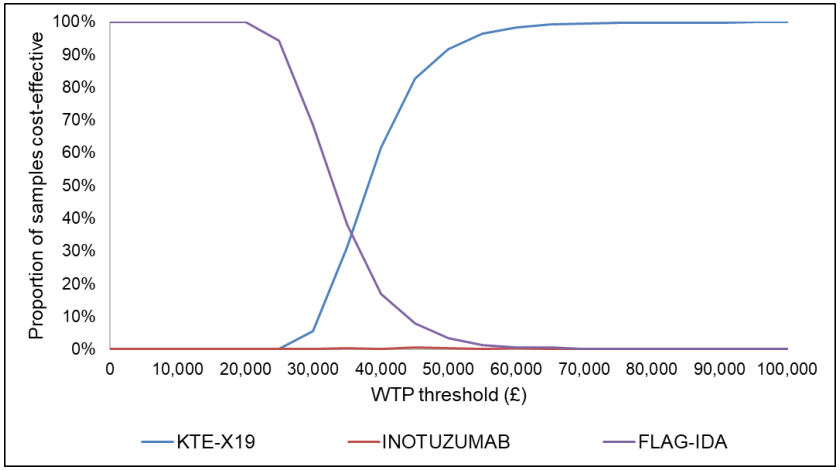


Figure 13: CEAC, Ph+ population

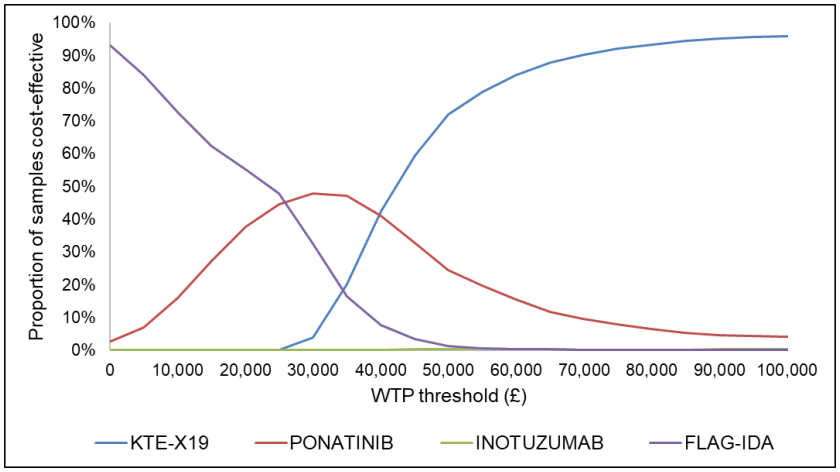
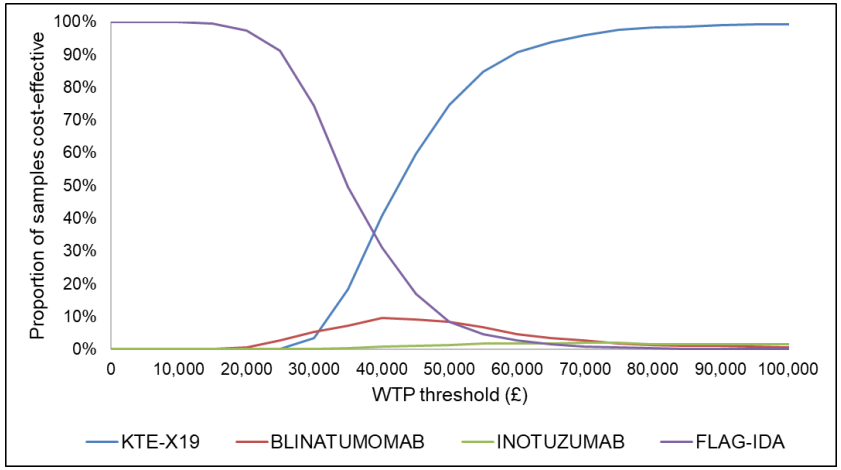


Figure 14: CEAC, Ph- population



B.1.2.3 Scenario analysis

Table 16: Results of scenario analysis – overall population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Inotuzumab**	[redacted]	[redacted]	**£18,671**
			FLAG-IDA	[redacted]	[redacted]	**£36,591**
Time horizon	57 years	20 years	Inotuzumab	[redacted]	[redacted]	£24,184
			FLAG-IDA	[redacted]	[redacted]	£48,574
Discount rate for costs and outcomes (QALYs)	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Inotuzumab	[redacted]	[redacted]	£14,688
			FLAG-IDA	[redacted]	[redacted]	£28,136
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Inotuzumab	[redacted]	[redacted]	£18,242
			FLAG-IDA	[redacted]	[redacted]	£35,670
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Inotuzumab	[redacted]	[redacted]	£18,053
			FLAG-IDA	[redacted]	[redacted]	£35,483
Modelling of clinical efficacy between treatment arms	Naïve comparison	MAIC	Inotuzumab	[redacted]	[redacted]	£20,772
			FLAG-IDA	[redacted]	[redacted]	£42,883

Excess mortality	SMR of 1.09	SMR of 2.5, as per TA541	Inotuzumab	[redacted]	[redacted]	£21,039
			FLAG-IDA	[redacted]	[redacted]	£41,412
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Inotuzumab	[redacted]	[redacted]	£18,866
			FLAG-IDA	[redacted]	[redacted]	£36,989
	General population utility	TA541	Inotuzumab	[redacted]	[redacted]	£20,802
			FLAG-IDA	[redacted]	[redacted]	£40,966
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Inotuzumab	[redacted]	[redacted]	£15,965
			FLAG-IDA	[redacted]	[redacted]	£35,409
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Inotuzumab	[redacted]	[redacted]	£21,311
			FLAG-IDA	[redacted]	[redacted]	£37,774
PD utility source	ZUMA-3	Blinatumomab SMC submission	Inotuzumab	[redacted]	[redacted]	£19,349
			FLAG-IDA	[redacted]	[redacted]	£36,796
		Tisagenlecleucel SMC submission	Inotuzumab	[redacted]	[redacted]	£18,673
			FLAG-IDA	[redacted]	[redacted]	£36,591
KTE-X19 AE disutility source	Literature	ZUMA-3	Inotuzumab	[redacted]	[redacted]	£18,981
			FLAG-IDA	[redacted]	[redacted]	£37,008

CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Inotuzumab	[redacted]	[redacted]	£18,661
			FLAG-IDA	[redacted]	[redacted]	£36,577
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Inotuzumab	[redacted]	[redacted]	£21,283
			FLAG-IDA	[redacted]	[redacted]	£39,809
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£18,455
			FLAG-IDA	[redacted]	[redacted]	£36,341
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£17,492
Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£32,938
SCT as subsequent treatment option for KTE-X19 patients	No SCT	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Inotuzumab	[redacted]	[redacted]	£24,204
			FLAG-IDA	[redacted]	[redacted]	£40,751

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model.

Table 17: Results of scenario analysis – Ph- population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Blinatumomab**	[redacted]	[redacted]	£31,089
			Inotuzumab	[redacted]	[redacted]	£20,648
			FLAG-IDA	[redacted]	[redacted]	£39,806
Time horizon	57 years	20 years	Blinatumomab	[redacted]	[redacted]	£41,584
			Inotuzumab	[redacted]	[redacted]	£26,708
			FLAG-IDA	[redacted]	[redacted]	£52,844
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Blinatumomab	[redacted]	[redacted]	£23,812
			Inotuzumab	[redacted]	[redacted]	£16,247
			FLAG-IDA	[redacted]	[redacted]	£30,596
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Blinatumomab	[redacted]	[redacted]	£31,174
			Inotuzumab	[redacted]	[redacted]	£21,159
			FLAG-IDA	[redacted]	[redacted]	£40,086
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Blinatumomab	[redacted]	[redacted]	£28,952
			Inotuzumab	[redacted]	[redacted]	£19,213.00
			FLAG-IDA	[redacted]	[redacted]	£37,793
Excess mortality	SMR of 1.09		Blinatumomab	[redacted]	[redacted]	£35,330

		SMR of 2.5, as per TA541	Inotuzumab	[redacted]	[redacted]	£23,233
			FLAG-IDA	[redacted]	[redacted]	£45,033
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Blinatumomab	[redacted]	[redacted]	£31,438
			Inotuzumab	[redacted]	[redacted]	£20,861
			FLAG-IDA	[redacted]	[redacted]	£40,238
		TA541	Blinatumomab	[redacted]	[redacted]	£34,930
			Inotuzumab	[redacted]	[redacted]	£22,977
			FLAG-IDA	[redacted]	[redacted]	£44,552
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Blinatumomab	[redacted]	[redacted]	£29,598
			Inotuzumab	[redacted]	[redacted]	£18,298
			FLAG-IDA	[redacted]	[redacted]	£38,839
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Blinatumomab	[redacted]	[redacted]	£32,599
			Inotuzumab	[redacted]	[redacted]	£22,991
			FLAG-IDA	[redacted]	[redacted]	£40,795
PD utility source	ZUMA-3	Blinatumomab SMC submission	Blinatumomab	[redacted]	[redacted]	£30,653
			Inotuzumab	[redacted]	[redacted]	£21,413
			FLAG-IDA	[redacted]	[redacted]	£39,919
			Blinatumomab	[redacted]	[redacted]	£31,087

		Tisagenlecleucel SMC submission	Inotuzumab	[redacted]	[redacted]	£20,650
			FLAG-IDA	[redacted]	[redacted]	£39,806
KTE-X19 AE disutility source	Literature	ZUMA-3	Blinatumomab	[redacted]	[redacted]	£31,568
			Inotuzumab	[redacted]	[redacted]	£21,048
			FLAG-IDA	[redacted]	[redacted]	£40,309
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Blinatumomab	[redacted]	[redacted]	£31,074
			Inotuzumab	[redacted]	[redacted]	£20,635
			FLAG-IDA	[redacted]	[redacted]	£39,790
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Blinatumomab	[redacted]	[redacted]	£32,888
			Inotuzumab	[redacted]	[redacted]	£23,721
			FLAG-IDA	[redacted]	[redacted]	£43,346
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£30,030
			Inotuzumab	[redacted]	[redacted]	£19,778
			FLAG-IDA	[redacted]	[redacted]	£38,682
Parametric function adopted to model EFS and OS for blinatumomab	1-knot spline hazard is used to model EFS, lognormal SPM is used to model OS	Lognormal SPM is used to model EFS, generalised gamma SPM is used to model OS	Blinatumomab	[redacted]	[redacted]	£31,207

Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£19,067
Parametric function adopted to model EFS and OS for Blinatumomab	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	Blinatumomab	[redacted]	[redacted]	£90,130
SCT as subsequent treatment option for KTE-X19 patients	Not included	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Blinatumomab	[redacted]	[redacted]	£36,570
			Inotuzumab	[redacted]	[redacted]	£27,185
			FLAG-IDA	[redacted]	[redacted]	£44,496

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model.

Table 18: Results of scenario analysis – Ph+ population

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. KTE-X19
Base-case			**Ponatinib**	[redacted]	[redacted]	£37,608
			Inotuzumab	[redacted]	[redacted]	£17,872
			FLAG-IDA	[redacted]	[redacted]	£36,166
Time horizon	57 years	20 years	Ponatinib	[redacted]	[redacted]	£49,387
			Inotuzumab	[redacted]	[redacted]	£23,139
			FLAG-IDA	[redacted]	[redacted]	£48,013
Discount rates	3.5% discount rate for costs and QALYs	1.5% discount rate for costs and QALYs	Ponatinib	[redacted]	[redacted]	£29,151
			Inotuzumab	[redacted]	[redacted]	£14,067
			FLAG-IDA	[redacted]	[redacted]	£27,808
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 mITT dataset	ZUMA-3 ITT dataset	Ponatinib	[redacted]	[redacted]	£35,907
			Inotuzumab	[redacted]	[redacted]	£17,262
			FLAG-IDA	[redacted]	[redacted]	£34,983
Source of patients' baseline characteristics and KTE-X19 EFS and OS	ZUMA-3 Phase 1 and Phase 2 combined dataset	ZUMA-3 Phase 2 dataset	Ponatinib	[redacted]	[redacted]	£36,842
			Inotuzumab	[redacted]	[redacted]	£17,052
			FLAG-IDA	[redacted]	[redacted]	£34,957
Excess mortality	SMR of 1.09		Ponatinib	[redacted]	[redacted]	£42,421

		SMR of 2.5, as per TA541	Inotuzumab	[redacted]	[redacted]	£20,134
			FLAG-IDA	[redacted]	[redacted]	£40,927
Source of utility values for cured patients	General population utility	Blinatumomab SMC	Ponatinib	[redacted]	[redacted]	£38,006
			Inotuzumab	[redacted]	[redacted]	£18,059
			FLAG-IDA	[redacted]	[redacted]	£36,560
		TA541	Ponatinib	[redacted]	[redacted]	£41,959
			Inotuzumab	[redacted]	[redacted]	£19,912
			FLAG-IDA	[redacted]	[redacted]	£40,490
Distribution of patients in the KTE-X19 arm that fail to receive infusion	Patients that fail to receive infusion due to AEs are assumed to receive FLAG-IDA, while the others are assumed to receive other comparators	All patients who fail to receive infusion are assumed to receive FLAG-IDA	Ponatinib	[redacted]	[redacted]	£36,729
			Inotuzumab	[redacted]	[redacted]	£15,965
			FLAG-IDA	[redacted]	[redacted]	£35,409
		All patients who fail to receive infusion are assumed to receive other comparators (not FLAG-IDA)	Ponatinib	[redacted]	[redacted]	£38,537
			Inotuzumab	[redacted]	[redacted]	£19,831
			FLAG-IDA	[redacted]	[redacted]	£36,975
PD utility source	ZUMA-3	Blinatumomab SMC submission	Ponatinib	[redacted]	[redacted]	£37,524
			Inotuzumab	[redacted]	[redacted]	£18,570
			FLAG-IDA	[redacted]	[redacted]	£36,424
			Ponatinib	[redacted]	[redacted]	£37,608

		Tisagenlecleucel SMC submission	Inotuzumab	[redacted]	[redacted]	£17,875
			FLAG-IDA	[redacted]	[redacted]	£36,167
KTE-X19 AE disutility source	Literature	ZUMA-3	Ponatinib	[redacted]	[redacted]	£38,138
			Inotuzumab	[redacted]	[redacted]	£18,173
			FLAG-IDA	[redacted]	[redacted]	£36,582
CRS utility decrement	Assumed 0	CRS utility decrement values based on Howell et al. 2020 (122)	Ponatinib	[redacted]	[redacted]	£37,591
			Inotuzumab	[redacted]	[redacted]	£17,863
			FLAG-IDA	[redacted]	[redacted]	£36,153
Time-point from when patients alive are considered cured (for both intervention and comparator)	3 years	4 years	Ponatinib	[redacted]	[redacted]	£41,699
			Inotuzumab	[redacted]	[redacted]	£20,412
			FLAG-IDA	[redacted]	[redacted]	£39,372
Parametric function adopted to model EFS and OS KTE-X19	Lognormal SPM is used to model EFS and OS	Log logistic SPM is used to model EFS, while the generalised gamma SPM is used to model OS	Ponatinib	[redacted]	[redacted]	£38,305
			Inotuzumab	[redacted]	[redacted]	£17,662
			FLAG-IDA	[redacted]	[redacted]	£35,918
Parametric function adopted to model EFS and OS for ponatinib	Lognormal SPM is used to model EFS and OS	Log logistic SPM are used to model EFS and OS	Ponatinib	[redacted]	[redacted]	£35,201
Parametric function adopted to model EFS and OS for inotuzumab	1-knot spline hazard is used to model EFS, 2-knot spline normal is used to model OS	Generalised gamma SPM is used to model EFS and OS	Inotuzumab	[redacted]	[redacted]	£16,660

Parametric function adopted to model EFS and OS for FLAG-IDA	Generalised gamma SPM is used to model EFS and OS	Log normal SPM is used to model EFS, Weibull is used to model OS	FLAG-IDA	[redacted]	[redacted]	£32,533
SCT as subsequent treatment option for KTE-X19 patients	Not included	Included (based on mITT ZUMA-3 Phase 1 and Phase 2 combined)	Ponatinib	[redacted]	[redacted]	£41,515
			Inotuzumab	[redacted]	[redacted]	£23,486
			FLAG-IDA	[redacted]	[redacted]	£40,402

Key: AE: adverse events; EFS: event-free survival; CRS: cytokine release syndrome; ITT, intention-to-treat; MAIC, matched-adjusted indirect treatment comparison; MCM, mixture-cure model; mITT, modified ITT; PD: progressive disease; SMC: Scottish Medicines Consortium; SPM, standard parametric model.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.5. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

Deadline for comments by **5pm** on **31st of August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating relapsed or refractory B-precursor acute lymphoblastic leukaemia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor David I Marks
2. Name of organisation	NCRI ALL group
3. Job title or position	Professor of Haematology and Stem cell transplantation
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with relapsed or refractory B-precursor acute lymphoblastic leukaemia? ☒ A specialist in the clinical evidence base for relapsed or refractory B-precursor acute lymphoblastic leukaemia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

Clinical expert statement

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for relapsed or refractory B-precursor acute lymphoblastic leukaemia? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Cure
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Molecular or flow remission
10. In your view, is there an unmet need for patients and healthcare professionals in relapsed or refractory B-precursor acute lymphoblastic leukaemia?	Yes
11. How is relapsed or refractory B-precursor acute lymphoblastic leukaemia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Inotuzumab and/or blinatumomab We have no published guidelines. EWALL are working on some, to be submitted to Blood. I am a co-author Reasonably well defined but there are some differences of opinion The technology offers a curative option especially to patients who relapse post SCT

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It will be used similar to the way it was in Zuma 3 Setting: specialist CAR T centres No extra investment except a need for more CAR T beds, and staf
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Tecartus will increase the chance of cure, and will extend duration of life Yes it will improve QoL
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Tecartus is better if blasts are <50%
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	CARs are more complex than current care but not more complex than an allograft. There will need to be therapy for CRS and ICANS

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	NA
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Patient stay is about 10 days post infusion This is better than an allograft and there is no gvhd
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It is innovative in the same way tisagenlecleucel was new May I be blunt? If you relapse post allograft with ALL you die. With tecartus you have a 40-50% chance of being cured. It is a massive step change and meets an unmet need

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Standard CAR toxicity: grade 3 or more CRS and ICANS in about 25%
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	In the main yes The use of allograft post CARs remains controversial
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA450, TA451, TA541 and TA554?	There are QoL studies after Ino (Marks DI et al) and blino (Topp M et al)
23. How do data on real-world experience compare with the trial data?	The US RWE experience is small and as yet unknown
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this	Not aware of any

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Presence of programming and implementation errors in the company's economic model	There wont be much vial sharing of blino or InO as relapsed ALL is a rare clinical scenario
Key issue 2: Uncertainty around the appropriateness of the company's	

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naïve comparison approach	
Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	
Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on autologous auto-CD19-transduced CD3+ cells	18% of patients had an allograft. We don't know why. It wasn't guided by persistence data, or by risk This % is likely to be reproduced in clinical practice. SCT will not be performed if the patient has had a prior transplant Some of the patients on the comparator side will have an allograft
Key issue 5: Concerns with life expectancy of cured patients compared to general population	The patients who have had an allograft will have a reduced life expectancy We do not know the LE of CAR T treated patients and in the absence of evidence it should be assumed to be the same as that of other patients cured of ALL by other means

	For InO patients we have 3 year follow up (Kantarjian, Cancer), for blino only one year follow up (Kantarjian, NEJM)
Key issue 6: Concerns with cured patients having the same utility values as general population. **Is life expectancy of cured patients equal to the general population?**	For patients who have had just CAR T cells I think it is broadly similar Allograft patients (who then go on to CARs), because they will be free of chronic GVHD will have a similar utility to the general population. cGVHD is the main cause of reduced utility (see NICE evaluation of InO)
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ cells and inotuzumab. **Are adverse events associated with the use of blinatumomab and FLAG-IDA captured in hospital care costs? Or are these separate?**	The costs of Flag Ida was a major bone of contention of the InO evaluation with patients needing to stay in for about 30 days (UCL and Bristol data). This makes this a very expensive treatment option especially with high dose antifungal use Inotuzumab causes VOD in 3-23% of patients and about 2/3 of these require defibrotide (which is separately funded)

Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	
Key issue 9: Uncertainty of the costs associated with delivering autologous auto-CD19-transduced CD3+ cells infusion	100K is a serious overestimate CAR T patients stay in for 10 days now (no longer 14), receive early tocilizumab which reduces severe CRS and ITU admissions The real cost is probably half this
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib. **How is FLAG-IDA administered in the clinical setting? Is there a maximum of cycles? Does it has to be administered with ponatinib?**	Nobody (and I really mean nobody who knows anything about ALL) uses FLAG Ida for R/R ALL any more We have 2 NEJM RCTs showing that targeted therapy is better
Are there any important issues that	

have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Tecartus offers a curative option to adult ALL patients who relapse post allograft and for relapsed patients who are unsuitable for transplant. We now have encouraging 24 month OS data
This was approved in the US over a year ago and in that time over 50 patients in the UK should have been offered this therapy. All those patients will now be dead. There have been significant delays
R/R adult ALL is an end of life situation. 80% of InO treated patients die, 93% of FLAG-Ida treated patients die. Median survival is very short
The comparators you have used, in themselves, offer no chance of cure. Tecartus does
The toxicity in the trial was significant but will be less in real life as we gain experience. The occasional patient will die
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

` for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with relapsed or refractory B-precursor acute lymphoblastic leukaemia or caring for a patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report section 1.5.

A patient perspective could help either:

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- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will

have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **31st of August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with this condition or caring for a patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia

Table 1 About you, relapsed or refractory B-precursor acute lymphoblastic leukaemia, current treatments and equality

1. Your name	Sophie Wheldon
2. Are you (please tick all that apply)	☒ A patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with relapsed or refractory B-precursor acute lymphoblastic leukaemia? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Leukaemia Care
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

Patient expert statement

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	☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with relapsed or refractory B-precursor acute lymphoblastic leukaemia? **If you are a carer (for someone with relapsed or refractory B-precursor acute lymphoblastic leukaemia) please share your experience of caring for them**	6. I was diagnosed with B-precursor ALL in June 2018 when I was 20 after experiencing very vague, non-specific symptoms. As a student, I put my persistent chest infection down to being run down due to a high work load at the time. I assumed that my headaches were the same, and thought my sore neck was because I had slept awkwardly. The diagnosis came as a complete shock. Once I was formally diagnosed after presenting in A&E, I was admitted for treatment. I received treatment under various protocols such as UKALL2011, NOPHO-B and NOPHO-C. These treatments were effective, but not effective enough for me, so I was told I would need an allogeneic stem cell transplant. My transplant, which took place in November 2018, was extremely difficult and took a big toll on my mind and body, leaving me with extreme weight loss, fatigue and sickness for many months after. It was an incredibly difficult time in my life and is something that continues to affect me physically and mentally, even now.

	My mom had to have a significant amount of time off of work to care for me once I was diagnosed and she stayed with me every single day and night that I was in hospital. My dad is self-employed, so he had to carry on working to pay the bills whilst my mom stayed with me in hospital. It was really difficult for them both to deal with, both financially and emotionally too. My niece, who was just 7 at the time of my diagnosis, found it really difficult to understand what was happening. It was incredibly difficult for us all as a family to cope with my diagnosis. After 100 days, I had my post-transplant bone marrow biopsy. The results of this biopsy confirmed that I had relapsed. I was told by my consultant during that appointment that there were very few options left for me at that point. Chemotherapy was likely to be futile, and a donor lymphocyte infusion would probably just give me really bad GvHD with little benefit. This was extremely scary and very isolating news to receive - I had essentially been told that I was terminally ill. This was until CAR T-therapy (Kymriah) was mentioned as a potential option. Once I had been told about the treatment, I was immediately told that I would be likely to need to travel for the treatment and stay nearby to the treatment centre for 4 weeks after the infusion, as it was not yet available at my hospital (Queen Elizabeth, Birmingham). I was told that this would need to be self-funded, which would have been a huge financial strain on my family, as I would have had to rely on my parents to fund this for me. My mom had recently returned to work when I relapsed, so she had to have even more time off of work to look after me. Thankfully, my treatment went ahead at the QE, but the initial thought of having to find the money for accommodation and travel was quite scary.

	I went on to receive an infusion of Kymriah CAR T cells on the day after my 21st birthday in June 2019. I am pleased to say that I have now been in remission for 3 years, and remain well post-infusion. As I did not receive the specific product being appraised here, I will be drawing on my experience as a recipient of CAR T therapy in general, as opposed to being specifically treated with this product.
7a. What do you think of the current treatments and care available for relapsed or refractory B-precursor acute lymphoblastic leukaemia on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a.** I feel that there are few treatment options currently available for adults with R/R B-ALL. Even though there are some options available, they aren't very effective and don't appear to improve quality of life very much. As I mentioned above, I was told that I might have been able to have a DLI, but this would have given me very bad GvHD and may not have even had an effect on my leukaemia, leaving me with even fewer options in the attempt to save my life. The use of monoclonal antibodies such as blinatumomab and inotuzumab have both shown some success for R/R ALL, but these treatments were not offered to me when I relapsed, meaning they must have been clinically inappropriate for my condition. This poses the key issue that, even though there are some treatment options available, they aren't always suitable for everyone. Without CAR T, I wouldn't be writing this statement. 7b. I believe that my view is shared by other ALL patients. We all want more treatments to be available for those who need them. I was treated with other young people who are now approaching the current age limit for CAR T. If they were to relapse in the years to come, I would want them to have the same opportunity as me to have CAR T, regardless of their age. Being in remission from leukaemia is scary – it often feels as though someone is waiting to pull the trigger of a gun, silently in the back of your mind. Sometimes,

	that trigger gets pulled, like it did for me. Nothing makes that easier, but knowing that there is hope in the form of innovative treatments like CAR T would help ease a lot of anxiety that patients face.
8. If there are disadvantages for patients of current NHS treatments for relapsed or refractory B-precursor acute lymphoblastic leukaemia (for example, how autologous auto-CD19-transduced CD3+ cells are given or taken, side effects of treatment, and any others) please describe these	8. I believe that the current treatments for R/R B-ALL in adults are quite limited. As I said above, not all of the available treatments are suitable for everyone, so it feels like a bit of a lottery. When I was told that I might be able to have a DLI, I felt sick with fear and anxiety because I knew it would be like my transplant. I did not want to get GvHD, I did not want to feel as awful as I had felt before because I knew how bad it could get and how long it would take to recover. If I would have needed a second transplant, I know that my mental and physical health would have suffered greatly. I don't know if I would have been able to cope with that. Also, I was advised that the DLI wouldn't even be likely to work, so I would have had to weigh up whether it would have been worth putting myself and my body through this trauma all over again. It's a scary concept to consider retrospectively.
9a. If there are advantages of autologous auto-CD19-transduced CD3+ cells over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	**9a.** I felt a huge amount of anxiety going into CAR T because I was extremely worried that it would be like my transplant again, which, as I mentioned, was a tremendously difficult and traumatic time for me. I was very worried, as I didn't have anyone who had received the treatment to talk to about their experience before going through it myself. However, I was pleasantly surprised by the experience and was very relived to realise that it was nothing like my transplant. One of the benefits was the reduced amount of time spent in hospital. As a recipient of Kymriah, I received all of my conditioning chemotherapy as an outpatient due to living relatively close to the treatment centre, which was a lovely bonus. The conditioning protocol for Kymriah was far less intensive than the one I had experienced previously with my transplant, and I was hugely relieved to have not needed any further radiotherapy. The time spent as an inpatient was also substantially shorter with CAR T – 11 days vs 4 weeks for transplant. This was a

	big boost to my mental health after having spent so much time in hospital over the past 12 months. The impact on my quality of life was immense. After feeling so unwell for so long, I felt like I could say that I was feeling “better” for the first time, shortly after my infusion. Again, this had a very positive impact on my mental health and helped me to progress and continue getting better. The physical recovery was much smoother than what I had previously experienced with the transplant. I was seen 3 times per week in clinic for blood tests and for supportive transfusions, but I actually quite enjoyed this as I knew I was being monitored closely – it gave me a lot of peace of mind to know that the team were keeping an eye on me. As I had mentioned previously, I was a student at University before my diagnosis. I had to take some time out from my education, which was really difficult mentally. After my transplant, there was no way that I could have even thought about getting back to university. However, CAR T allowed me to get back to my studies within 3 months. I returned to university in the September to live in halls of residence, and ended up graduating with a First – I couldn’t have returned so quickly if it wasn’t for CAR T. Not only was CAR T effective in the months after my infusion, but years after, too. It has been more than 3 years since I was told that I was in remission, thanks to CAR T therapy. The side effects were much more manageable that those that I had experienced with my previous treatments. I look back every day and remember how I felt on the day I was told that I was in remission. I will be forever thankful to have been able to access the treatment, and cannot imagine what might have happened if I wasn’t able to have it.

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	9b. I would say that the most important advantage of receiving CAR T therapy for me was the rapid return to 'normal life'. For someone who had been feeling so unwell for so long, it was a massive revelation to finally be able to say that I was starting to feel better. The follow up period was intense, but it was made better by having such a supportive healthcare team around me. All I could think about was how much easier this had been in comparison to my transplant. To be able to start getting out and about, and to get back to University within 3 months of having my treatment was just a dream come true. It felt to me like I was getting some control back during a time where everything felt completely chaotic. CAR T was a welcomed calm to such a vicious 12 months for both myself and also my family. Without CAR T, I would not have been able to get back to my studies when I did. I would not have been able to go out with my family without feeling violently ill, as I had done before with my transplant. CAR T gave me my life back.
9c. Does autologous auto-CD19-transduced CD3+ cells help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	9c. Yes. CAR T is derived from your own cells, meaning there was no risk of rejection or GvHD because the cells were my own. This was a big relief, as I was extremely anxious about whether the side effects of CAR T would be like the ones I had with transplant. I felt nowhere near as awful as I had felt with my transplant. With CAR T, I felt like I could function again. I felt like "me" again, after such a long, gruelling year. It was a welcomed surprise.
10. If there are disadvantages of autologous auto-CD19-transduced CD3+ cells over current treatments on the NHS please describe these. For example, are there any risks with autologous auto-CD19-transduced CD3+ cells? If you are concerned about any potential side effects you have heard about, please describe them and explain why	10. In order to receive CAR T, you must be relatively well in order to undergo the apheresis process, and also to wait for the cells to be manufactured, which can take around 4 weeks. This might be difficult for some cases, as some relapses are more rapid than others. The side effects of CAR T can vary in severity too, which can be an issue. I was relatively lucky and experience grade II CRS, which was treated effectively with tocilizumab and 24 hours in intensive care for my low blood pressure. I am aware

	that some patients can face severe CRS or neurotoxicity, which can sometimes be fatal. This is a risk that must be considered carefully by patients before consenting to the treatment. Another disadvantage is potentially needing to travel a long way to a suitable specialist treatment centre. I was extremely lucky to have been able to have my treatment at my consulting hospital, but I am aware that others may live much further away, meaning they will need to pay out for any costs associated with travel and accommodation during and after their treatment.
11. Are there any groups of patients who might benefit more from autologous auto-CD19-transduced CD3+ cells or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	11. I think that a major benefit of CAR T therapy is the fact that it is autologous. This means that there is no need to find a donor, which can be notoriously difficult for patients who are from an ethnic minority or those with mixed heritage. Removing this barrier would give many more patients a chance to survive their disease, regardless of their background. This also feeds into question 12.
12. Are there any potential equality issues that should be taken into account when considering relapsed or refractory B-precursor acute lymphoblastic leukaemia and autologous auto-CD19-transduced CD3+ cells ? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	12. When I was told I needed CAR T therapy, I was with my sister. My consultant looked to her and asked her age. She responded with 28. My consultant then said to her “if this was you, you wouldn’t be able to have this treatment, as you are too old to fit the criteria”. This was a scary concept to hear, to think that there were only a few years in age that could have made the difference between life and death for me. It didn’t seem fair. As mentioned in question 11, CAR T cells are self-derived, meaning there is no need to find a donor or a match. This is an issue that is faced by many patients

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	who are from ethnic minority backgrounds, or those who have mixed heritage, due to the lack of diverse donors on stem cell registries.
13. Are there any other issues that you would like the committee to consider?	13. No.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Key issue 1: Presence of programming and implementation errors in the company's economic model	
Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach	

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Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	
Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on autologous auto-CD19-transduced CD3+ cells	
Key issue 5: Concerns with life expectancy of cured patients compared to general population	Speaking as an individual who has received a variation of CAR T therapy, my life expectancy without CAR T would have been months, maybe even weeks. This treatment has allowed me to get my life back. Now that I am 3 years into my remission, I have been advised that I should have a near-normal life expectancy, comparable to other healthy people in the general population.
Key issue 6: Concerns with cured patients having the same utility values as general population	My quality of life was improved massively once I had received CAR T therapy. I was able to return to education with 3 months of my treatment – this simply would not have been possible if it wasn't for CAR T. I am now able to live a near-normal life, working a full-time job, just like anyone else who hasn't been through what I have been through.
Key issue 7: Concerns around	

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quantifying AE-related costs for autologous auto-CD19-transduced CD3+ cells and inotuzumab	
Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	
Key issue 9: Uncertainty of the costs associated with delivering autologous auto-CD19-transduced CD3+ cells infusion	
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	
Are there any important issues that have been missed in ERG report?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Being diagnosed with ALL had a significant impact on my quality of life, and that of my family too
- More innovative treatments are needed for ALL, as relapse is common and many of the existing treatments aren't always suitable for every patient, meaning there is an unmet need for treatments like CAR T
- CAR T therapy improved my quality of life substantially. It had an overall positive impact on my physical and mental health and wellbeing in comparison to my other treatments, such as my stem cell transplant
- CAR T is a self-derived cellular therapy, meaning there is no risk that the cells will be rejected, or that patients will develop GvHD, which can be extremely debilitating
- There is currently an age inequality in accessing CAR T therapy – this should not stand in the way of a potentially curative treatment that could benefit many patients in the future who are otherwise left with very few options

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **31st of August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults
ID1494

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Leukaemia Care
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Presence of programming and implementation errors in the company's economic model	No	No comment
Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach	No	No comment
Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	No	No comment
Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on autologous auto-CD19-transduced CD3+.	No	No comment

Key issue 5: Concerns with life expectancy of cured patients compared to general population	No	We disagree with the assumption that patients will have a significantly lower life expectancy when cured. The risk of relapse reduces over time and a near normal life expectancy is common.
Key issue 6: Concerns with cured patients having the same utility values as general population	No	Cured patients have a very good quality of life, as CAR-T has fewer known long term side effects than other treatments like transplant (e.g. no GVHD) or chemotherapy (e.g. no long term nerve damage). We believe quality of life to be close to that of the general population if cured.
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ and inotuzumab	No	No comment
Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	No	No comment
Key issue 9: Uncertainty of the costs associated with delivering autologous auto-CD19-transduced CD3+ infusion	Yes/No	We disagree with the tariff being used in this appraisal. In the ACD for the appraisal of axicabtagene ciloleucel for follicular lymphoma (ID1685), it was noted that a tariff was applied to the decision making model and came with significant uncertainty; *"The committee noted that it was not provided with the full details about how the NHS tariff cost was derived.* We assume this to be the same tariff applied here to the model. Therefore we urge the committee to ask NHS England to provide the information as to how this figure was derived, so it can be fully compared to that of the company and the level of uncertainty associated with the figure should be clarified before it can be used in an appraisal. To use the tariff figure without clarifying the calculations involved would be unreasonable.

Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	No	No comment

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Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults ID1494

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

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Technical engagement response form

Autologous auto-CD19-transduced CD3+ cells for treating relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults
ID1494

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Presence of programming and implementation errors in the company's economic model	No	Agree with ERG to assume no vial sharing. Also relates to additional issue 1 below.
Key issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach	No	These indirect comparisons whether naïve or MAIC are both imperfect. They have their inherent biases. In the absence of randomised comparison data, it is not possible to have much confidence when comparing across studies.
Key issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	No	No additional comment
Key issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on autologous auto-CD19-transduced CD3+.	No	The ERG state in section 4.2.3 "despite the fact that 18% of patients received allo-SCT in the ZUMA-3 mITT Phases 1 and 2 combined dataset, no KTE-X19 patients are assumed to receive allo-SCT in the model. The two reasons provided by the company were: (i) the positioning of KTE-X19 does not allow patients to receive a

		second SCT or even receive a first SCT as a consolidation therapy following a CAR T-cell therapy, and (ii) no difference was shown in survival outcomes when patients who had SCT in ZUMA-3 were censored (Figure 5). The ERG believes that given that the modelled outcomes are based on those observed in ZUMA-3, the costs and health outcomes of allo-SCT should also be included." According to the company's clinical experts, "no patients would receive a second allo-SCT and allo-SCT is not expected to be given as consolidation following a CAR T-cell therapy" (4.3.3.4). We as clinical experts agree with this assertion and it is anticipated that KTE-X19 will be delivered as definitive therapy to eligible patients with no routine plan for consolidation with allogeneic stem cell transplant.
Key issue 5: Concerns with life expectancy of cured patients compared to general population	No	In 4.4.2.4 "an SMR of 4 applied to an age- and sex-matched general population mortality risk for cured patients (instead of 1.09) increased the ICER by over £7000". Evidence is weak for both the company and the ERG's estimated SMR. Not aware of any data to support assumption of SMR of 4.0 for patients surviving post CAR T therapy for ALL.
Key issue 6: Concerns with cured patients having the same utility values as general population	No	Whilst utility values may be lower for patients with relapsed/ refractory ALL, much of it may be related to previous treatments and evidence post CAR T is lacking.
Key issue 7: Concerns around quantifying AE-related costs for autologous auto-CD19-transduced CD3+ and inotuzumab	No	No additional comment

Key issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	Yes/No	No additional comment
Key issue 9: Uncertainty of the costs associated with delivering autologous auto-CD19-transduced CD3+ infusion	No	NHSE has a specified tariff for delivery of CAR T therapy. This tariff is of course subject to review and may be revised in future.
Key issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	No	Agree we as clinical experts agree with the ERG assumption that FLAG-Ida is usually delivered for 2 cycles maximum.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Comparators	Please indicate the section(s) of the ERG report that discuss this issue: 2.3.3 and 4.4.2, 3.1.2	No	The ERG states the comparators are dependent on the patient's Ph status. Inotuzumab, FLAG-IDA, and blinatumomab were the considered comparators for the Ph-subgroup, whereas inotuzumab, FLAG-IDA, and ponatinib were considered for the Ph+ subgroup (4.2.2). In clinical practice FLAG-IDA is only one chemotherapy backbone option chosen for individuals with R/R ALL and is used very infrequently due to toxicity and lack of efficacy in this palliative scenario. Inotuzomab or Blinatumomab are preferentially chosen if patient is eligible. In Ph- R/R ALL low dose palliative chemotherapy is often administered (e.g. vincristine and dexamethasone). Ponatinib is often given in combination with this low dose chemotherapy for Ph+ patients. Ph+ patients will sometimes be given chemotherapy alone (vinc+dex or FLAG-IDA more rarely) when they are intolerant to the 2 licensed TKIs in England (imatinib and ponatinib). No other TKI should be used as a comparator in England where their use in unfunded. In 2.3.3 it says "clinical advice to the ERG stated that some of the comparators are not similar in their indication. For instance, blinatumomab is reserved for chemo-responsive cases where it can be a bridging therapy to allo-SCT as it has high response rates for those cases with low disease burden."

			We disagree with this assertion, as blinatumomab is also given in patients who are chemo refractory and not always used as a bridge to allograft, although we agree this is where it is most effectively used. It is also used post allograft and in patients ineligible for allograft. Inotuzumab similarly is used in patients R/R pre or post allograft. Patients may receive both Blinatumomab and Inotuzumab sequentially in either order based on funding and clinical decision. The ERG also notes “that imatinib can be used as a subsequent treatment for patients who cannot tolerate dasatinib, and that ponatinib is only used if imatinib is not clinically appropriate”. In R/R Ph+ ALL by definition adult patients are not suitable for imatinib as it is always used first line outside of clinical trials, and it therefore it would not be used in this R/R scenario. Dasatinib is unfunded in England and would not be used. Therefore, the rationale stated by the company “that these therapies either would not be used in a R/R population as it was used as a first-line treatment in Ph+ (imatinib) or are not currently reimbursed in the UK (dasatinib)” is correct. And when a PH+ patient is R/R to both TKIs (imatinib and ponatinib) comparators are Inotuzumab or chemotherapy without TKI.

Additional issue 2: Conclusions of the clinical effectiveness section	Please indicate the section(s) of the ERG report that discuss this issue: Section 1.4, 3.5	No	The ERG states the "study included no UK patients and it is debatable whether the study population reflects the population of patients who would be likely to be eligible for KTE-X19 in clinical practice in England". We disagree with the ERG statement here. Even though the study did not include UK patients, or ECOG2, patients matching the inclusion criteria are seen regularly in most large ALL centres in the UK. In fact, the inclusion criteria are very similar to the Auto1 clinical trial which is recruiting successfully in the UK.
Additional issue 3: Comparison of AEs between CAR T products	Please indicate the section(s) of the ERG report that discuss this issue: 3.2.4.4	No	The ERG states "Clinical advice received by the ERG suggested that the frequency of the most common CRS and neurological AEs was higher than might be expected for other CAR-T and comparator therapies". This is not evidence based and no randomised control data exists.

Additional issue 4: Threshold for MRD	Please indicate the section(s) of the ERG report that discuss this issue: 3.2.2.5	No	The ERG states “threshold for MRD negative remission was defined as MRD < 10-4 threshold, clinical advice received by the ERG indicated that the threshold used for the outcome MRD, while standard in trials in this population, is higher than the threshold used in clinical practice where further treatment would be initiated before the study threshold is reached. As a result, the efficacy of KTE-X19 in obtaining MRD- in accordance with clinical practice may be overestimated” We do not agree with this statement as MRD 10-4 is the standard limit of detection of assays available in the UK and is the threshold for decision making in the adult ALL practice (due to drug licensing) is often even >10-3.
Additional issue 5: AE assumptions	Please indicate the section(s) of the ERG report that discuss this issue: 4.3.3.9	No	In section 4.3.3.9, “the ERG is therefore concerned that the provision of KTE-X19 specialist centres may require that ICU beds are left vacant during the period that a patient is considered at risk of CRS to ensure availability. This may lead to additional costs which have not been included in the company’s base-case model.” We think this is unlikely to occur in clinical practice in the UK CAR-T centres where managing CRS is standard.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal: ERG comments on company's technical engagement response

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Andrew Metry, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Christopher Carroll, Reader in Systematic Review and Evidence Synthesis, ScHARR, University of Sheffield, Sheffield, UK Shijie Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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Date completed	21st September 2022

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

1 Introduction

In September 2022, the company submitted its technical engagement (TE) response for the appraisal of autologous anti-CD19-transduced CD3+ cells for treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults (henceforth the technology and indication are referred to as KTE-X19 and R/R ALL respectively for brevity).[1] The company's response was structured around the ten key issues raised within the Evidence Review Group (ERG) report,[2] and included an additional 9 months of efficacy data for KTE-X19 taken from ZUMA-3, the key clinical study. In line with the CHMP positive opinion for KTE-X19,[3] the patient population has also been restricted to 26 years of age and over. The company's TE response includes a written technical engagement response document, including appendices, together with updated version of the executable model.

This document provides a commentary on the company's TE response and should be read in conjunction with the ERG report and the original company submission (CS).[4] Section 2 provides a summary of the company's changes in the updated model and provides information relating to the new analyses of time-to-event data from ZUMA-3 based on a data cut-off the 23rd of July 2021. Section 3 provides a detailed description of the company's TE response and the ERG's critique of these points. Section 4 presents the results of the company's updated base case and scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 5.

All results presented in this document include the Patient Access Scheme (PAS) discount for KTE-X19 ([redacted]). The results of the company's analyses when applying the confidential PASs for blinatumomab, inotuzumab ozogamicin (henceforth referred to as inotuzumab for brevity), ponatinib, and tocilizumab (which is used to treat cytokine release syndrome (CRS) a potential adverse event (AE)) are presented in a separate confidential appendix.

In order to aid reading this report, the key limitations in the company's updated base case are summarised in advance of the more detailed critique, along with the approaches undertaken by the ERG to provide incremental cost-effectiveness ratios (ICERs), expressed in terms of cost per quality-adjusted life year (QALY) gained, that attempt to address these limitations.

1.1 Key limitations within the company's updated base case

The ERG believes that the company's base case following TE has the following limitations

- That naïve analyses are assumed for the comparison with FLAG-IDA, inotuzumab, and ponatinib. The ERG believes that the populations in the pivotal studies are different and that the matching-adjusted indirect comparison (MAICs) are a better approach in these circumstances.

- That patients are considered functionally cured at 3 years, with only a small increase in the risk of mortality (a standardised mortality rate (SMR) of 1.09) and no utility loss compared with the current population. The ERG believes the SMR should be higher and that the patients would not have the same utility as the general population.
- The fact that the costs and QALY losses associated with allogeneic stem cell transplant (allo-SCT) for patients in ZUMA-3 have been excluded from the model. The ERG believes these costs should be included as they may have provided benefit to the patients.
- The costs of providing a KTE-X19 infusion and in managing any AEs associated with the treatment assumed by the company are believed to be underestimated. The clinical advice provided to the ERG suggests that these should be higher.

The ERG has attempted to address these limitations where possible in providing its own estimate of the ICER.

2 Summary of the company's response to technical engagement

The CS was submitted in November 2021; subsequently, further data relating to the pivotal study, ZUMA-3, have become available. The company's TE response presents additional clinical effectiveness evidence from an updated database lock (DBL) (data cut-off 23rd July 2021), compared with a DBL of 9th September 2020, thus providing approximately an additional 9 months of follow-up and extending the median follow-up period from 12 months to 21 months among the Phase 2 modified intention to treat (mITT) population. The company reiterates that it believes that the end-of-life criteria are met in this decision problem.

For the Philadelphia chromosome-negative patients (Ph- subgroup), in the CS the company's base case deterministic ICER, expressed in terms of cost per quality-adjusted life year (QALY) gained, was £36,380 when compared to fludarabine, cytarabine (Ara-C) granulocyte-colony stimulating factor idarubicin (FLAG-IDA) with both blinatumomab and inotuzumab extendedly dominated in a full incremental analysis. The company's post-TE base case is £39,806 with probabilistic results similar to deterministic estimates in this analysis. The company presented scenario analyses although not all are presented in this document for brevity. The ICER for the Philadelphia chromosome-positive patients (Ph+ subgroup) subgroup was estimated to be £33,972 compared with FLAG-IDA in the CS with both ponatinib and inotuzumab extendedly dominated in a full incremental analysis. In the company's post-TE submission, ponatinib was no longer extendedly dominated but had an ICER of £29,689 compared with FLAG-IDA, with the ICER for KTE-X19 compared with ponatinib being estimated to be £37,608.

Table 1 summarises the company's original base case model, the ERG's preferred analysis at the time of the ERG report and the company's updated base case model as presented in the TE response. A more detailed discussion of each issue including an ERG critique and, where appropriate, changes to the ERG base case is provided in Section 3. A summary of the more mature data from ZUMA-3 is provided in Section 2.1.

Table 1: Summary of company's original base case (CS), ERG preferred analysis (ERG report) and company's updated base-case (TE response)

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
Amendments relating to key issues presented in ERG Report				
Issue 1: Presence of programming and implementation errors in the company's economic model	Contained apparent errors identified in the way the model was programmed and populated.	The ERG corrected the perceived errors.	The company accepted the ERG's corrections	Yes
Issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach with inotuzumab and FLAG-IDA	The company's model uses relative treatment effect estimates from the naïve indirect comparisons. This approach was preferred to the estimates obtained from the MAICs for the comparison of KTE-X19 against inotuzumab and FLAG-IDA.	The MAIC approach was preferred to explicitly attempt to adjust for the differences between study populations in the comparisons with inotuzumab and FLAG-IDA. However, there was a limitation in that the efficacy estimates were only estimated for the overall population and not by Ph subgroup.	The company still prefers using the naïve indirect comparisons. New parametric distributions were fitted to the updated event-free survival (EFS) and overall survival (OS) data.	No
Issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data	The company fitted a log-normal model to ponatinib OS data and did not perform a separate model selection exercise for the ZUMA-3 MAIC-adjusted populations.	The Gompertz model was the preferred fit for ponatinib OS data. In absence of other evidence, the ERG used the same models as selected for the naïve comparisons.	The company accepted the Gompertz model for ponatinib. Separate survival analyses were conducted for the MAICs with the same distributions chosen as for the naïve analyses with no formal justification.	Partially
Issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19	The company excluded costs and QALY losses related to the transplant based on clinical expectations and a post hoc analysis of OS conditional on whether allo-SCT was received.	The ERG included the costs and QALY loss associated with allo-SCT for patients who received KTE-X19 as there is potential that patients benefitted from allo-SCT.	The company still excludes these costs and QALY losses.	No

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
Issue 5: Concerns with life expectancy of cured patients compared to general population	The company's base case applies an SMR of 1.09 to model the mortality risk of patients considered cured (that is, those patients alive after 3 years) compared to that of the age- and sex-matched UK general population.	The ERG reviewed SMR values used in previous NICE appraisals in R/R ALL and used a 'conservative' value of 4 for patients alive at 3 years.	The company still applies an SMR of 1.09.	No
Issue 6: Concerns with cured patients having the same utility values as general population	The company's base case assumes that the utility values for cured patients is the same as an age- and sex-matched population.	Using a utility multiplier of 0.92 applied to the age- and sex-matched general population utility.	The company still assumes the same utility values for cured patients as an age- and sex-matched population.	No
Issue 7: Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab	The company's estimate of costs for management of AEs associated with KTE-X19 does not align with clinical expectations. For inotuzumab, the estimated costs and QALY loss associated with veno-occlusive disease (VOD) includes a degree of double counting.	The ERG assumes AE-related costs for KTE-X19 to be the same as that for inotuzumab. Half the costs and associated disutility were removed for VOD.	The company accepts removing half the costs and QALY loss associated with VOD. However, the company adopted a new approach where only AEs that incur an Intensive Care Unit (ICU) stay were included.	Yes
Issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA	The company estimates separate AE costs for patients on either blinatumomab or FLAG-IDA.	Both comparators are administered within hospital care with costs captured as administration costs. The ERG believes that AEs would be treated within the hospital stay and should not be costed again.	A new approach was adopted where only AEs that incur an ICU stay were included.	Yes
Issue 9: Uncertainty of the costs associated with delivering KTE-X19 infusion	In its model the company assume a cost of [redacted] for a CAR-T infusion based on an estimated [redacted] days of hospitalisation.	The ERG was made aware of a tariff available for the delivery of a CAR-T therapy. Based on expert advice, this was assumed to cost [redacted]. The ERG used this	The company's updated base maintained the cost of [redacted] for a CAR-T infusion.	No

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
		figure to account for other costs such as AEs, leukapheresis, and bridging chemotherapy.		
Issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib	The company's model allows FLAG-IDA to be administered for a maximum of 4 cycles. The company also assumed FLAG-IDA is administered with ponatinib	The ERG applied a cap of two cycles for FLAG-IDA and removes the costs of FLAG-IDA for patients receiving ponatinib.	The company accepts the ERG's cap for FLAG-IDA but assumes 15% of patients on ponatinib will receive adjunctive FLAG-IDA.	Yes

2.1 Additional data from ZUMA-3

The company's TE response reports new EFS and OS data from ZUMA-3, an ongoing Phase III, international, multi-centre, single-arm study. The updated data had an additional 9 months' follow-up, and the population was restricted to those aged 26 years and over. The updated patient characteristics used in the economic model from ZUMA-3 mITT Phase 1+2 are summarised in Table 2. The ERG notes that the response rate was not updated in the new data submitted.

Table 2: Updated patient characteristics

Model parameter	Value in the original submission	Value in the TE submission
Mean age	43.2	48.2
Percentage male	53.8%	47.6%
Mean weight	81.00 kg	81.08 kg
Mean BSA	1.92 m^2	1.93 m^2
Percentage receiving the KTE-X19 infusion	78.8% of the ITT population	77.8% of the ITT population
Response rate	[redacted]	Not updated

Figure 1 and Figure 2 show the OS and EFS Kaplan-Meier (KM) data respectively for the updated population post-TE compared to the data provided and used in the economic model in the original submission. The company provided two KM for EFS for KTE-X19 with Figure 2 having a smaller time horizon and not showing that [redacted] as shown in Figure 3. As such, it is unclear if the company have used the full EFS data in distribution fitting. If the full data were not used, then the EFS distributions are likely to be inaccurate.

For both OS and EFS, the company maintained the functional distributions used in the CS which was a log-normal distribution for both OS and EFS; both distributions had different parameter values than in the CS to reflect fitting a different data set. These distributions were only used for a time horizon of 3 years, after which the general population rate of mortality was used in conjunction with an SMR of 1.09. For EFS, the log-normal distribution was applied only to responders, with non-responders having an event in the first week. After 3 years, it was assumed that there were no relapses.

Figure 1: Kaplan-Meier plot of OS (Phase 1 + 2 combined, data cut-off 23/07/21) compared to data cut-off September 2020

Figure 2: Kaplan-Meier plot of EFS (Phase 1 + 2 combined, data cut-off 23/07/21) compared to data cut-off September 2020

Figure 3: The extended Kaplan-Meier plot of EFS (Phase 1 + 2 combined, data cut-off 23/07/21)

The company also provided data on the goodness of fit of parametric and spline models for the Ph- subgroup. For both OS and EFS, a lognormal distribution was chosen as it had the lowest BIC value, although alternative distributions had relatively close BIC values.

In addition, the company provided new MAICs where the KTE-X19 data were adjusted to approximate the population characteristics for inotuzumab, FLAG-IDA and blinatumomab, however, these data were not used in the company's base case.

2.2 Updated analysis of SCHOLAR-3

In the CS, a post hoc analysis from a retrospective study, SCHOLAR-3,[4] was used for the comparison with blinatumomab. The company had access to patient-level data for this study and created a "synthetic control arm" (SCA-3) by matching patients from historical trials who had not previously received blinatumomab therapy with [redacted] ZUMA-3 patients (full details are stated in CS Section B.2.9).

Since the data for ZUMA-3 has longer follow-up, the company reran the analysis and provided new KM data for SCHOLAR-3 SCA-3 and updated survival analyses. Figure 5 (OS) and Figure 6 (EFS) show the KM data and the distributions preferred by the company in the TE response versus that used in the original CS. The company maintained the lognormal distribution to fit the OS. For EFS, a 1-knot hazard spline fit was used for those patients that had not relapsed before receiving blinatumumab.

Figure 4: SCHOLAR-3 KM OS data and the company's preferred fits used in the original CS versus the TE response

Figure 5: SCHOLAR-3 KM EFS data and the company's preferred fits used in the original CS versus the TE response

3 ERG critique of the company's TE response

This ERG addendum is structured around the ten key issues contained in the initial ERG report which are detailed in Sections 3.1 to 3.10, and adds a further issue raised by the company in its TE response related to end-of-life criteria, contained in Section 3.11. Sections 3.1 to 3.10 summarise the issues as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new ICERs generated when using the company's preferred assumptions. Each section also includes the ERG's opinion on the new data and assumptions. The impact of these assumptions on the ICER is presented in Section 4 alongside the company's preferred ICER and the ERG's exploratory analyses. All results presented in this report include the company's agreed PAS ([redacted] simple price discount) but use the list price for comparators. The results of the company's analyses based on the confidential PAS for blinatumomab, inotuzumab, ponatinib, and tocilizumab are presented in a separate appendix.

3.1 Key Issue 1: Presence of programming and implementation errors in the company's economic model

In the CS, the ERG identified some programming and implementation errors where: (a) vials of injectable treatments were assumed to be shared; (b) dose calculations based on body surface area were only assumed for the vial sharing scenario; (c) an error was identified in calculating the cyclophosphamide acquisition cost; (d) errors were identified with fludarabine dose and cost calculations; (e) double counting issues for pump and intravenous (IV) administration costs associated with blinatumomab; and (f) inotuzumab spline selections were not linked correctly in the model. The ERG amended the model as described in the ERG report Section 4.4.2.1,[2] and the company accepts these amendments. The ERG considers this issue to be resolved.

3.2 Key Issue 2: Uncertainty around the appropriateness of the company's naïve comparison approach

The company preferred using relative treatment effect estimates from the naïve indirect comparisons with inotuzumab and FLAG-IDA. The ERG preferred estimates obtained from the MAICs of KTE-X19 due to clinical advice confirming that there were differences in prognostic factors between populations. A MAIC balances the observed baseline characteristics between the arms and generates an alternative data set, where survival analyses can be performed. The ERG notes that the company used data from comparator studies, which the company believes is not reflective of patients in England who will receive KTE-X19. The comparison with blinatumomab did not have this issue as the synthetic data set was matched against ZUMA-3.

The ERG highlights an additional limitation in the naïve analyses that has arisen in the TE process due to the CHMP positive opinion restricting the use of KTE-X19 to patients aged 26 years or older whilst the data for comparator studies include a younger population (18 years old and above).

The company put forward another reason for its preference in that the similarity of the hazard ratio (HR) calculated from the SCHOLAR-3 analysis for blinatumomab was similar to that calculated from the naïve comparison of data from ZUMA-3 versus TOWER (a blinatumomab study). The ERG notes that it is not appropriate to validate the naïve analysis using the results from the SCHOLAR-3 study as the two analyses estimate the treatment effect in different populations and used different data for the comparator arm. The robustness of the analysis should be evaluated based on whether there is a difference in the baseline characteristics between the two arms which could lead to biased results and whether the analysis has addressed the issues and would reduce bias. The company also provided two published MAICs and simulated treatment comparison (STC) estimating the relative treatment effect of blinatumomab versus inotuzumab from TOWER and INO-VATE (an inotuzumab study), where the differences between the naïve and adjusted comparisons remained small. The ERG highlights that they did not raise any concerns regarding the comparability of patient populations between TOWER and INO-VATE and would thus expect similar results between naïve and MAIC analyses. The ERG's primary concern remains that there is a likely mismatch between the ZUMA-3 population and those of the comparator trials which would be explicitly accounted for in a MAIC.

The company maintained its view that ZUMA-3 population is the most generalisable to the one likely to receive KTE-X19 in the UK clinical practice. The ERG further notes that if the company believes that the ZUMA-3 population is more appropriate than those of the comparators to the decision problem then this indicates a difference in the populations and implies that naïve analyses are not appropriate, and the populations should be adjusted.

The ERG stated that it would have liked the company to explore the effect on the ICER of adjusting the populations of the other comparators to that of ZUMA-3 by using the inverse hazard ratios derived from the MAICs. However, these exploratory analyses have not been performed by the company despite these being requested in priority clarification question B12 and comments in the overall conclusion section of the ERG report, which highlighted that the requested analyses had not been undertaken.

The ERG critiqued the company's approach of using only ZUMA-3 Phase 2 data in the matching for SCHOLAR-3 blinatumomab data. The ERG's view is that data from Phase 1 should also be included. The company '*disagrees that the use of Phase 2 data only in the SCHOLAR-3 study compromises the results*' given that the baseline characteristics of the two cohorts (Phase 2 cohort and the pooled Phase 1+2 cohort) are '*in close alignment*' and provided a table comparing between five '*key*' prognostic

factors (data marked academic-in-confidence) although the ERG notes the potential meaningful difference in patients with prior allo-SCT between the two groups. It is unclear if unreported baseline characteristics are similar, with text in the ERG report states that *"compared with Phase 1 participants, Phase 2 participants were substantially more likely to be male (60% vs [redacted]), and had more risk factors for poor prognosis than Phase 1 participants: in Phase 2 there were more Ph+ patients (27% vs [redacted]), more patients with a complex karyotype (≥ 5 chromosomal abnormalities) (25% vs [redacted]), more patients had already received prior allo-SCT (42% vs [redacted]), and more were R/R following allo-SCT (44% vs [redacted])"* to which the company did not respond. Given the company has the data for the pooled cohort, the ERG believes that as a minimum, analyses using data from the Phase 1 and 2 patients should be provided to the Appraisal Committee.

In conclusion, the ERG remains concerned that the naïve comparisons do not reflect the true relative treatment effect of KTE-X19 and prefers the MAIC results. As demonstrated by the company if populations are similar than the MAIC would be expected to have little impact. The ZUMA-3 population may be the most generalisable to the patient population likely to receive KTE-X19 in clinical practice, however the requested analyses estimating ICERs using the HRs derived from the MAIC to estimate the efficacy in a ZUMA-3 population was not performed by the company. Finally, the ERG stands its view that SCHOLAR-3 data should be matched to datasets using both Phase 1 and 2 of ZUMA-3, not just Phase 2.

3.3 Key Issue 3: Uncertainty about model choice for fitting and extrapolating ponatinib OS data and MAIC-adjusted ZUMA-3 survival data

In its report, the ERG preferred using the Gompertz model to the log-normal distribution to represent ponatinib OS data. In its TE response the company changed to a Gompertz distribution, and the ERG considers this matter resolved.

It its initial TE response, the company assumed that the previously used distributions to model OS and EFS in KTE-X19 were unaffected by the updated data set. Following a request from the ERG, the company provided further analysis and data and fitted parametric models and spline models to the KTE-X19 OS data with the parametric distributions shown in Figure 6. The company selected the log-normal in its base case, assuming that all patients were functionally cured at 3 years.

The ERG noted that the goodness-of-fit statistics were close for many parametric distributions with a difference of less than [redacted] in the Bayesian Information Criterion between the best fitting model (the exponential) and the Weibull, log-normal, log-logistic, the Gompertz and the Gamma distributions.

Figure 6: Parametric distribution fits to the OS KM data for KTE-X19

The parametric fits to the EFS data are shown in Figure 7. The company assumed a log-normal distribution. The ERG was comfortable with the choice of the log-normal distribution as it had the lowest BIC value although noted that the BIC values for the exponential, Weibull, log-logistic and the Gamma were within [redacted] of the log-normal. The spline models did not fit as well as the parametric models.

Figure 7: Parametric distribution fits to the EFS KM data for KTE-X19

The plots for the Ph- subgroup were not provided by the company although the ERG conclusion is that these would likely be similar to those for the full population, with the log-normal distribution selected by the company being a plausible choice, although other distributions are plausible.

Regarding the company's updated comparison of KTE-X19 with blinatumomab from SCHOLAR-3, the ERG is comfortable with the log-normal distributions used in the company's base case for OS, and the 1 knot hazard distribution for EFS although the company did not provide the plots of distributions against the updated KM. The ERG comments that as these data are matched to a ZUMA-3 population there would be no requirement to adjust these data further.

As detailed in Section 3.2, the ERG preferred the use of the MAIC analyses for comparing KTE-X19 with inotuzumab and FLAG-IDA, and the use of the synthetic data set from SCHOLAR-3 data for the comparison of KTE-X19 with blinatumomab. Due to the lack of data for comparisons, the ERG had to use the naïve comparison with ponatinib although it comments that this is not ideal due to potential biases.

Following a request from the ERG, the company provided data on the goodness of fit of parametric distributions when the KTE-X19 data were matched to the inotuzumab population, and when matched to the FLAG-IDA population. The plots of spline models and parametric distributions for the OS KM derived from the MAIC for an inotuzumab population are shown in Figure 8 and Figure 9. Corresponding figures for the KM derived from a FLAG-IDA population are shown in Figure 10 and Figure 11. The spline models were marginally better than the parametric distributions for the inotuzumab population and the FLAG-IDA population although the differences in BIC are small, typically below [redacted]. The 1 knot hazard had the lowest BIC value in the inotuzumab population whilst the 1 knot normal had the lowest BIC in the FLAG-IDA population, although in both instances all spline models were comparable fits. The same distribution for OS was used for EFS in both the inotuzumab population and the FLAG-IDA population.

As detailed in Section 3.2, the ERG prefers the MAICs in estimating the ICER for KTE-X19, however would prefer to see the cost-effectiveness of KTE-X19 in the ZUMA-3 population. The company, however, have not undertaken these analyses and so the ERG has had to use the comparator populations. The spline models did not fit as well as the parametric models. Whilst the ERG believes that for many parameters the log-normal is a reasonable fit, it notes that in its preferred analysis a Weibull distribution may be better as it would allow an HR calculated from the MAIC to be applied to the KTE-X19 distribution from ZUMA-3.

Figure 8: Spline model fits to the OS KM data for KTE-X19 matched to the inotuzumab population

Figure 9: Parametric fits to the OS KM data for KTE-X19 matched to the inotuzumab population

Figure 10: Spline model fits to the OS KM data for KTE-X19 matched to the FLAG-IDA population

Figure 11: Parametric fits to the OS KM data for KTE-X19 matched to the FLAG-IDA population

Table 3: Goodness of fit statistics for parametric distributions and spline model for OS derived from the MAICs

	FLAG-IDA		Inotuzumab	
Model	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
1 knot odds	[redacted]	[redacted]	[redacted]	[redacted]
1 knot hazard	[redacted]	[redacted]	[redacted]	[redacted]
1 knot normal	[redacted]	[redacted]	[redacted]	[redacted]
2 knot odds	[redacted]	[redacted]	-	-
2 knot hazard	[redacted]	[redacted]	-	-
2 knot normal	[redacted]	[redacted]	-	-

AIC: Akaike information criteria; BIC – Bayesian information criteria

* Taken from the model due to typographical errors in the company's submission

There is uncertainty in the positioning of the knot, the lack of an updated hazard plot, and whether the generated distribution has biological plausibility. The ERG comments that the log-normal distribution had clinical plausibility in that the risk of death was decreasing over time and had previously been used by the company. Therefore, the ERG has provided results based on the MAIC using both a spline fit (1 knot normal for FLAG-IDA and 1 knot hazard for inotuzumab which had the lowest BIC values) and a log-normal fit. Although the log-normal was not the parametric distribution with the lowest BIC value, the ERG believes that this gives a noticeably different fit to the spline model, did not have a large difference in BIC, and used this to provide the Appraisal Committee with a larger range in modelled distributions. The results from the spline models are more favourable to KTE-X19 as these result in a higher proportion of patients being alive at 3 years compared to the parametric models.

3.4 Key Issue 4: Exclusion of allo-SCT related costs and QALY loss for patients on KTE-X19

In ZUMA-3, 14 of the 78 patients who received the infusion went on to receive subsequent allo-SCT. However, this was not accounted for either in cost calculation or QALY impacts for the KTE-X19 arm in the company's model.

The company highlights again the sensitivity analyses where OS data were stratified by censoring at allo-SCT and showed no statistical difference although they noted in their response to clarification questions that their sensitivity analysis was not sufficiently powered, and the ERG report states that *"the ERG remains uncertain of the imbalance in baseline characteristics between patients who received allo-SCT versus those who did not."*

Additionally, the company contends that use of allo-SCT in ZUMA-3 was pre-planned and that it would not be used in the UK clinical practice. The ERG highlights that the issue is not the usability of allo-SCT in practice, but whether patients who received allo-SCT in ZUMA-3 had a survival benefit due to this procedure. The company reiterates that [redacted] of the 14 patients receiving allo-SCT had achieved complete remission, however, as stated in the ERG report, this *"does not rule out the possibility of minimal residual disease (MRD) detection which would trigger the initiation of subsequent therapy"*. Clinical advice to the ERG confirmed that they would consider allo-SCT for patients who had relapsed in ZUMA-3 and who were fit enough for this procedure, noting the mean age of patients in ZUMA-3.

The ERG maintains its view that *"the fact that allo-SCT was delivered to some ZUMA-3 patients means that they may have benefitted from it, costs were incurred, and patients' HRQoL was affected"* and that the costs and QALY implications should be considered in the model.

3.5 Key Issue 5: Concerns with life expectancy of cured patients compared to general population

The company applied an SMR of 1.09 to model the mortality risk for patients who are alive after three years compared to that of an age- and sex-matched population. This was sourced from Maurer *et al.*,[7] a study conducted in R/R DLBCL patients and was used by the company in TA567 (tisagenlecleucel in R/R DLBCL).[8] The clinical advisors to the ERG had concerns that this is a different patient population and agreed with the ERG for TA677 (KTE-X19 in mantle cell lymphoma) that this estimate is irrelevant.[9] The ERG looked at previous TAs of the comparators, and decided to use the approach in TA541 where a '*conservative*' SMR value of 4 which was used by the ERG for 5-year surviving patients after receiving SCT in the appraisal of inotuzumab, which was extracted from Martin *et al.*[10] This study evaluated mortality and causes of death in a cohort of 2574 patients who survived without recurrence of the original disease for at least 5 years after SCT. In the discussion of Martin *et al*. it states that mortality rates '*remain four- to nine-fold higher than in the general population for at least 25 years thereafter*' The midpoint SMR estimated in Table 3 of this paper was 4.5.

In their TE response, the company argues that the SMR value from Martin *et al.*,[10] reflects only post-SCT patients whose non-relapse mortality could be higher due to graft versus host disease which may require long-term treatment with immunosuppressants. The ERG notes that this study found the leading causes of death after 5 years to be second malignancies (26%), recurrent disease (19%), infections

(15%) cardiovascular (11%) then graft versus host disease (9%) . The company also mentioned that only "*16% of the patient population in Martin et al., (2010) had ALL, and it is not reported whether any of these patients had R/R disease*". The ERG highlights that sourcing the SMR from a study with 16% with ALL is likely to be more appropriate than a study with 0%, and also that if patients did not have R/R disease then the reported SMR is likely conservative.

The ERG additionally noted that in TA559 (axicabtagene ciloleucel in DLBCL), the ERG report states that "*the assumption of cure at two years is based on one US study i.e. Maurer (n=767) where no statistical difference was reported between the mortality of DLBCL survivors and that of the general population after two years post-diagnosis. However, the ERG identified several other studies that suggest that significant excess mortality remains up until at least five years post-diagnosis."*[11,12] Therefore, the ERG maintains its assumption of an SMR of 4 to be applied to the mortality risk of the general population. It is also noted that [redacted]

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

The company assumed that the utility for patients alive after 3 years was equal to that of an age- and sex-matched population, however, the advice from ERG's clinical experts indicated that having "*received at least two therapies prior to receiving KTE-X19 and subsequent therapies, and that cumulative drug toxicity on its own – let alone the disease itself – would impact the quality of their remaining lives.*" Hence, the ERG assumed a utility multiplier of 0.92 applied to general population utility values to adjust for lower HRQoL for cured patients after 3 years, which was calculated using the ratio between the utility values for post-infusion pre-relapse and that for general population of similar age.

The company stated that "*the ERG inherently assumes that HRQoL of a patient who has been cured of ALL for years is the same as that in a patient who has recently undergone treatment for their R/R ALL and does not yet know their long-term outcome*", and "*this very clearly lacks face validity*". This assumption also exists in the company's approach, albeit to a smaller degree in that a person who has not relapsed after 2.9 years would have the same utility as a person who has not relapsed after 1 week. The ERG believes that patients who have had R/R ALL will not have the same utility as that of the general population, as evidenced in the increased SMR and have thus used a utility multiplier.

The company stated that in five of the other STAs of CAR-T infusions or treatments in R/R ALL, three appraisals applied the general population utility to cured patients; these were TA559, TA554, and TA450. The ERG regards this statement to be inaccurate. In TA554, the company applied the event-

free survival utility value to the long-term survivors rather than using general population values. For TA559 the justification was that the SMR used to model excess mortality was equal to 1, the ERG commented that "*if the survival of 'cured' patients remains affected by excess mortality this is also likely to be reflected in lower HRQoL than that of the general population for the period where excess mortality applies*." The ERG applied general population utility only after progression-free survival and OS curves converged. Finally, the ERG for TA450 was not sure of the uncertainty concerning applying the GP utility and performed a scenario analysis where "*people alive after four years are assumed to have the same utility as the general population and are only at risk of all-cause mortality. All-cause mortality rates were based on UK general population mortality rates*."

The ERG did not identify any precedents where a general population utility was applied to a population whose SMR higher than 1. The ERG therefore maintains its logic that "*the assumption that patients are cured without residual comorbidities would not appear consistent with the assumption that patients have an increased risk of death compared to the age- and sex-matched population*" and maintains its utility multiplier of 0.92.

3.7 Key Issue 7: Concerns around quantifying AE-related costs for KTE-X19 and inotuzumab

In its report, the ERG identified areas where costs and QALY loss due to AEs associated with KTE-X19 were poorly reflected. These included: underestimating ICU stay associated with CRS from ZUMA-3 data; not accounting for vasopressors being administered in ICU; and exclusion of costs related to management of neurological AEs requiring hospital admission. The ERG assumed the AE-related costs for KTE-X19 were equal to those for inotuzumab but assumed these to be subsumed in the tariff associated with providing CAR-T infusions (see Sections 4.4.2.7 and 4.4.2.9 of the ERG report).

In its updated base case, the company used an alternative approach for calculating costs associated with management of AEs where only costs associated with AEs that incurred an ICU stay, namely VOD and CRS, were included. This resulted in costs of [redacted] for KTE-X19, £421 for blinatumomab, £8907 for inotuzumab, £0 for ponatinib and £915 for FLAG-IDA. For AEs related to inotuzumab, the company agreed with the ERG assumption that half the costs and QALY losses are to be removed due to double counting issues. The ERG considers that this AE costs related to inotuzumab has been resolved.

Based on clinical advice, the ERG stated that "*vasopressors received by 30-40% of ZUMA-3 population are administered in ICU, and that neurological AEs experienced by at least 25% of the population need hospital readmission and stay supervised for a minimum of two weeks*". Following TE, clinicians confirmed again that the value assumed by the company appears to be a significant underestimate when interventions such as antibiotics are required following adverse events or the increased costs associated with high dependency unit care are considered. As such, the ERG is still concerned that the costs of

AEs associated with KTE-X19 is underestimated. The ERG also noted that "*a US economic study sponsored by the company estimated costs related to AE management following KTE-X19 infusion for R/R mantle cell lymphoma patients at $72,297 although the ERG acknowledges the difference between the US and English healthcare systems*" to which the company did not comment. The ERG notes that this appears markedly higher than the [redacted] assumed by the company in the model. The ERG has thus assumed that the costs of AEs for KTE-X19 is equivalent to that of inotuzumab (£8907) although clinical advice suggests that this still may be an underestimate. The costs for managing AEs following a KTE-X19 infusion is an area of uncertainty.

The ERG notes that the company has underestimated the ICU duration following CRS. The company uses [redacted] days however the weighted average of time reported in ZUMA-3 CSR (Table 14.3.18.1.1 and Table 14.3.18.1.2) was [redacted] days ([redacted] days and [redacted] days for Phase 2 and Phase 1 respectively). However, changing this value made little difference to the ICER and the ERG has used the company's value in its base case.

3.8 Key Issue 8: Concerns of double counting the AE costs associated with blinatumomab and FLAG-IDA

In its base case, the ERG removed costs associated with AE management for blinatumomab and FLAG-IDA as these costs are accounted for during hospital stay for drug administration. As discussed in Key issue 7, the company included only costs associated with CRS and VOD in their updated base case. The ERG believes that the company's assumption is reasonable and accepts this change.

3.9 Key Issue 9: Uncertainty of the costs associated with delivering KTE-X19 infusion

The ERG used a tariff of [redacted] to account for all costs associated with delivering a CAR-T infusion (KTE-X19 for this TA) in its base case. The company raised concerns with the accuracy and transparency of this estimate, and its true reflection of the true costs incurred by the NHS. The company had calculated a cost of delivering a KTE-X19 infusion as being [redacted] derived mainly from an average of [redacted] days in hospital per patient. Clinical advice provided to the ERG suggested that the value assumed by the company appears to be an under-estimate of the true costs.

Guidance from NICE stated that the tariff should not be used in the base case and explored as scenario analyses. The latest communicated tariff was [redacted], although at a recent Appraisal Committee for axicabtagene ciloleucel for treating relapsed or refractory follicular lymphoma (ID1685) a representative for NHS England stated that the NHS tariff may have over-estimated the true costs to the NHS. The ERG has used the company's value of [redacted] in its base case and has undertaken scenario analyses using £50,000, and [redacted] for delivering a KTE-X19 infusion to provide additional information

to the Appraisal Committee. In contrast to the approach taken in the ERG report, the costs of AEs for KTE-X19, the costs of leukapheresis, conditioning and bridging chemotherapies, administration costs, assumed by the company to be £7,152 are now additional to the costs of delivering the infusion rather than subsumed within the tariff. This results in the highest value in the sensitivity analysis being [redacted].

3.10 Key Issue 10: Issues with dosing regimens used for FLAG-IDA and ponatinib

The ERG applied a maximum cap of two cycles for FLAG-IDA reflecting its use at both clinical practice and the two trials (INO-VATE and TOWER). The company agreed, and this aspect is now considered resolved by the ERG.

For patients on ponatinib, the ERG assumed no adjunct chemotherapy in line with data from the PACE study that is used to estimate the efficacy of ponatinib. In response, the company decreased the proportion receiving chemotherapy from 100% to 15% to reflect clinical practice. Whilst the ERG accepts that the company's figure may reflect current clinical practice, it would be expected that the adjunct chemotherapy would provide additional benefit for patients compared with no adjunct chemotherapy. The ERG considers that the proportion of patients on ponatinib receiving chemotherapy should remain at 0% in the model so that treatment costs and efficacy are aligned.

3.11 End of life criteria

NICE End of Life criteria are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

In its discussion of the first criterion, the ERG provided median and mean OS estimates for the different comparators. Median OS data were 5.3, 5.3, 6.9, 7.3 months for patients receiving FLAG-IDA, inotuzumab, blinatumomab, and ponatinib respectively (CS, Table 34). However, the company's base case post-TE model estimates mean life years to be 3.2, 4.7, 5.4, 6.8 years for patients receiving FLAG-IDA, blinatumomab, ponatinib, and inotuzumab, respectively. The median values indicated that KTE-X19 would meet the criterion, whereas the mean values do not. The ERG report highlighted that "*reason for the large difference between mean and median survival values is attributed to the 3-year cure assumption applied in the model, where the proportions remaining alive at 3 years accrue most of the survival gain*."

The company argues that median values should be used in accordance with previous instances with TA450, TA541, TA451, and with appeal panel conclusions for TA788. Having witnessed Appraisal Committee deliberations related to the end-of-life criteria, the ERG believes it likely that KTE-X19 does meet the short-life expectancy criterion as the survival proportions modelled by the company for the comparators are lower than the 35% in TA788 on which the appeal panel stated that '*NICE stakeholders would consider it unreasonable to state that life expectancy for this population was normally more than 24 months*'.[13] 2-year survival probabilities were 13%, 19%, 20%, and 22% for patients receiving FLAG-IDA, blinatumomab, ponatinib, and inotuzumab respectively in the company's base case post-TE model.

One potential aspect that the Appraisal Committee may wish to consider is that the company has not modelled the survival associated with comparators within the ZUMA-3 population. If the ZUMA-3 population was decided to be most representative of patients treated in England, then the survival percentages at year 2 for the comparators are unknown.

4 Additional analyses undertaken by the company and the ERG

4.1 Quantitative changes to the company's base case for the Ph- subgroup

Table 4 presents the results of the ERG's adjustments to the naïve comparison analyses for the Ph- subgroup, however, the ERG stresses that this approach has many limitations and that the MAIC-approach is preferred as it explicitly attempts to adjust for differences in key characteristics in study populations. The answers based on a MAIC-approach could only be generated for the full population are provided in Section 4.3 and may give the Appraisal Committee a good indication on the likely increase in the ICER when using MAICs.

The naïve analyses for FLAG-IDA and inotuzumab have assumed that the overall study population results are applicable to both the Ph- and the Ph+ subgroups. For KTE-X19 only the Ph- population in ZUMA-3 was used. Blinatumumab is only indicated for Ph- patients.

The company's base case ICER is £39,806 compared with FLAG-IDA, with inotuzumab and blinatumomab being extendedly dominated; the ICERs of KTE-X19 compared with inotuzumab and blinatumomab were £20,648 and £31,089, respectively. The largest change in the ICER occurs using an SMR of 4 instead of 1.09, which increases the ICER to £49,329 versus FLAG-IDA. Including the costs and QALY losses associated with allo-SCT for patients who received KTE-X19 increased the ICER by over £4000; and assuming cured patients have lower HRQoL than the general population (using a multiplier of 0.92), increased the ICER by over £2000.

When including all the changes preferred by the ERG for the naïve comparison, the deterministic ICER increases to £60,585 for KTE-X19 versus FLAG-IDA (probabilistic ICER = £62,720). The deterministic ICERs of KTE-X19 versus inotuzumab and blinatumomab were £37,760 and £50,946 respectively (probabilistic ICERs are £40,753 and £53,944 respectively).

Assuming a tariff cost for delivering KTE-X19 of 50,000 and [redacted] increased the ICER for KTE-X19 against FLAG-IDA to £68,932 and £78,139 respectively in the ERG's deterministic preferred naïve comparison.

Table 4: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph-subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.74	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.65	[redacted]	[redacted]	9.43	[redacted]	[redacted]	£39,806
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £20,648 and £31,089, respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.74	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.65	[redacted]	[redacted]	9.43	[redacted]	[redacted]	£44,496
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £24,209 and £40,473, respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.46	[redacted]	[redacted]				ED
Inotuzumab	4.80	[redacted]	[redacted]				
KTE-X19	8.83	[redacted]	[redacted]	6.44	[redacted]	[redacted]	£49,329
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £25,333 and £38,842, respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.74	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.65	[redacted]	[redacted]	9.43	[redacted]	[redacted]	£42,653

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £22,049 and £33,389, respectively.							
ERG exploratory analysis 7: Assuming the management costs of AEs with KTE-X19 equivalent to those of inotuzumab							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.74	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.65	[redacted]	[redacted]	9.43	[redacted]	[redacted]	£40,728
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £22,052 and £32,210, respectively.							
ERG preferred naïve comparison (Exploratory analyses 4-7) – deterministic results							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.46	[redacted]	[redacted]				ED
Inotuzumab	4.80	[redacted]	[redacted]				
KTE-X19	8.83	[redacted]	[redacted]	6.44	[redacted]	[redacted]	£60,585
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £37,760 and £50,946, respectively.							
ERG preferred naïve comparison (Exploratory analyses 4-7) – probabilistic results							
FLAG-IDA	2.45	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.54	[redacted]	[redacted]				ED
Inotuzumab	4.84	[redacted]	[redacted]				
KTE-X19	8.83	[redacted]	[redacted]	6.38	[redacted]	[redacted]	£62,720
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £40,753 and £53,944, respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate

4.2 Quantitative changes to the company's base case for the Ph+ subgroup

Table 5 presents the results of the ERG's adjustments to the naïve comparison analyses for the Ph+ subgroup. Due to the naïve analyses being conducted for the overall population in TOWER and INO-VATE the results for FLAG-IDA and inotuzumab are the same as for the Ph- subgroup. Due to the small population that were Ph+ in the ZUMA-3 study the full ZUMA-3 population was used for KTE-X19. Ponatinib is only indicated for Ph+ patients.

The company's base case ICER is £37,608 compared with ponatinib, with inotuzumab being extendedly dominated; the ICERs of KTE-X19 compared with inotuzumab and FLAG-IDA were £17,872 and £36,166, respectively. The largest change in the ICER occurs using an SMR of 4 instead of 1.09, which increases the ICER to £46,350 versus ponatinib. Including the costs and QALY losses associated with allo-SCT for patients who received KTE-X19 increased the ICER by over £5000; and assuming cured patients have lower HRQoL than the general population (using a multiplier of 0.92), increased the ICER by over £2500. The ICER was relatively insensitive to the other exploratory analyses.

When including all the changes preferred by the ERG for the naïve comparison, the deterministic ICER increases to £59,624 for KTE-X19 versus ponatinib (probabilistic ICER = £60,839). The deterministic ICERs of KTE-X19 versus inotuzumab and FLAG-IDA were £32,614 and £54,939 respectively (probabilistic ICERs are £34,187 and £56,352 respectively). Assuming a tariff cost for delivering KTE-X19 of 50,000 and [redacted] increased the ICER for KTE-X19 against ponatinib to £68,859 and £79,044 respectively in the ERG's deterministic preferred naïve comparison.

Table 5: Results of the ERG's deterministic naïve comparison exploratory analyses – Ph+ subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£37,608
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £17,872 and £36,166, respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£42,781
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £23,438 and £40,347, respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Ponatinib	3.88	[redacted]	[redacted]	1.49	[redacted]	[redacted]	£37,803
Inotuzumab	4.80	[redacted]	[redacted]				ED
KTE-X19	9.49	[redacted]	[redacted]	5.61	[redacted]	[redacted]	£46,350
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £21,975 and £44,842, respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£32,118
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£40,221
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £19,098 and £38,759, respectively.							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ERG exploratory analysis 7: Assuming the management costs of AEs with KTE-X19 equivalent to those of inotuzumab							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£38,634
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £19,092 and £37,005, respectively.							
ERG exploratory analysis 10: Assuming no adjunctive chemotherapy with ponatinib							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£24,374
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£38,791
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £17,872 and £36,166, respectively.							
ERG preferred naïve comparison (Exploratory analyses 4-7, 10) – deterministic results							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Ponatinib	3.88	[redacted]	[redacted]	1.49	[redacted]	[redacted]	£33,504
Inotuzumab	4.80	[redacted]	[redacted]				ED
KTE-X19	9.49	[redacted]	[redacted]	5.61	[redacted]	[redacted]	£59,624
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £32,614 and £54,939, respectively.							
ERG preferred naïve comparison (Exploratory analyses 4-7, 10) – probabilistic results							
FLAG-IDA	2.45	[redacted]	[redacted]	-	-	-	
Ponatinib	3.92	[redacted]	[redacted]	1.47	[redacted]	[redacted]	£35,224
Inotuzumab	4.81	[redacted]	[redacted]				ED
KTE-X19	9.57	[redacted]	[redacted]	5.65	[redacted]	[redacted]	£60,839
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £34,187 and £56,352, respectively.							

AE - adverse event, ED - extendedly dominated, HRQoL - Health-related quality of life, SMR - standardised mortality rate

4.3 Quantitative changes to the company's base case to show impact of using MAICs to adjust for differences among populations

The ERG could not explore the MAIC analyses for the subgroups as this information was not provided by the company. Hence, the overall population was used to show the impact on the ICERs of using MAIC adjusted populations in combination with the other ERG preferred analyses. The ERG notes that only inotuzumab and FLAG-IDA are comparators for the overall population. As the MAICs adjusted the ZUMA-3 data to match the studies of each comparator an incremental analysis was not possible and pairwise comparisons have been presented. As discussed in Section 3.3, the 1 knot hazard splines were used to fit the EFS and OS KTE-X19 data adjusted per the inotuzumab population, whereas 1 knot normal splines were the selected fits in the FLAG-IDA population.

Table 6 presents the results for the company's naïve comparisons and the ERG's preferred naïve comparison, and the results when the naïve comparison is replaced with the MAIC when KTE-X19 is compared with FLAG-IDA. The MAIC results are presented with a spline model and a log-normal fit. Table 7 contains the same information for the comparison of KTE-X19 with inotuzumab.

The ERG explored how the MAIC impacted on the ICER of KTE-X19 in the company's base case versus FLAG-IDA. The increase was dependent on whether a spline model or a log-normal distribution was used, with a range of approximately £1000 to £6000 for the comparison with FLAG-IDA. When using the ERG preferred base case, the ICERs increase by approximately £1000 to £9000 compared with FLAG-IDA. For the comparison with inotuzumab, the change in the company's base case ranged from a decrease of approximately £3000 to an increase of £4000; for the ERG's preferred analysis the range was from a decrease of approximately £2000 to an increase of £2000 compared with inotuzumab. The MAICs had less of an impact in the updated analysis, but nevertheless, the ERG believes that it is technically the correct approach to take.

The ERG's preferred probabilistic MAIC analysis is in the range of £58,551 to £66,939 compared with FLAG-IDA and in the range of £32,908 to £40,523 compared with inotuzumab. These results, however, use a tariff for the KTE-X19 infusion of [redacted]. If this value is increased to £50,000 the range of ICERs become £64,691 to £73,774 compared with FLAG-IDA and £40,407 to £49,188 compared with inotuzumab; assuming a value of [redacted] the range of ICERs become £73,204 to £83,469 compared with FLAG-IDA and £51,282 to £62,380 compared with inotuzumab.

Table 6: Results of the ERG's deterministic MAIC exploratory analyses – overall ZUMA-3 population matched to FLAG-IDA

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
KTE-X19	13.69	[redacted]	[redacted]	10.46	[redacted]	[redacted]	£36,591
ERG preferred analyses (Deterministic) – naïve comparison against FLAG-IDA							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
KTE-X19	9.54	[redacted]	[redacted]	7.15	[redacted]	[redacted]	£55,476
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (1 knot normal)							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
KTE-X19	13.56	[redacted]	[redacted]	10.34	[redacted]	[redacted]	£37,370
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (log-normal)							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
KTE-X19	12.13	[redacted]	[redacted]	8.91	[redacted]	[redacted]	£42,883
ERG preferred analyses (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (1 knot normal)							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
KTE-X19	9.42	[redacted]	[redacted]	7.03	[redacted]	[redacted]	£56,973
ERG preferred analyses (Deterministic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (log-normal)							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
KTE-X19	8.49	[redacted]	[redacted]	6.10	[redacted]	[redacted]	£64,984
ERG preferred analyses (Probabilistic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (1 knot normal)							
FLAG-IDA	2.43	[redacted]	[redacted]	-	-	-	
KTE-X19	9.45	[redacted]	[redacted]	7.03	[redacted]	[redacted]	£58,551
ERG preferred analyses (Probabilistic) – MAIC-adjusted ZUMA-3 to FLAG-IDA population (log-normal)							
FLAG-IDA	2.43	[redacted]	[redacted]	-	-	-	
KTE-X19	8.51	[redacted]	[redacted]	6.08	[redacted]	[redacted]	£66,939

Table 7: Results of the ERG's deterministic MAIC exploratory analyses – overall ZUMA-3 population matched to inotuzumab

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	6.75	[redacted]	[redacted]	-	-	-	
KTE-X19	13.69	[redacted]	[redacted]	6.93	[redacted]	[redacted]	£18,671
ERG preferred analyses (Deterministic) – naïve comparison against inotuzumab							
Inotuzumab	4.80	[redacted]	[redacted]	-	-	-	
KTE-X19	9.54	[redacted]	[redacted]	4.74	[redacted]	[redacted]	£33,619
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population (1 knot hazard)							
Inotuzumab	6.75	[redacted]	[redacted]	-	-	-	
KTE-X19	14.65	[redacted]	[redacted]	7.90	[redacted]	[redacted]	£16,854
Company base case (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population (log-normal)							
Inotuzumab	6.75	[redacted]	[redacted]	-	-	-	
KTE-X19	13.03	[redacted]	[redacted]	6.28	[redacted]	[redacted]	£20,772
ERG preferred analyses (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population (1 knot hazard)							
Inotuzumab	4.80	[redacted]	[redacted]	-	-	-	
KTE-X19	10.14	[redacted]	[redacted]	5.35	[redacted]	[redacted]	£30,547
ERG preferred analyses (Deterministic) – MAIC-adjusted ZUMA-3 to inotuzumab population (log-normal)							
Inotuzumab	4.80	[redacted]	[redacted]	-	-	-	
KTE-X19	9.09	[redacted]	[redacted]	4.29	[redacted]	[redacted]	£37,228
ERG preferred analyses (Probabilistic) – MAIC-adjusted ZUMA-3 to inotuzumab population (1 knot hazard)							
Inotuzumab	4.83	[redacted]	[redacted]	-	-	-	
KTE-X19	10.10	[redacted]	[redacted]	5.27	[redacted]	[redacted]	£32,908
ERG preferred analyses (Probabilistic) – MAIC-adjusted ZUMA-3 to inotuzumab population (log-normal)							
Inotuzumab	4.86	[redacted]	[redacted]	-	-	-	
KTE-X19	9.08	[redacted]	[redacted]	4.23	[redacted]	[redacted]	£40,523

4.4 The ERG's estimate of the ICER

The exploratory analyses conducted by the ERG indicate that there are plausible changes to parameter values which would increase the company's estimates of the ICERs but where the most appropriate value remains uncertain. Such parameters include: the cost of providing a KTE-X19 infusion; the appropriate adjustment for differences in study populations; the magnitude by which the risk of mortality is increased; and whether there is a reduced HRQoL for patients assumed to be cured.

The exploratory analysis which has the largest impact on the ICER is the cost of providing a KTE-X19 infusion which currently has large uncertainty. Using a value of £50,000, increased the ERG's preferred ICERs in the naïve analyses of KTE-X19 compared with FLAG-IDA to £68,932. Using an SMR of 4, rather than 1.09 generated the largest change in the ICER between the company's preferred naïve analysis and the ERG's preferred analysis when using the company's estimate of the costs of a KTE-X19 infusion. This change typically added approximately £10,000 to the ICER.

The ERG, however, believes that naïve analyses are inappropriate and prefer using MAICs when there are differences in the patient populations, and highlights that the company states that "*ZUMA-3 is the most generalisable population to patients likely to receive KTE-X19 in UK clinical practice"* suggesting that there is a difference between populations. The change in the ICER from using the company's MAICs is less than the change in the SMR and could conceivably decrease the ICER. However, the ERG believes that the MAIC should be adjusted to be in the ZUMA-3 population, rather than matching to the trial populations of either FLAG-IDA or inotuzumab. This could be operationalised by deriving a HR from the current MAIC and using this in the ZUMA-3 population. This analysis was requested twice by the ERG but was not undertaken by the company. As the MAIC analyses were only undertaken for both Ph- and Ph+ combined, results by subgroup could not be generated and the impact of different populations are unknown.

In the naïve analyses for the Ph- subgroup, blinatumomab was estimated to be extendedly dominated. In the Ph+ subgroup the ICER for KTE-X19 compared to ponatinib was estimated to be £60,839.

The ICERs generated by the ERG suggest a range in the ICER of £58,551 to £66,939 compared with FLAG-IDA and of £32,908 to £40,523 compared with inotuzumab. Given that this is using a cost for the delivery of a KTE-X19 infusion that clinical experts believe is too low, it is highly likely that the ICER of KTE-X19 compared with FLAG-IDA is in excess of £60,000 and that the ICER compared with inotuzumab is in excess of £35,000.

5 Overall conclusions

Some of the key issues the ERG raised to the original CS were resolved in the company's TE response. However, the ERG believes that the base case ICER is likely to be higher than that estimated by the company and believes that the ICER for KTE-X19 against FLAG-IDA in the overall population is highly likely to be in excess of £60,000. The ICER for KTE-X19 against FLAG-IDA in the overall population is highly likely to be in excess of £35,000 compared with inotuzumab. The ERG estimates that the ICER compared with blinatumomab is £53,944, although there is uncertainty caused by the fact that patients in the Phase 1 KTE-X19 study were not included in the comparison with blinatumomab. As these analyses were not conducted by the company, it is inferred by the ERG that this may increase the ICER.

The probabilistic ICER of KTE-X19 compared to ponatinib in the Ph+ subgroup was over £60,000 at the infusion cost thought to be an underestimate. In the Ph- group, blinatumomab was extendedly dominated, although the ICER of KTE-X19 compared to blinatumumab was approximately £54,000 at the infusion cost thought to be an underestimate.

The ERG would have preferred that the company used HRs derived from the MAICs to estimate ICERs in a population matching those recruited to the ZUMA-3 study, however, the company did not provide these analyses.

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Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal: ERG addendum post Appraisal Committee Meeting

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1 Background

On the 28th of September 2022, the company submitted an updated version of the model used for the technical engagement (TE) process for the appraisal of autologous anti-CD19-transduced CD3+ cells for treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults (henceforth the technology and indication are referred to as KTE-X19 and R/R ALL respectively for brevity). This was because SCHOLAR-3 survival data had not been fitted to the newer data from ZUMA-3 which included 9 additional months of follow-up and was restricted only to patients aged 26 years or older.

Additionally, during the process of tracking the changes between the different model versions, the Evidence Review Group (ERG) discovered that the post TE model versions did have the function to model the comparator arms using the inverse of hazard ratio (HR) estimates from the matching-adjusted indirect comparisons (MAICs). The ERG had stated that this would be its preferred approach for many analyses, as the company stated that the ZUMA-3 population was most pertinent to the decision problem. As the company did not present results using this functionality the ERG had not identified earlier that these results could be generated. The ERG did not have enough time to generate these results prior to the first appraisal committee meeting (the 4th of October 2022).

Following the Appraisal Committee meeting NHS England submitted additional information regarding the tariff charged for delivering CAR-T therapies. This report provides a critique of the NHS tariff and results generated using the most current NHS England estimate for the costs of providing CAR-T treatment.

All results presented in this document include the Patient Access Scheme (PAS) discount for KTE-X19 ([redacted]). The results of the company's analyses when applying the confidential PASs for blinatumomab, inotuzumab ozogamicin (henceforth referred to as inotuzumab for brevity), ponatinib, and tocilizumab (which is used to treat cytokine release syndrome (CRS) a potential adverse event (AE)) are presented in a separate confidential appendix.

2 Critique of the NHS tariff submission and description of the updated exploratory analyses undertaken by the ERG

The company assumed a cost of [redacted] for a CAR-T infusion based on an estimated [redacted] days of hospitalisation. The ERG was made aware of a tariff available for the delivery of a CAR-T therapy, and at the time this was assumed to cost [redacted] based on expert advice. In addition to hospitalisation costs, the ERG used this estimate to account for other costs such as AEs, leukapheresis, and bridging chemotherapy. During the TE process, the company maintained its estimate and the ERG presented scenario analyses using £50,000, and [redacted] to provide additional information to the Appraisal Committee. The costs of AEs for KTE-X19, the costs of leukapheresis, conditioning and bridging chemotherapies, administration costs, assumed by the company to be £7,152 were all added to the costs of delivering the infusion rather than subsumed within the tariff. This results in the highest value in the sensitivity analysis being [redacted].

Following the committee, NHS England submitted a tariff breakdown of £65,415 which covered the pre-infusion phase to 100 days after the infusion delivery, and comprised the following:

- Direct paid medical staff costs (£35,329) which includes consultant and junior medical staff, general nursing staff, specialist CAR-T nursing staff, pharmacists, physiotherapy and occupational therapy, and counselling services,
- Indirect paid medical staff costs (£10,166) which includes consultants from supporting services (radiology, pathology, laboratory services, quality management, and admin support), and
- Non-pay costs (£19,920) which includes clinical supplies, leukapheresis kits, consumables, aphresis infusion, hospital bed costs, and local accommodation post discharge to 28 days post infusion.

The ERG notes that the costing exercise was a rapid review of financial inputs of 6 NHS providers of CAR-T services and was not implementing a micro-costing approach. The ERG could not critique the cost components robustly due to the lack of alternative data sources for some costs and has had to assume in its base case that £65,415 is the true cost to the NHS for delivering such services. The ERG assumed that the costs of leukapheresis, conditioning and bridging therapy (£7152), hospitalisation costs ([redacted]), and management of adverse events ([redacted]) are included in the £65,415.

The ERG base case adopts an approach where the event-free survival (EFS) and overall survival (OS) of the comparator arms (inotuzumab and FLAG-IDA) are modelled applying the inverse of HR derived from the MAIC to the parametric fits of KTE-X19. The ERG preferred this approach as it adjusts the

populations of the other comparators to that of ZUMA-3 which is assumed to be the most representative of patients eligible to receive KTE-X19 treatment in clinical practice.

The ERG presents two different analyses for blinatumomab matched to the ZUMA-3 population in the Ph- subgroup. The first (2a) uses the SCHOLAR-3 blinatumomab individual patient data (IPD) matched to ZUMA-3 Phase 2, and the second (2b) using the inverse of HR estimated from ZUMA-3 versus the aggregate data from the TOWER study. Technically, the ERG prefers 2a as it included IPD which allowed fitting separate curves for blinatumomab and not having to rely on a proportionate hazard assumption. However, the company only matched SCHOLAR-3 to the Phase 2 data from ZUMA-3 and the ERG would have preferred that SCHOLAR-3 data were matched to both Phase 1 and Phase 2 data. In contrast, 2b does include data from Phase 1. The ERG has used 2a in its base case but notes that the ICER generated may be inaccurate due to the omission of Phase 1 data from ZUMA-3.

3 Updated results of the company and the ERG's base cases

3.1 Quantitative changes to the company's base case for the Ph- subgroup

Table 1 presents the results of the ERG's adjustments to the company's base case for the Ph- subgroup.

The company's base case ICER is £39,833 compared with FLAG-IDA, with inotuzumab and blinatumomab being extendedly dominated; the ICERs of KTE-X19 compared with inotuzumab and blinatumomab were £20,669 and £30,654, respectively. The largest change in the ICER occurs using an SMR of 4 instead of 1.09, which increases the ICER to £49,361 versus FLAG-IDA. Assuming the NHS tariff for CAR-T delivery increased the ICER by approximately £7000, whereas using the inverse of HRs derived from MAIC to model the comparator arms increased the ICER by approximately £5500. The ERG notes that the life years and QALYs gained through FLAG-IDA and blinatumomab treatment are similar in scenario 2a. This is because using the inverse of HR considerably increased the survival gain for FLAG-IDA, an issue that illustrates the uncertainty generated from using different matching methodologies (IPD for blinatumomab from SCHOLAR-3 versus aggregate data for FLAG-IDA from TOWER and INO-VATE), and modelling assumptions (i.e., a proportional hazard assumption for FLAG-IDA versus separate survival distributions for SCHOLAR-3). In the final appraisal determination for TA589 it is stated that the committee '*concluded that blinatumomab is clinically effective, but the lack of direct comparative data means the size of this benefit is still unclear.*'[1]

When including all the changes preferred by the ERG for the naïve comparison, the deterministic ICER increases to £79,379 for KTE-X19 versus FLAG-IDA (probabilistic ICER = £81,380). The deterministic ICERs of KTE-X19 versus inotuzumab and blinatumomab were £47,563 and £59,127 respectively (probabilistic ICERs are £49,033 and £60,306 respectively).

[1] 3 Committee discussion | Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity | Guidance | NICE

Table 1: Results of the ERG's exploratory analyses – Ph- subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population And naïve indirect comparison for inotuzumab and FLAG-IDA							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.58	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.64	[redacted]	[redacted]	9.42	[redacted]	[redacted]	£39,833
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £20,669 and £30,654, respectively.							
ERG exploratory analysis 2a: Using SCHOLAR-3 data to adjust population on blinatumomab to ZUMA-3 population with the inverse of HRs derived from MAIC to model inotuzumab and FLAG-IDA							
FLAG-IDA	4.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.58	[redacted]	[redacted]				ED
Inotuzumab	6.54	[redacted]	[redacted]				
KTE-X19	12.80	[redacted]	[redacted]	8.13	[redacted]	[redacted]	£45,714
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £19,379 and £30,141, respectively.							
ERG exploratory analysis 2b: Using the inverse of HRs derived from MAIC to model blinatumomab, inotuzumab and FLAG-IDA							
FLAG-IDA	4.67	[redacted]	[redacted]	-	-	-	
Blinatumomab	6.11	[redacted]	[redacted]				ED
Inotuzumab	6.54	[redacted]	[redacted]				
KTE-X19	12.88	[redacted]	[redacted]	8.21	[redacted]	[redacted]	£45,323
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £19,190 and £35,853, respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.58	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.64	[redacted]	[redacted]	9.42	[redacted]	[redacted]	£44,528
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £27,215 and £36,035, respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.35	[redacted]	[redacted]				ED
Inotuzumab	4.80	[redacted]	[redacted]				
KTE-X19	8.82	[redacted]	[redacted]	6.43	[redacted]	[redacted]	£49,361

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £25,357 and £38,335, respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.58	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.64	[redacted]	[redacted]	9.42	[redacted]	[redacted]	£42,682
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £22,070 and £32,935, respectively.							
ERG exploratory analysis 9: Assuming the NHS tariff for CAR-T delivery costs							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Blinatumomab	4.58	[redacted]	[redacted]				ED
Inotuzumab	6.75	[redacted]	[redacted]				
KTE-X19	12.64	[redacted]	[redacted]	9.42	[redacted]	[redacted]	£46,773
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £31,236 and £38,951, respectively.							
ERG base case (Exploratory analyses 2a, 4-6, 9) – deterministic results							
FLAG-IDA	3.38	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.35	[redacted]	[redacted]				ED
Inotuzumab	4.67	[redacted]	[redacted]				
KTE-X19	8.93	[redacted]	[redacted]	5.55	[redacted]	[redacted]	£79,379
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £47,563 and £59,127, respectively.							
ERG base case (Exploratory analyses 2a, 4-6, 9) – probabilistic results*							
FLAG-IDA	3.53	[redacted]	[redacted]	-	-	-	
Blinatumomab	3.46	[redacted]	[redacted]				ED
Inotuzumab	4.79	[redacted]	[redacted]				
KTE-X19	8.96	[redacted]	[redacted]	5.44	[redacted]	[redacted]	£81,380
ICERs of KTE-X19 versus inotuzumab and blinatumomab are £49,033 and £60,306, respectively.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported
AE - adverse event, ED - extendedly dominated, HR - hazard ratio, HRQoL - Health-related quality of life, MAIC - matching-adjusted indirect comparison, SMR - standardised mortality rate

3.2 Quantitative changes to the company's base case for the Ph+ subgroup

Table 2 presents the results of the ERG's adjustments to the company's base case for the Ph+ subgroup.

The company's base case ICER is £37,608 compared with ponatinib, with inotuzumab being extendedly dominated; the ICERs of KTE-X19 compared with inotuzumab and FLAG-IDA were £17,872 and £36,166, respectively. The largest change in the ICER occurs using an SMR of 4 instead of 1.09, which increases the ICER to £46,350 versus ponatinib. Using the inverse of HRs derived from MAIC to model inotuzumab and FLAG-IDA increases the ICER of KTE-X19 by over £8400 and £1100, respectively. The ERG notes that the life years and QALYs gained through FLAG-IDA treatment are greater than that of ponatinib. This is due to the fact that using the inverse of HR considerably increased the survival gain for FLAG-IDA. This is because using the inverse of HR considerably increased the survival gain for FLAG-IDA, an issue that illustrates the uncertainty generated from using a matched comparison for one comparator (FLAG-IDA) and naïve comparison for the other (ponatinib). In TA451 the committee '*concluded that the results of the PACE study demonstrated that ponatinib is an effective treatment in Ph+ ALL patients.*'[2]

Including the costs and QALY losses associated with allo-SCT for patients who received KTE-X19 increased the ICER by over £5000; and assuming cured patients have lower HRQoL than the general population (using a multiplier of 0.92), increased the ICER by over £2500. The ICER was relatively insensitive to the other exploratory analyses.

When including all the changes preferred by the ERG for the naïve comparison, the deterministic ICER increases to £77,685 for KTE-X19 versus FLAG-IDA (probabilistic ICER = £79,312). The deterministic ICERs of KTE-X19 versus inotuzumab and ponatinib were £47,086 and £66,218 respectively (probabilistic ICERs are £48,463 and £67,968 respectively).

[2] 4 Committee discussion | Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia | Guidance | NICE

Table 2: Results of the ERG's exploratory analyses – Ph+ subgroup

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
Company base case (Deterministic) – Naïve indirect comparison							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£37,608
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £17,872 and £36,166, respectively.							
ERG exploratory analysis 2: Using the inverse of HRs derived from MAIC to model inotuzumab and FLAG-IDA							
Ponatinib	5.39	[redacted]	[redacted]	-	-	-	Dominated
FLAG-IDA	5.60	[redacted]	[redacted]	0.21	[redacted]	[redacted]	
Inotuzumab	7.61	[redacted]	[redacted]				ED
KTE-X19	13.94	[redacted]	[redacted]	8.34	[redacted]	[redacted]	£44,600
ICERs of KTE-X19 versus inotuzumab and ponatinib are £19,050 and £36,333, respectively.							
ERG exploratory analysis 4: Including allo-SCT associated costs and QALY loss for the KTE-X19 patients							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£42,781
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £23,438 and £40,347, respectively.							
ERG exploratory analysis 5: Using SMR of 4 applied to general population mortality for cured patients							
FLAG-IDA	2.39	[redacted]	[redacted]	-	-	-	
Ponatinib	3.88	[redacted]	[redacted]	1.49	[redacted]	[redacted]	£37,803
Inotuzumab	4.80	[redacted]	[redacted]				ED
KTE-X19	9.49	[redacted]	[redacted]	5.61	[redacted]	[redacted]	£46,350
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £21,975 and £44,842, respectively.							
ERG exploratory analysis 6: Assuming cured patients have lower HRQoL than the general population							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£32,118
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£40,221
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £19,098 and £38,759, respectively.							
ERG exploratory analysis 9: Assuming the NHS tariff for CAR-T delivery costs							

Option	Life years	QALYs	Costs	Incremental			ICER
				Life years	QALYs	Costs	
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£29,689
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£45,321
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £27,042 and £42,474, respectively.							
ERG exploratory analysis 10: Assuming no adjunctive chemotherapy with ponatinib							
FLAG-IDA	3.22	[redacted]	[redacted]	-	-	-	
Ponatinib	5.39	[redacted]	[redacted]	2.17	[redacted]	[redacted]	£24,374
Inotuzumab	6.75	[redacted]	[redacted]				ED
KTE-X19	13.61	[redacted]	[redacted]	8.23	[redacted]	[redacted]	£38,791
ICERs of KTE-X19 versus inotuzumab and FLAG-IDA are £17,872 and £36,166, respectively.							
ERG preferred naïve comparison (Exploratory analyses 2, 4-6, 9, 10) – deterministic results							
Ponatinib	3.88	[redacted]	[redacted]	-	-	-	Dominated
FLAG-IDA	4.04	[redacted]	[redacted]	0.16	[redacted]	[redacted]	
Inotuzumab	5.42	[redacted]	[redacted]				ED
KTE-X19	9.71	[redacted]	[redacted]	5.67	[redacted]	[redacted]	£77,685
ICERs of KTE-X19 versus inotuzumab and ponatinib are £47,086 and £66,218, respectively.							
ERG preferred naïve comparison (Exploratory analyses 2, 4-6, 9, 10) – probabilistic results*							
Ponatinib	4.04	[redacted]	[redacted]	-	-	-	Dominated
FLAG-IDA	4.18	[redacted]	[redacted]	0.16	[redacted]	[redacted]	
Inotuzumab	5.54	[redacted]	[redacted]				ED
KTE-X19	9.76	[redacted]	[redacted]	5.58	[redacted]	[redacted]	£79,312
ICERs of KTE-X19 versus inotuzumab and ponatinib are £48,463 and £67,968, respectively.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported
AE - adverse event, ED - extendedly dominated, HR - hazard ratio, HRQoL - Health-related quality of life, MAIC - matching-adjusted indirect comparison, SMR - standardised mortality rate

Confidential until published

Autologous anti-CD19-transduced CD3+ cells for previously treated B-precursor acute lymphoblastic leukaemia in adults [ID1494]. A Single Technology Appraisal: ERG additional analyses requested by NICE

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Neither of the authors has any conflicts of interest to declare.

1 Introduction

In November 2022, the NICE appraisal committee met for the appraisal of autologous anti-CD19-transduced CD3+ cells for treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia in adults (henceforth the technology is referred to as KTE-X19 for brevity). Following the meeting NICE requested that the ERG provides additional analyses to inform the committee.

The request was that the ERG maintain its base cases for the Philadelphia chromosome-negative patients (Ph-) subgroup) and for the Philadelphia chromosome-positive patients (Ph+) subgroup with the following two changes:

1) Assuming that the total costs of providing CAR-T was £60,000 per patient
2) Removing FLAG-IDA as a comparator from the analyses

All results presented in this document include the Patient Access Scheme (PAS) discount for KTE-X19 ([redacted]). The results of the company's analyses when applying the confidential PASs for blinatumomab, inotuzumab ozogamicin (henceforth referred to as inotuzumab for brevity), ponatinib, and the Commercial Medicines Unit price for fludarabine are presented in a separate confidential appendix.

Recapping, for both the Ph- and Ph+ subgroups the ERG's base case makes the following changes from the company's base case

- Using the inverse of HRs derived from MAIC to model inotuzumab in a ZUMA-3 population
- Including allo-SCT associated costs and QALY loss for the KTE-X19 patients
- Using an SMR of 4 applied to general population mortality for cured patients
- Assuming cured patients have lower HRQoL than the general population
- Assuming that the costs for undertaking CAR-T is £60,000 per patient

For the Ph- subgroup the ERG base case uses the SCHOLAR-3 data adjusted to a ZUMA-3 population to model blinatumomab. For the Ph+ subgroup the ERG assumes that there is no adjunctive chemotherapy use with ponatinib.

2 Additional analyses undertaken by the company and the ERG

2.1 The ERG base case for Ph- patients

ERG base case – deterministic results							
	Life Years	QALYS	Costs	Inc Life years	Inc QALYs	Inc Costs	ICER
Blinatumomab	3.35	[redacted]	[redacted]	-	-	-	-
Inotuzumab	4.67	[redacted]	[redacted]				ED
KTE-X19	8.93	[redacted]	[redacted]	5.58	[redacted]	[redacted]	£57,594
ICER of KTE-X19 versus inotuzumab is £45,704.							
ERG base case – probabilistic results*							
Blinatumomab	3.43	[redacted]	[redacted]	-	-	-	-
Inotuzumab	4.83	[redacted]	[redacted]				ED
KTE-X19	9.01	[redacted]	[redacted]	5.57	[redacted]	[redacted]	£58,290
ICER of KTE-X19 versus inotuzumab is £47,329.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported

2.2 The ERG base case for Ph+ patients

ERG base case – deterministic results							
	Life Years	QALYS	Costs	Inc Life years	Inc QALYs	Inc Costs	ICER
Ponatinib	3.88	[redacted]	[redacted]	-	-	-	-
Inotuzumab	5.42	[redacted]	[redacted]				ED
KTE-X19	9.71	[redacted]	[redacted]	5.84	[redacted]	[redacted]	£64,852
ICER of KTE-X19 versus inotuzumab is £45,235.							
ERG base case – probabilistic results*							
Ponatinib	4.01	[redacted]	[redacted]	-	-	-	-
Inotuzumab	5.53	[redacted]	[redacted]				ED
KTE-X19	9.76	[redacted]	[redacted]	5.75	[redacted]	[redacted]	£66,329
ICER of KTE-X19 versus inotuzumab is £46,374.							

*The uncertainty in the HRs could not be included in the PSA as the confidence intervals were not reported