NICE National Institute for Health and Care Excellence

KTE-X19 for treating relapsed or refractory mantle cell lymphoma

Clinical effectiveness

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Company: Kite (a Gilead company)

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Key issues (Clinical effectiveness)

Issue 1

- Are the results of ZUMA-2 (mean age of 63 years, median of 3 prior therapies, 100% with an ECOG 0/1 and 43% having received a stem cell transplant) generalisable to people eligible to receive KTE-X19 in the NHS?
- How would people be selected for treatment with KTE-X19 and are they easily identifiable in the NHS?

Issue 4

- Is relapsed or refractory mantle cell lymphoma curable?
- Do the Kaplan-Meier curves from ZUMA-2 support the possibility of long-term cure?
- Could only people who achieve a complete response have the potential for cure?
- Does the additional data from December 2019 cut-off reduce uncertainty in the results and support assumption of long term cure following treatment with KTE-X19?

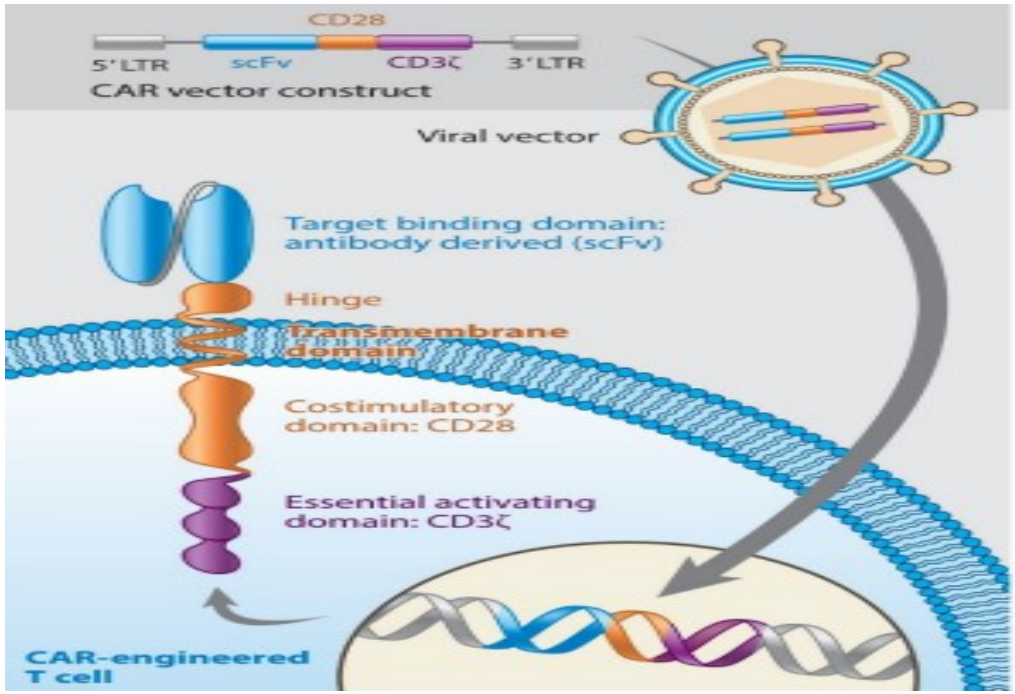
KTE-X19 (Kite, a Gilead company)

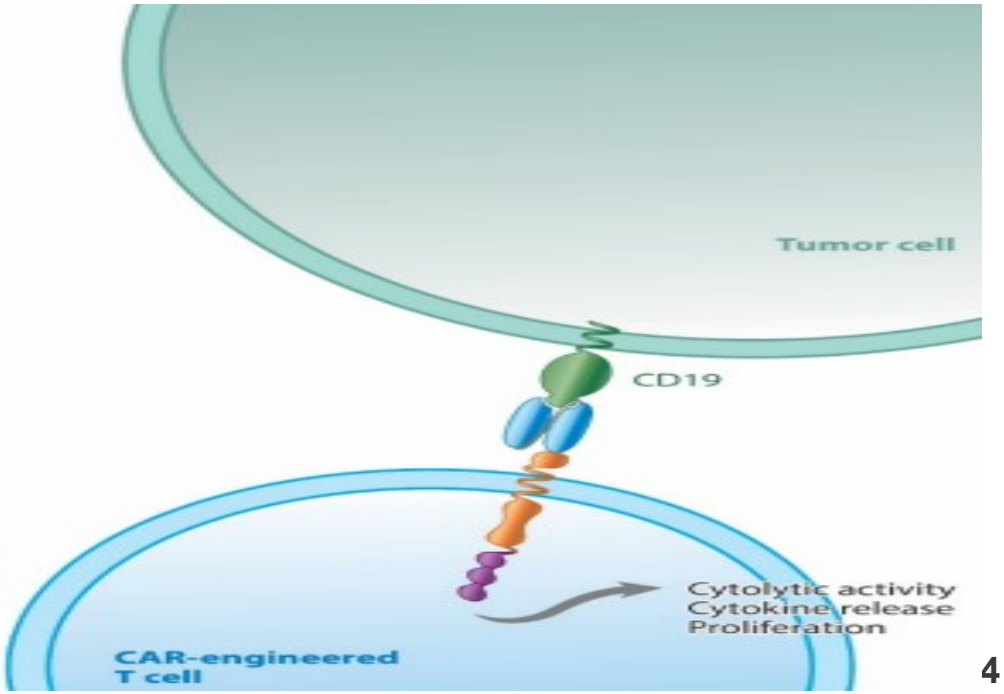
Anticipated marketing authorisation indication	[redacted] CHMP positive opinion expected: [redacted] Marketing authorisation expected: [redacted]
Mechanism of action	Single-chain anti CD19 antibody fragment. Patients' T-cells are engineered to express CD19 antigen-specific CAR, and given back to the patient enabling them to kill CD19-expressing tumour
Administration and dose	Single-infusion containing anti-CD19 CAR T-cells in approximately 68 mL for a target dose of 2 x 10^6 CAR T-cells/kg body weight Patients pre-treated treated with iv fludarabine and cyclophosphamide for 3 days
List price	List price: £[redacted] Average cost of a course of treatment including leukapheresis, bridging therapy, conditioning chemotherapy and administration: £[redacted]
Proposed commercial arrangements	[redacted]

CAR T-cell therapy

- Chimeric antigen receptor (CAR) T-cell therapy is specifically developed for each individual patient and involves reprogramming the patient's own immune system cells. A sample of a patient's T cells are collected from the blood, then modified to produce chimeric antigen receptors (CARs) on their surface. When these CAR T- cells are reinfused into the patient, they latch onto a specific antigen on the patient's tumour cells and kill them.
- It is a highly complex and potentially risky treatment but it has been shown in trials to cure some patients, even those with quite advanced cancers and where other available treatments have failed.

KTE-X19 mechanism of action

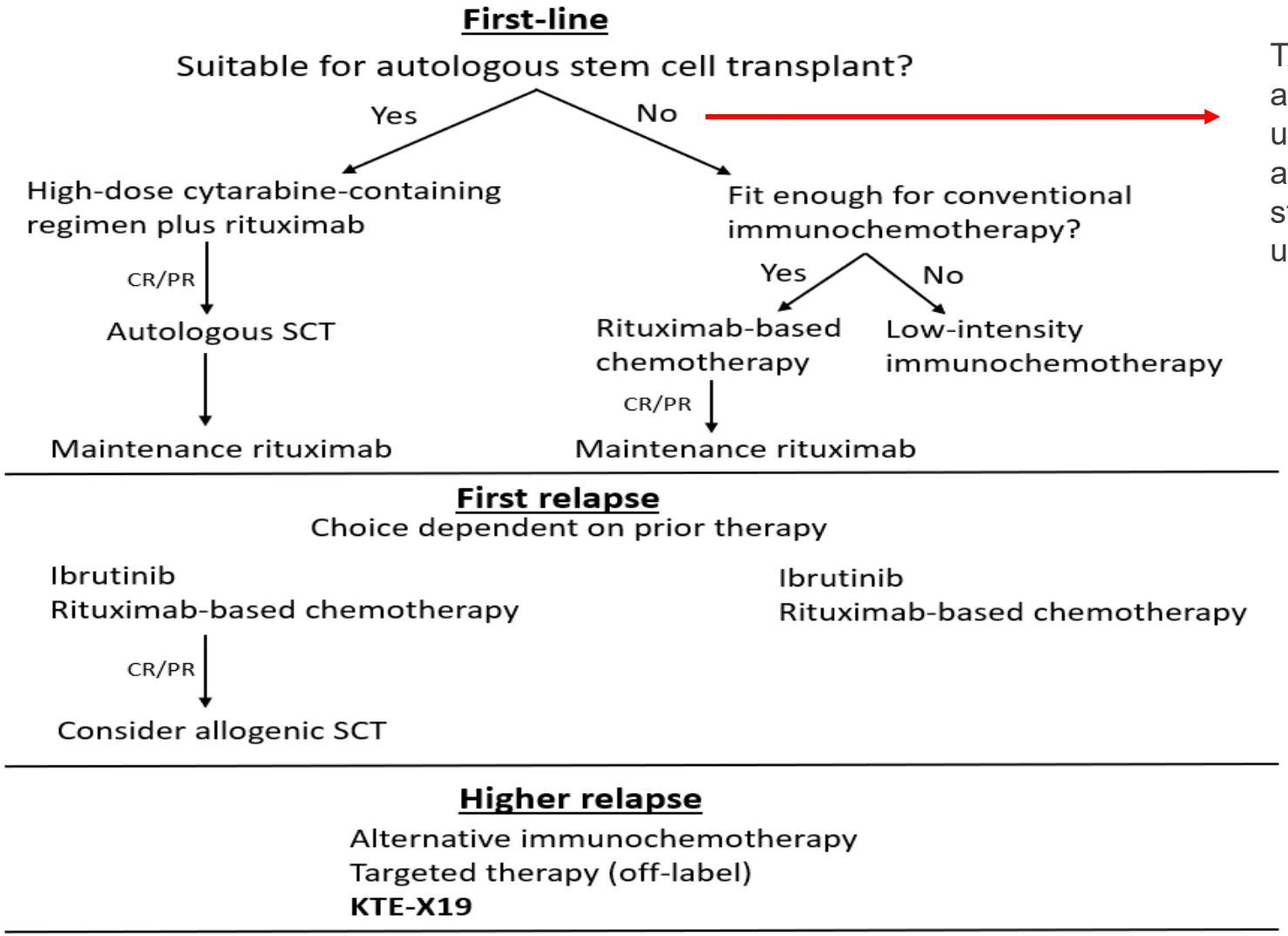




Mantle cell lymphoma (MCL)

- Aggressive sub-type of Non-Hodgkin's Lymphoma (NHL): generally considered incurable.
- Involves lymph nodes & spleen, bone marrow but also extra nodal sites such as liver & gut
- Approximately 560 people are diagnosed with MCL in the UK each year (~5% of all NHL) ~370 will require therapy for refractory or relapsed (r/r) disease
- More common in men (3:1 ratio) and older people (median age at diagnosis 72.9 years)
- Symptoms include fever, loss of appetite, sickness, anaemia, fatigue, night sweats

Treatment pathway



TA 370 recommends bortezomib as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable

Key: CR, complete response; MCL, mantle cell lymphoma; PR, partial response; SCT, stem cell transplant.

Current management

- First-line treatment may include rituximab+chemotherapy and, if fit, stem cell transplant
- NICE recommends bortezomib as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable (**TA 370**)
- NICE recommends ibrutinib as an option for relapsed or refractory mantle cell lymphoma (r/r MCL) in adults after one previous line of therapy and under a commercial access agreement (**TA502**)
- No uniformly accepted standard of care for relapsed or refractory mantle cell lymphoma (r/r MCL). May include:
  - **Ibrutinib most likely treatment to be used second-line,** but also
  - Rituximab plus bendamustine (R-bendamustine)
  - Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP)
  - Rituximab, bendamustine and cytarabine (R-BAC)
- Treatment options at higher relapse (3rd+ line) are not well established and normally produce lower responses and rapid progression
- **KTE-X19 is proposed to be positioned as a 3rd or later-line treatment option post-ibrutinib treatment.**

Previous NICE CAR T-cell therapy appraisals

- No previous CAR T-cell therapy appraisals in r/r MCL. Previous NICE appraisals for CAR T-cell therapies recommended for use within the Cancer Drugs Fund and within a managed access agreement include:
  - **TA554** recommending tisagenlecleucel for relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years
  - **TA567** recommending tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after 2 or more systemic therapies.
  - **TA559** recommending axicabtagene ciloleucel for treating relapsed or refractory DLBCL or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies

Decision problem

	NICE scope	Company submission	Rationale for difference
Population	People with r/r MCL who have received at least two previous lines of therapy	Adult patients with r/r MCL who have previously received a BTK inhibitor	Wording change to align with the anticipated marketing authorisation.
Comparator	Established clinical management including but not limited to: • Chemotherapy with or without rituximab • Allogeneic stem cell transplant (Allo-SCT)	Established clinical management including but not limited to: • Chemotherapy with or without rituximab	Allo-SCT is not an alternative treatment to KTE-X19 for patients after BTKi failure. KTE-X19 is positioned as 3rd-line treatment after BTKi failure.

Patient and carer perspectives

- Impact of a diagnosis of and treatment for Mantle Cell Lymphoma.
- MCL almost always relapses and requires more treatment.
- No uniformly accepted standard of care for relapsed/refractory MCL.
- Treatment options at higher relapse (3rd+ line) normally produce lower responses and rapid progression.
- Patients would welcome a well tolerated treatment that provides longer-lasting /complete remissions – or, ideally, a cure.
- Whilst KTE-X19 treatment can have serious and even life-threatening side effects, many patients would accept that risk for the potential of a cure.
- Not all patients would be able to afford to arrange appropriate accommodation near the treatment centre, in order to access treatment.

Primary clinical evidence: ZUMA-2

Design	Phase III, open-label, single-arm, multicentre (n=105 enrolled)
Location	International: 33 sites in Europe and USA 92% of the full analysis (FAS) n=74 set from US Of the 74 patients in the FAS, 5 patients not treated, 1 not treated after conditioning chemotherapy, found to ineligible) = 68 who received licensed dose
Population	Relapsed/refractory MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTKi (ibrutinib and/or acalabrutinib)
Intervention	KTE-X19 (n=68, modified intent to treat (mITT))
Comparator	None
Outcomes	**Primary outcome**: Overall response rate (ORR) **Secondary outcomes:** • Overall survival • Progression-free survival • Duration of response • Adverse effects of treatment • Health-related quality of life

ZUMA-2 patient baseline characteristics

Characteristics	mITT (n = 68)
Median age, years (range)	65 (38-79)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
Intermediate/high-risk s-MIPI, n (%)	38 (56) Intermediate: 29 (43%), High: 9 (13%)
Median no. of prior therapies (range)	3 (1-5)
Prior auto-SCT, n (%)	29 (43)
Prior BTKi, n (%)	68 (100)

ZUMA-2 results (mITT population, n=68)

	KTE-X19
RESPONSE	
Objective response rate (CR + PR), n (%) [95% CI]	[redacted]
Complete response (CR) rate, n (%) [95% CI]	[redacted]
Partial response (PR) rate, n (%) [95% CI]	[redacted]
Progressive disease, n (%) [95% CI]	[redacted]
SURVIVAL	
Progression-free survival, median [95% CI]	[redacted]
Overall survival, median [95% CI]	[redacted]

NICE

ZUMA-2 results used in company model: PFS (data cut-off July 2019)

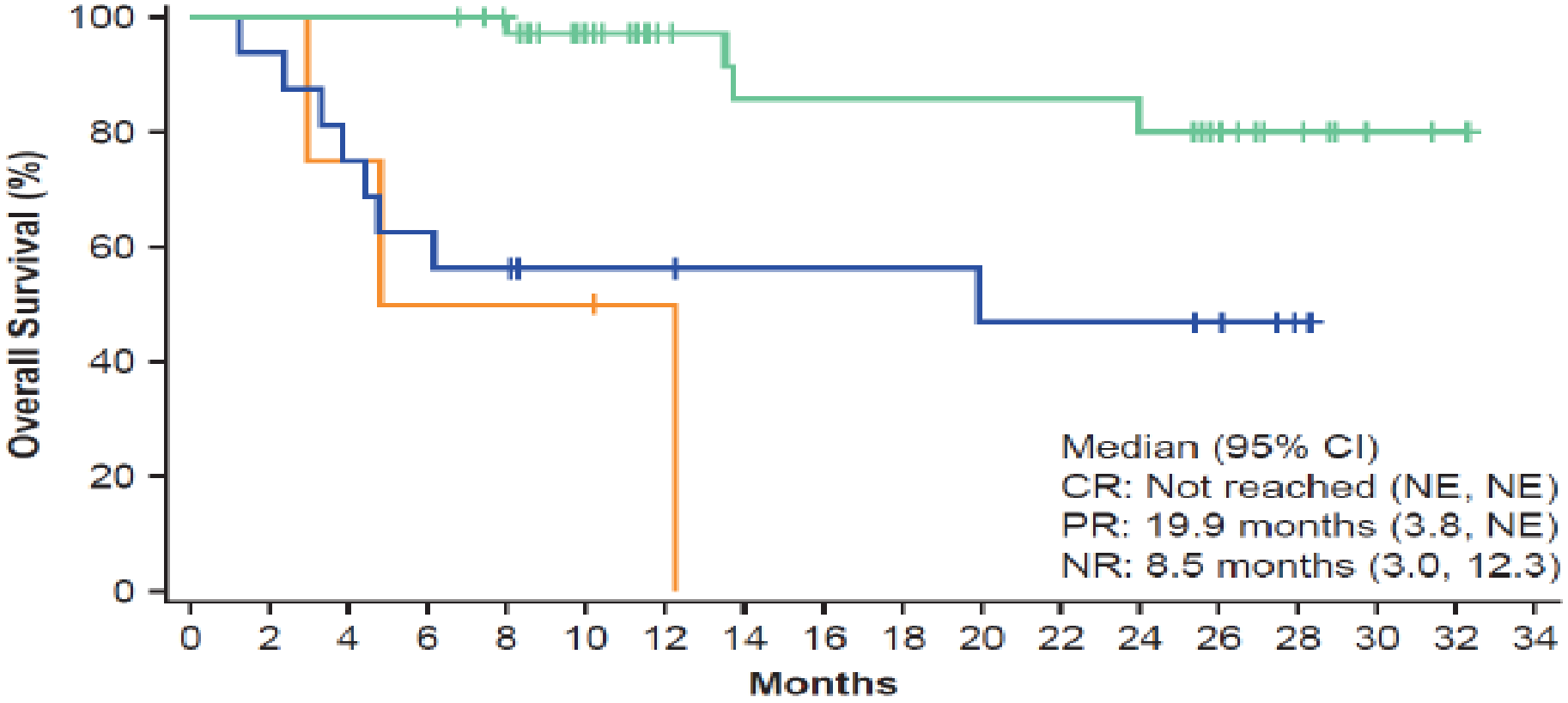
PFS using central assessment (IRRC) per IWG Lugano classification (modified intent-to-treat group)

ZUMA-2 results used in company model : OS (data cut-off July 2019)

OS (modified intent-to-treat group)

ZUMA-2 results used in company model : survival by best objective response

OS by best objective response using central assessment (IRRC) per Lugano classification (inferential analysis set)



Patients at risk

CR	40	40	40	40	35	27	19	15	15	15	15	15	14	11	6	2	1	0
PR	16	15	12	10	9	7	7	6	6	6	5	5	5	4	1	0		
NR	4	4	3	2	2	2	1	0										

Issue 1: Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice

Background

- **ERG:** ZUMA-2 population is likely to be younger and fitter than people in NHS with r/r MCL that have received previous BTKI therapy and have had 2 prior lines of therapy before treatment with KTE-X19.
- **ERG**: risk that the trial population may have a more favourable prognosis than people who would be eligible for KTE-X19

Stakeholder comments

- **Clinical expert**: most patients in clinical practice have a median of 3 prior lines of therapy are older and have a worse ECOG performance status. Patients matching ZUMA-2 eligibility criteria however do exist in clinical practice.
- **Company:** agree that mean age of 63 years is younger than expected in the UK but is likely reflective of people that would be eligible for CAR T-cell treatment in clinical practice.
- With ibrutinib as the SoC in 2nd line, it is likely that patients will have received less prior treatments before KTE-X19 in clinical practice.

How would people be selected for this treatment ?

Issue 1: Generalisibility of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice

- **ERG comments**: agree with the company that the median age and fitness status of patients with high-grade r/r DLBCL approved for CAR-T therapy through the CDF up to January 2020 presented in Kuhnl (2020) are broadly comparable to patients included in the ZUMA-1 and Juliet trials.
- Response and survival results of the real-world CAR-T cohort were not as favourable as those reported in the CAR-T pivotal trials
- ERG scenario analyses show that even small variations in mean baseline age at treatment initiation can have a significant impact on ICER estimates.
- Access to KTE-X19 for eligible r/r MCL patients via the CDF would significantly reduce the uncertainty associated with the generalisability of ZUMA-2 results to patients who would receive KTE-X19 in NHS clinical practice

Are the results of ZUMA-2 generalisable to people who would be eligible to receive KTE-X19 in NHS clinical practice?

Issue 4: Long term survival data from ZUMA-2

Background

- PFS and OS data from ZUMA-2 is immature. Median PFS and OS were not reached and median follow-up was [redacted] months.

- **Company:** results show an extension to life for patients experiencing a complete response (CR) to KTE-X19, i.e. no detectable disease, compared with partial response (PR). Assumption of long-term survivorship based on:
  - plateau in the Kaplan-Meier (KM) curves,
  - precedent from company submissions in previous appraisals of CAR T-cell therapies (used for r/r B-cell acute lymphoblastic leukaemia and r/r DLBCL)

- **ERG**: plateaus in the KM curves are not robust evidence of the extent of long-term survivorship following KTE-X19 because of censoring and short follow-up.
- No evidence of cure with standard care in MCL (in contrast with DLBCL): Eskelund et al reports that, of the 90% patients with CR or unconfirmed CR after auto-SCT in 1st line, ~50% had progressed/relapsed at 12 years.
- Evidence of cure with CAR T-cell therapy in r/r DLBCL is uncertain given short follow-up (e.g. < 3 years in ZUMA-1 trial)

Issue 4: Long term survival data from ZUMA-2

Stakeholder comments
Clinical expert:

- High CR rates in ZUMA-2 show strong proof of principle of efficacy of KTE-19
- Trial follow up is far too short to talk about cure. Want to see follow-up of minimum 3 years
- PET-CT scans were used in the trial (and often aren't in clinical practice). PET-CT : may increase the rate of CR diagnosis.
- 30% of people with CR might end up being cured.

Stakeholder comments
Company

- ZUMA-2 only source of direct evidence.
- Expected at least a proportion of patients will experience long-term survivorship following KTE-X19 treatment
- 3-year survival data from ZUMA-1: 4 deaths since the 2-year follow-up (patients at risk, n=51). No such survival curve plateau is observed with conventional immunochemotherapy
- Updated ZUMA-2 results in Dec 2019 (median follow-up in the mITT group of [redacted] months) -median OS has still not been reached, and the estimated 36-month OS rate of [redacted] (compared to estimated 24-month OS rate of [redacted] in previous data cut) results in an extended Kaplan-Meier plateau and further supports the belief of long-term survivorship.
- The estimated 24-month PFS rate slightly reduced from [redacted] to [redacted] and the estimated 33-month PFS rate was [redacted].

Issue 4: KM curves for PFS and OS using original and new data-cut (mITT, n=68)

Issue 4: Long term survival data from ZUMA-2

ERG comments

- ZUMA-2 data are associated with considerable uncertainty (small sample size, short follow-up and extent of censoring**)**
- Updated data from ZUMA-2 from 31st Dec 2019 was not used in the company's revised model but demonstrates that there is less than [redacted] of the original sample at risk at [redacted] months for PFS and at approximately [redacted] months for OS (calculated based on data in revised model)
- Despite additional data, the follow-up is still insufficient to robustly support an assumption of long-term survivorship.
- Data on CAR T-cell therapy in r/r DLBCL (including DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma) is immature (available follow-up is less than 3 years). The extent of long-term remission with CAR T-cell therapies in r/r DLBCL is therefore uncertain, as well as its generalisability to long-term remission in r/r MCL.

Are the data on long term survival robust?

Key issues (Clinical effectiveness)

Issue 1

- Are the results of ZUMA-2 (mean age of 63 years, median of 3 prior therapies, 100% with an ECOG 0/1 and 43% having received a stem cell transplant) generalisable to people eligible to receive KTE-X19 in the NHS?
- How would people be selected for treatment with KTE-X19 and are they easily identifiable in the NHS?

Issue 4

- Is relapsed or refractory mantle cell lymphoma curable?
- Do the Kaplan-Meier curves from ZUMA-2 support the possibility of long-term cure?
- Could only people who achieve a complete response have the potential for cure?
- Does the additional data from December 2019 cut-off reduce uncertainty in the results and support assumption of long term cure following treatment with KTE-X19?

Key issues (cost effectiveness)

- **Issue 7 mortality risk adjustment:** is it more appropriate to base the excess mortality risk of long-term survivors of r/r MCL post KTE-X19 on data from people with MCL or from people with diffuse large B-cell lymphoma (DLBCL)?
  - **Company's base-case**: mortality adjustment (hazard ratio = 1.09) compared to the age- and sex-matched general population, sourced from Maurer et al. in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months.
  - **ERG base-case**: mortality adjustment (hazard ratio = 2.36 to 4.37) based on an analysis of Eskelund et al. published data, reporting the long-term survival of newly diagnosed MCL patients mostly treated with autologous stem cell transplant and who achieved complete remission for 1 or 5 years (n=160).

The impact of uncertainty is related to:

- **Issue 5 age at treatment initiation:** is the mean age of 63 years in the ZUMA-2 population reflective of the age of patients with relapsed or refractory mantle cell lymphoma that are likely to be treated with KTE-X19 in NHS clinical practice
- **Issue 8 health-related quality of life in the long-term**: would long term survivors experience the same health related quality of life as the age-and sex-matched general population i.e. they would be considered cured and to have the same mortality risk as the general population?

Company's revised model (post technical engagement)

Characteristics	Company's revised model
Model type	3-state partitioned survival model With decision tree to account for long-term outcomes and costs of patients who had leukapheresis but who did not receive KTE-X19
Population	mITT population from ZUMA-2 (24th July 2019 cut-off) • Mean age = [redacted] years • [redacted] female • Average body weight = [redacted] Kg
Intervention	KTE-X19
Comparators	Standard of care, assumed to be R-BAC

Company's revised base-case	Discounted costs		Discounted QALYs		ICER (£/QALY)
	KTE-X19	SoC	KTE-X19	SoC	
List price	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Simple discount PAS*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAS + CDF risk sharing scheme*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*[redacted]

NICE

Issue 7: Excess mortality risk experienced by long-term survivors

Background

- In the revised company's model, patients who had KTE-X19 and survived beyond the ZUMA-2 trial follow-up are assumed to experienced the age- and sex-matched general population mortality, adjusted with a mortality adjustment to represent their excess mortality risk.

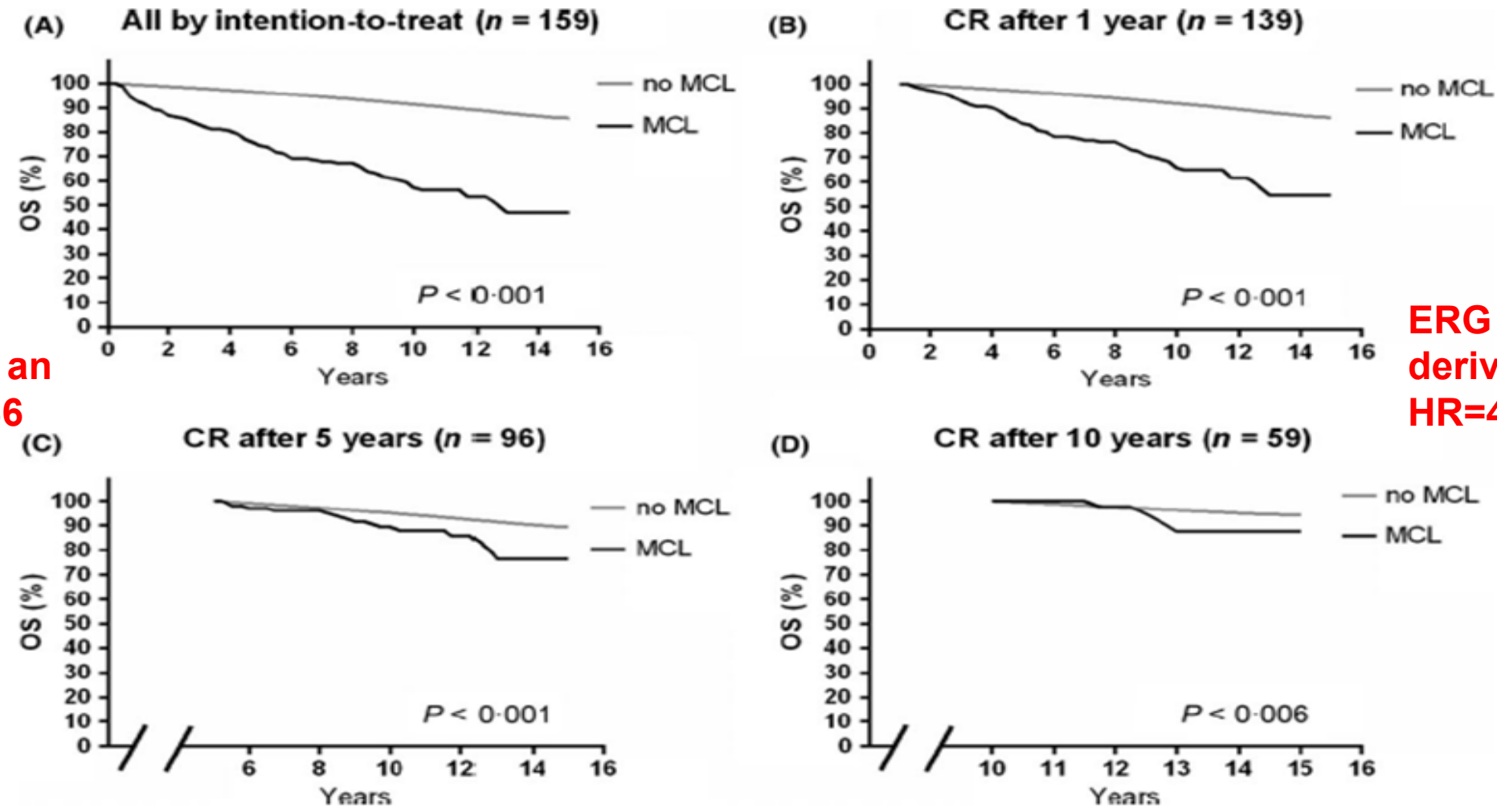
- **Company**: long-term KTE-X19 survivors have a 9% higher probability of death compared to the general population
- Sourced from Maurer et al. in people with DLBCL (n=820) who were event-free at 24 months
- Maurer et al was used in TA559.
- Used to reflect the negative impact of prior treatment on survival, even if cured.

Issue 7: Excess mortality risk experienced by long-term survivors

- **ERG:**
  - Precedent from TA559 in another condition is not a valid justification.
  - ERG's clinical advisors considered that:
    - the excess mortality risk from DLBCL is not generalisable to r/r MCL
    - the excess mortality risk compared to the general population is likely to be higher in r/r MCL than in DLBCL.
  - More appropriate to base the adjustment on data from people with MCL rather than on people with DLBCL.
  - Eskelund et al reports the follow-up of newly diagnosed patients with MCL (n=160) after first line treatment with chemotherapy followed by autologous SCT for up to 15 years (median follow-up = 11.4 years).
  - ERG derived hazard ratios from the OS curves comparing age- and sex-matched general population with MCL patients in complete remission for at least 1 year (HR=4.37) and at least 5 years (HR=2.36).
  - It is possible that excess mortality for people treated with KTE-X19 is similar to those with MCL who achieved and sustained CR, regardless of whether this was via stem cell transplant or CAR-T cell therapy.
  - **ERG uses the lower and higher hazard ratio, estimated from Eskelund, as the lower and upper mortality range of the excess mortality adjustment, and presents results as a range**.

Issue 7: Survival in the Eskelund et al study compared to the general population (reproduced from Figure 3 in the original paper)

ERG derived an HR =2.36



ERG derived an HR=4.37

Fig 3. Conditional survival of the MCL2 patients compared to the estimated survival, had they not acquired MCL (based on data from the Human Mortality data base; http://www.mortality.org). (A) All patients. Patients in first complete remission after (B) 1 year, (C) 5 years and (D) 10 years, respectively. In (C) and (D) the *x*-axis has been adjusted to match the curves starting at 5 and 10 years, respectively. MCL, Mantle cell lymphoma; CR, complete remission; OS, overall survival.

Company's revised base-case after technical engagement compared with ERG base-case

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
Company's revised base-case Mortality adjustment = 1.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case Mortality adjustment 2.36-4.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: [redacted]

Issue 7: Excess mortality risk experienced by long-term survivors

Stakeholder comments after TE
Clinical expert:

- The risk of death is expected to be slightly higher in a heavily pre-treated r/r MCL population than in a front line DLBCL population. Long-term KTE-X19 survivors experiencing a 9% higher probability of death compared to the general population is probably reasonable.
- Death rate in the short term will be probably higher in patients with r/r DLBCL than r/r MCL.
- Eskelund data suggests that patients still have a higher overall mortality that the general population, but this is in the context where patients are known to **not** be cured. Neither Eskelund nor Maurer are truly comparable.

Stakeholder comments after TE
Company

- Lack of evidence on the excess mortality risk also occurred in NICE TA559 in which committee accepted the assumption that long-term survivors are at 9% greater risk of death than the age- and sex-matched general population, based on Maurer et al.
- Longer-term data from ZUMA-2 supports long-term survival. Further ZUMA-2 data collection via the CDF can better inform assumptions for this issue.
- Patients in Eskelund et al were treated with autologous SCT which can not be expected to achieve the same response rate and length of remission as KTE-X19.
- ERG's method for deriving estimates for long-term excess mortality has limitations. The quality of the KM curves from which the hazard ratios have been produced is poor. Censoring points are not shown, nor are changes in the number remaining at risk over time.
- Independent reproduction of ERG analysis produced different HR values estimates highlighting the inherent uncertainty

Issue 7: Excess mortality risk experienced by long-term survivors

- **In critique post-TE, ERG re-iterated previous comments:**
  - Precedent in another condition is not a valid justification
  - Advice from ERG clinical advisors
  - Advantages of Eskelund-based adjustment outweigh downsides because it refers to MCL patients who achieved complete remission (vs. Maurer et al in DLBCL)
- ERG conducted scenario analysis using the lower and upper bound of the company's estimated HRs based on Eskelund et al
- ERG conducted univariate sensitivity analysis to the mortality adjustment

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
ERG base-case Mortality adjustment 2.36-4.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario Mortality adjustment 2.07-4.45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note : [redacted]

Issue 7: Excess mortality risk experienced by long-term survivors

Issue 5: Uncertainty in age at treatment

Background

- Cost effectiveness analysis is very age dependent
- Impact depends on the extent to which the age of the patient population in clinical practice departs from the patients in ZUMA-2.
- Driven mostly by the general population mortality risk, used to inform the mortality risk of long-term survivors in the company's base-case
- Also affects age adjustment to health-related quality of life (HRQoL), and to the generalisability of the HRQoL data from ZUMA-2.

Stakeholder comments

Clinical expert:

- ZUMA-2 median age (65 years) approximately 8-10 years younger than typical population having had 3 prior lines of treatment for MCL.

Company

- CAR T-cell therapy generally only suitable for fitter patients.
- Patients receiving KTE-X19 should undergo same rigorous selection criteria as currently available CAR T-cell treatments, resulting in a younger population.
- UK real world evidence to date- of 183 patients with R/R DLBCL treated with CAR T-cell treatments, median age is 57.
- This was consistent with the median ages of patients in the ZUMA-1 (for axicabtagene ciloleucel) and Juliet (for tisagenlecleucel) pivotal studies, where the median ages were 58 and 56 respectively.
- Therefore, median age of 65 is reflective of patients potentially eligible for KTE-X19.

Issue 5: Uncertainty in age at treatment

ERG comments

- Considerable difference in age between ZUMA-2 (median age 65 years) and age of MCL patients at diagnosis in the UK (median age 72.9 years). **Mean** age of patients in ZUMA-2 (used in economic analysis) is 63.2.
- Agree with the company that the population eligible for KTE-X19 is likely to be significantly younger and fitter than the broader r/r MCL population in clinical practice.
- Agree with the company that median age of patients with r/r high grade lymphoma treated with CAR-T through CDF to date is comparable with Zuma-1 and Juliet trial populations.
- Unclear whether the same difference in age between real-world and trial data would be observed for the r/r MCL population.
- ERG illustrative scenario analyses show that even small variations in mean baseline age has a significant impact on ICER

	Discounted costs		Discounted QALYs		
Scenario	KTE-X19*	SoC	KTE-X19	SoC	ICER*
ERG base-case Mean age = 63.2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario Mean age = 65.2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario Mean age = 73.2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* [redacted]

Issue 5: Age at treatment of patient population

ERG comments

- Considerable difference in age between ZUMA-2 (median age 65 years) and age of MCL patients at diagnosis in the UK (median age 72.9 years). **Mean** age of patients in ZUMA-2 (used in economic analysis) is 63.2.
- Agree with the company that the population eligible for KTE-X19 is likely to be significantly younger and fitter than the broader r/r MCL population in clinical practice.
- However, median age of patients with r/r high-grade lymphoma receiving CAR-T therapy through the CDF up to July 2019 is higher than that of phase II CAR-T trials in large B-cell lymphoma (median 62 years versus 58 and 56 in Zuma-1 and Juliet trials respectively).
- Unclear whether the same difference in age between real-world and trial data would be observed for the r/r MCL population.
- ERG scenario analyses show that even small variations in mean baseline age has a significant impact on ICER
- An additional scenario after technical engagement using company's revised model follows

Issue 8: Uncertainty in health related quality of life (HRQoL) of long-term survivors

Background

- **Company** model assumes patients who have not progressed at 5 years following KTE-X19 have the same HRQoL as the general population.
- **ERG** considers trial data insufficient to support this assumption and considers this to be a significant area of uncertainty.
- ERG uses this assumption in its base-case but explores alternative lower QoL estimates for people progression free for 5 years and in scenario analyses which increase the ICERs

Stakeholder comments

- **Clinical expert**: Long-term survivors will have slightly higher mortality and a worse HRQoL. Causes: secondary solid tumours, cardiovascular mortality, infections, secondary blood cancers. They will have had 4 lines of treatment for MCL. Even if 'cured' this will have an effect. We know there are some issues with longer term immunosuppression/infection risk post CAR-T.
- **Company:** view not provided as question was considered unclear

Issue 8: Uncertainty in health related quality of life of long-term survivors

ERG comments

- If long-term survivors are at an excess risk of mortality compared to the general population, their HRQoL may also be affected, and be lower than the HRQoL of the general population.
- Illustrative scenario analysis reducing HRQoL by 10% and 20% of long-term survivors compared to the age- and sex-matched general population.

	Discounted costs		Discounted QALYs		
Scenario	KTE-X19	SoC	KTE-X19	SoC	ICER
ERG base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario HRQoL reduced by 10%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario HRQoL reduced by 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: [redacted]

Revised ERG base case after technical engagement

- The ERG maintains that, despite the limitations and uncertainties, Eskelund et al. is a more appropriate source of evidence to inform the mortality adjustment given that it refers to patients with MCL who were in complete remission, albeit newly diagnosed and who received a different treatment and incorporate this in their base-case
- Longer follow up of ZUMA-2 has the potential to address the uncertainties relating to the PFS and OS extrapolation and around the excess mortality risk, depending on the maturity of the data.
- Different mortality risk adjustments used is the main difference between company and ERG base-case.

Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
Company's revised base-case Mortality adjustment = 1.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case Mortality adjustment 2.36-4.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: [redacted]

Company's revised base-case after technical engagement compared with ERG base-case including simple PAS and outcome base rebate

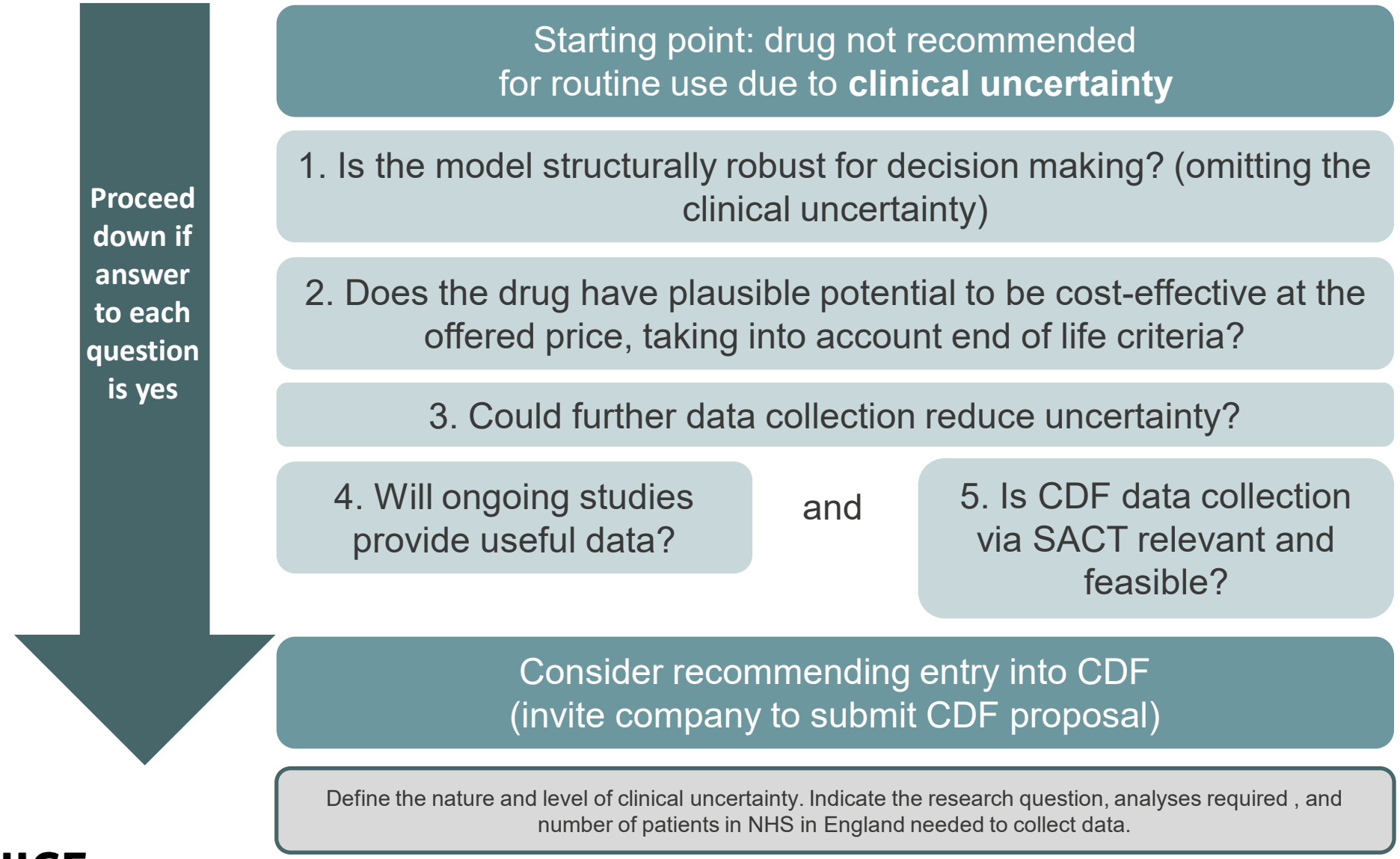
Scenario	Discounted costs		Discounted QALYs		ICER (KTE-X19 vs SoC)
	KTE-X19	SoC	KTE-X19	SoC	
Company's revised base-case Mortality adjustment = 1.09	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base-case Mortality adjustment 2.36-4.37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: [redacted]

End of Life

- The company considers KTE-X19 to be an end-of-life therapy, arguing that it satisfies both criteria that
  - **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 with current NHS treatment.**
- Expected survival without KTE-X19; Company and ERG agree 24 month survival criterion met
- Extension to life with KTE-X19 was based on survival estimates from MAIC modelling and from the company economic model. The ERG found that the assumption holds in the ERG base
- Therefore **end of life criteria** met.

Committee decision making: CDF recommendation criteria



NICE

Key issues (cost effectiveness)

- **Issue 7 mortality risk adjustment:** is it more appropriate to base the excess mortality risk of long-term survivors of r/r MCL post KTE-X19 on data from people with MCL or from people with diffuse large B-cell lymphoma (DLBCL)?
  - **Company's base-case**: mortality adjustment (hazard ratio = 1.09) compared to the age- and sex-matched general population, sourced from Maurer et al. in a cohort of French newly diagnosed patients with DLBCL (n=820) who were event-free at 24 months.
  - **ERG base-case**: mortality adjustment (hazard ratio = 2.36 to 4.37) based on an analysis of Eskelund et al. published data, reporting the long-term survival of newly diagnosed MCL patients mostly treated with autologous stem cell transplant and who achieved complete remission for 1 or 5 years (n=160).

The impact of uncertainty is related to:

- **Issue 5 age at treatment initiation:** is the mean age of 63 years in the ZUMA-2 population reflective of the age of patients with relapsed or refractory mantle cell lymphoma that are likely to be treated with KTE-X19 in NHS clinical practice
- **Issue 8 health-related quality of life in the long-term**: would long term survivors experience the same health related quality of life as the age-and sex-matched general population i.e. they would be considered cured and to have the same mortality risk as the general population?

Backup slides

Issues resolved after technical engagement and updated in revised model

	Summary	Stakeholder responses
2	**Blended SoC comparator** • Based on clinical expert opinion, the company considered SoC comprising of 65% rituximab-bendamustine cytarabine (R-BAC), 30% rituximab plus bendamustine (R-bendamustine), and 5% rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) as representative of clinical practice in the UK • The ERG considered the use of McCulloch et al. 2020 alone is more appropriate as the study best represents the patient population in the NHS. The study reports appropriate survival data, used R-BAC in the UK and avoids issues around the heterogeneity of the identified SoC studies. • For the purposes of costing, the revised company's base-case aligns with the ERG's preferred assumption of R-BAC.	R-BAC is the most well recognised SoC in people who have had anthracycline (nearly all <65 years and many over)
3	**Indirect treatment comparison** • Due to lack of direct evidence comparing KTE-X19 to a SoC comparator, an indirect treatment comparison was conducted by the company originally. • Indirect comparisons were severely limited by the paucity of evidence and were subject to significant risk of bias and uncertainty. • ERG considered the study population in McCulloch et al. more representative of the NHS population expected to receive KTE-X19. • Revised model uses McCulloch et al. (2020) as the single source of data to inform the progression-free and overall survival with SoC.	Indirect comparison results are plausible and in line with standard clinical practice.

Issue 1: Characteristics and results of real-world CAR-T data and pivotal trials in r/r large B-cell lymphoma

	ZUMA-1 (Phase 2, n=101)	Juliet (n=111)	Kuhnl (2020) (n=183)
Median age (range)	58 (51–64) Note, range is IQR	56 (22-76)	57 (18-75)
Male %	68 (67%)	Not reported	61%
Prior therapies			
1	3 (3%)	5 (5%)	
2	28 (28%)	49 (44%)	
3+	70 (69%)	57 (52%)	41%
Stage III/IV	85%	76% (Stage III, 20%; Stage IV (56%)	76%
ECOG 0/1	100% (42%/58%)	100% (55%/45%)	100% (48%/52%)
PR/CR	74% (IRC assessed)	52%	42%
CR	54%	40%	29%
Median PFS (95% CI)	5.9 months (3.3-15.0)	Not reported	3.2 months (3.0-4.6)
Median OS (95% CI)	Not reached at 2 yrs	8.3 months (5.8-11.7) (mITT)	8.1 months (7.0-10.0) (mITT)

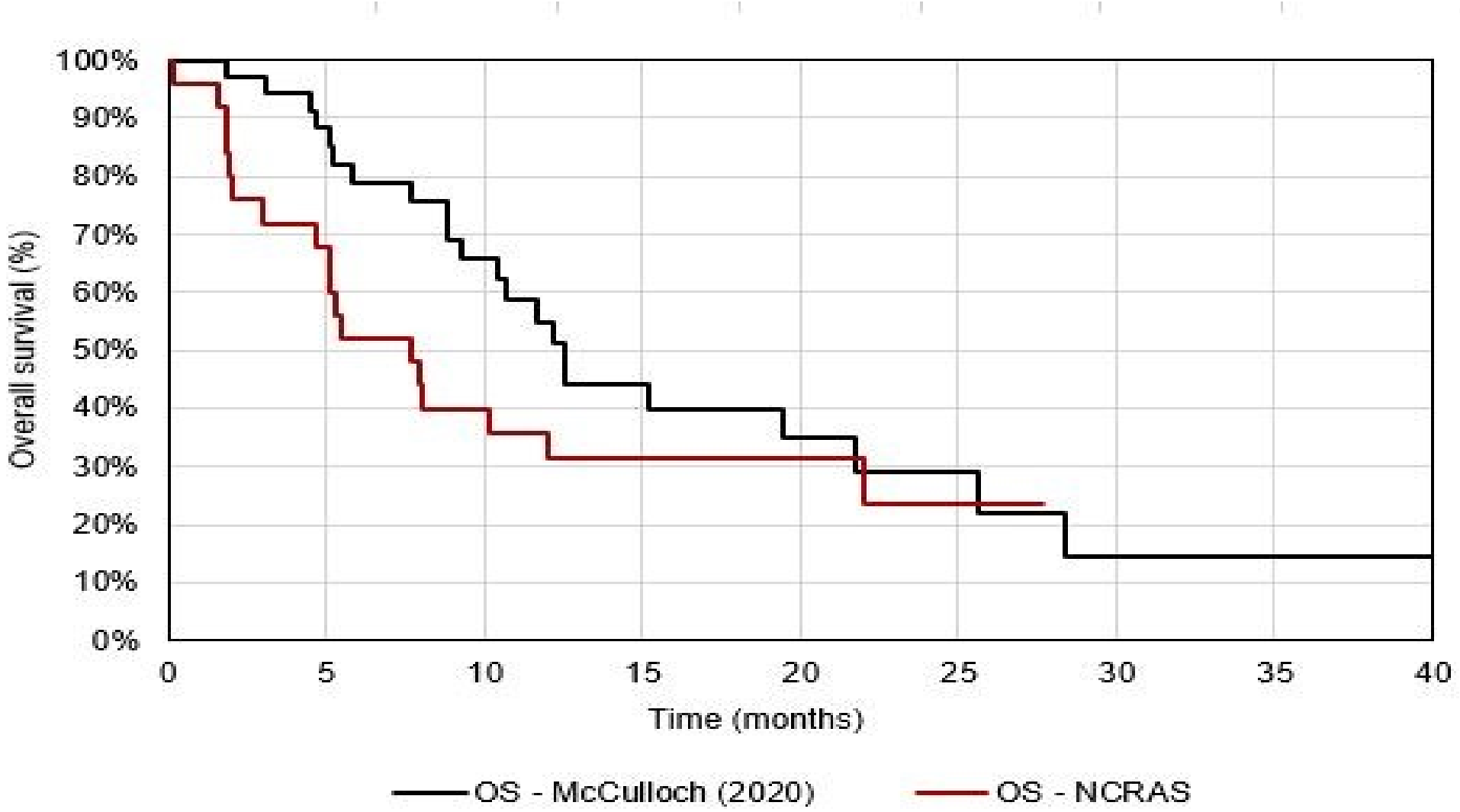
Additional evidence after technical engagement

- The company submitted additional data for validation purposes only. The data is not updated in the cost-effectiveness analysis:
  - Efficacy data for standard of care – overall survival data based on the National Cancer Registration and Analysis Service (NCRAS) dataset
  - Efficacy data for KTE-X19 – data from the ZUMA-2 trial with an additional 6 months' follow-up (Dec 2019 data-cut)
- Company notes that had the NCRAS data been included in the model, it may have reduced the ICER estimates for KTE-X10 as survival outcomes in clinical practice are poorer than reported in McCulloch et al.
- NCRAS data includes a retrospective cohort review of 58 patients with MCL who failed BTKi, then received subsequent treatment from NCRAS dataset in England. Of these patients: 8 (13.8%) had been treated with BTKi at 1st line; 25 (43.1%) at 2nd line and 25 (43.1%)at 3rd + line.
- The starting point for tracking was at the start of treatment initiated following BTKi. OS results for the McCulloch 2020 population which included post-BTKi high-grade MCL patients receiving R-BAC, were fitted in a naïve unadjusted comparison.
- The KM curves show poorer survival outcomes for the NCRAS BTKi failure cohort compared with McCulloch 2020, with curves converging at approximately 20 months. The median OS in the BTKi cohort was 8.1 months (7.8 months in the 25 patients who received BTKi at second line). In comparison, patients receiving R-BAC in McCulloch 2020 had a median OS of 12.5 months.

Additional evidence after technical engagement- baseline characteristics of NCRAS (BTKi failure), ZUMA-2 and McCulloch 2020

	ZUMA-2 (mITT) (n=68)	McCulloch 2020 (n=36)	NCRAS (n=58)
Mean age	63	65.2 (at start of R-BAC)	67
Median age	65	66 (at start of R-BAC)	70
Prior therapies			
1	1 (1%)	2 (5.6%)	8 (13.8%)
2	12 (18%)	30 (83.3%)	25 (43.1%)
3+	55 (81%)	4 (11.1%)	25 (43.1%)
		Note, at initial diagnosis	Note, line at which BTKi was used
Stage III/IV	97% (Stage III, 12%; Stage IV, 85%)	100% (no break down by III and IV)	77.5% (Stage III, 60.3%; Stage IV 17.2%)
ECOG 0/1	100% (ECOG 0: 65%, ECOG 1: 35%)	80% Note, at start of R-BAC	96% (data on 50 patients available only)
Median OS	NR (median follow up = 11.6 months)	12.5 months	8.1 months

Additional evidence after technical engagement-OS for patients who failed 2nd-line BTKi: NCRAS data versus McCulloch 20



Additional evidence after technical engagement- ERG critique of NCRAS data

- NCRAS BTKi failure cohort is not directly comparable with cohort included in McCulloch 2020, nor with the ZUMA-2 population due to significant differences in patient characteristics
- The NCRAS BTKi failure cohort was significantly older on average (mean/median age 67/70 years) compared with the ZUMA-2 mITT (63/65 years) and McCulloch 2020 populations (65/66 years).
- Nearly half of patients (approximately 47%) in the NCRAS population were 71 years old or above, and about 10% were 81 years old or above. Conversely, NCRAS patients had fewer prior therapies overall, and the proportion of stage III/IV patients was lower.
- Given these differences in key prognostic characteristics and the absence of adjustments for covariates in the company's additional analyses (such as treatment post-BTKi), the ERG believe that the comparison between NCRAS and McCulloch 2020 cohorts is at high risk of confounding and unlikely to be reliable.
- Incorporating the NCRAS data would not likely significantly reduce the ICER estimates for KTE-X19.

Additional evidence after technical- Follow-up analyses of ZUMA-2 (Dec 2019 cut-off)

- Additional 6 months data was submitted for (1) response and duration of response, (2) PFS and 3) OS for the inferential analysis (IAS) set and for the modified intention to treat group.
- The IAS set (n=60) corresponds to the 1st 60 patients treated with KTE-X19 at the licensed dose. In the Dec 2019 data cut-off, the median follow-up is [redacted] months. The mITT (n=68) corresponds to patients who received KTE-X19 at the licensed dose. In the Dec 2019 cut-off, the median follow-up is [redacted] months.

PFS

Data set	n	progressed or died	24-month PFS rate	33-month PFS rate
IAS (all patients	60	[redacted]	[redacted]	[redacted]
mITT (all patients)	68	[redacted]	[redacted]	[redacted]

OS

Data set	n	progressed or died	24-month PFS rate	33-month PFS rate
IAS (all patients	60	[redacted]	[redacted]	[redacted]
mITT (all patients)	68	[redacted]	[redacted]	[redacted]

ZUMA-2: PFS and OS (data cut-off Dec 2019)

Additional evidence after technical- comparison of additional data to survival curves predicted by the cost-effectiveness model

- Across all responders (n=[redacted] in IAS, n= [redacted] in mITT), [redacted]% of IAS participants ([redacted]% mITT) remained in response at the time of follow-up analyses.
- The ERG note that the CR rate maintaining is positive but additional data on PFS and OS is limited especially accounting for the extent of censoring and the small number of patients at risk.
- KM curves and the model predictions for OS and PFS for alternative mortality adjustments, namely 1.09, based on Maurer et al as preferred by the company (A) and 4.45 (B) based on the company's analyses of Eskelund et al. show that substantial uncertainty remains.

A

B