Cost-effectiveness for KTE-X19 CAR T therapy for adult patients with relapsed/refractory mantle cell lymphoma in the United States

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Aims: The objective of this study is to estimate the cost-effectiveness of KTE-X19 versus standard of care (SoC) in the treatment of relapsed/refractory (R/R) mantle cell lymphoma (MCL) patients from a US healthcare perspective.

Materials and methods: A three-state partitioned-survival model (pre-progression, post-progression, and death) with a cycle length of 1 month was used to extrapolate progression-free and overall survival (OS) over a lifetime horizon. Due to the long tail of the OS curve, OS was modeled applying a mixture–cure methodology, using the assumption that patients whose disease had not progressed after 5 years experienced long-term remission. Population inputs were derived from the ZUMA-2 trial. This was also the source of KTE-X19 efficacy and safety data, while this data was obtained from the literature. Costs and resource use inputs were derived from the published literature and publicly available data sources. Health state utilities were derived from the ZUMA-2 trial (NCT02601313), applying the US tariff. Adverse event disutilities were derived from the published literature. Costs and health outcomes were discounted at 3% per year. The model estimated expected life years (LY), quality-adjusted life years (QALY), and total costs for KTE-X19 vs SoC. Deterministic and probabilistic sensitivity analyses were performed.

Results: Median survival was 9.71 years for KTE-X19 and 2.13 for SoC. Discounted LYs, QALYs, and lifetime costs were 8.99, 7.39, and $693,832 for KTE-X19 vs 4.47, 3.65, and $574,263 for SoC, respectively. The KTE-X19 vs SoC cost per QALY was $31,985. The most influential model parameter was the utility for patients with long-term remission. At a willingness-to-pay threshold of $150,000 per QALY, the probability that KTE-X19 was cost-effective was 99%.

Conclusion: The treatment of R/R MCL with KTE-X19 presents a potentially cost-effective alternative to the current SoC, deriving its value from incremental survival and health-related quality-of-life benefits.

Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma (NHL). In the US, MCL accounts for up to 6% of all NHL diagnoses annually. The US population’s incidence of MCL has increased from 0.80 persons per 100,000 per year in 1995–1999 to 1.15 persons per 100,000 per year in 2009–2013. Most patients with MCL relapse after first-line therapy (chemo-immunotherapy with/without autologous stem cell transplant). Subsequently, these patients experience reduced survival, with a median progression free survival (PFS) on standard of care (SoC) following relapse of less than 2 years. Similarly, only one-third of patients who receive allogeneic stem cell transplant (alloSCT) experience long-term survival.

In the US, preferred treatment options for patients with relapsed or refractory (R/R) MCL are outlined in the National Comprehensive Cancer Network (NCCN) guidelines and differ depending on the duration of response to prior chemomunotherapy. Preferred regimens for patients with a short response duration are Bruton tyrosine kinase (BTK) inhibitors (acalabrutinib, ibrutinib with or without rituximab, zanubrutinib), lenalidomide with or without rituximab, or venetoclax single agent. For patients with an extended response duration to prior chemomunotherapy, preferred regimens comprise BTK inhibitors and lenalidomide with or without rituximab, as well as bendamustine or bortezomib, each with or without rituximab. Additional regimens are available for both groups, with alloSCT considered as a consolidation strategy for patients in remission following treatment for R/R MCL. Ultimately, the choice of regimen is influenced by prior therapy, comorbidities, and tumor chemosensitivity. Nonetheless, intolerances and treatment failures, especially as patients move into later lines of therapy, present a challenge for clinicians.

ABSTRACT

Aims: The objective of this study is to estimate the cost-effectiveness of KTE-X19 versus standard of care (SoC) following relapse of less than 2 years.

Materials and methods: A three-state partitioned-survival model (pre-progression, post-progression, and death) with a cycle length of 1 month was used to extrapolate progression-free and overall survival (OS) over a lifetime horizon. Due to the long tail of the OS curve, OS was modeled applying a mixture–cure methodology, using the assumption that patients whose disease had not progressed after 5 years experienced long-term remission. Population inputs were derived from the ZUMA-2 trial. This was also the source of KTE-X19 efficacy and safety data, while this data was obtained from the literature. Costs and resource use inputs were derived from the published literature and publicly available data sources. Health state utilities were derived from the ZUMA-2 trial (NCT02601313), applying the US tariff. Adverse event disutilities were derived from the published literature. Costs and health outcomes were discounted at 3% per year. The model estimated expected life years (LY), quality-adjusted life years (QALY), and total costs for KTE-X19 vs SoC. Deterministic and probabilistic sensitivity analyses were performed.

Results: Median survival was 9.71 years for KTE-X19 and 2.13 for SoC. Discounted LYs, QALYs, and lifetime costs were 8.99, 7.39, and $693,832 for KTE-X19 vs 4.47, 3.65, and $574,263 for SoC, respectively. The KTE-X19 vs SoC cost per QALY was $31,985. The most influential model parameter was the utility for patients with long-term remission. At a willingness-to-pay threshold of $150,000 per QALY, the probability that KTE-X19 was cost-effective was 99%.

Conclusion: The treatment of R/R MCL with KTE-X19 presents a potentially cost-effective alternative to the current SoC, deriving its value from incremental survival and health-related quality-of-life benefits.
therapy, are common. Outcomes are especially poor in patients who progress after BTK inhibitor therapy, and suggests the need for the introduction of new treatments to the R/R MCL treatment paradigm.

KTE-X19 is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy. It recently obtained approval through the FDA accelerated approval process for the treatment of adults with R/R MCL in the US, contingent on the confirmatory trial. KTE-X19 was investigated in the phase 2, multicenter, open-label ZUMA-2 trial (NCT02601313) in patients with R/R MCL. The trial showed remission with KTE-X19, with an independent review committee objective response rate of 93% and a complete response rate of 67%. Median duration of response, PFS, and overall survival (OS) were not reached with a minimum follow-up of 12.3 months with KTE-X19. Evaluations of outcomes over longer follow-up are underway.

This paper investigates the comparative effectiveness and cost-effectiveness of KTE-X19 vs SoC, comprising cytotoxic chemotherapy, proteasome inhibitors, immunomodulatory drugs, Bcl-2 protein inhibitors, and BTK inhibitors in the treatment of R/R MCL patients, based on evidence synthesized from the ZUMA-2 trial and the literature. To this end, a three-state partitioned survival model, utilizing a mixture cure modeling (MCM) methodology, was developed. The analyses were conducted from a US payer perspective.

Materials and methods

Overview

The population for the cost-effectiveness analysis reflected the ZUMA-2 population. Model inputs included important predictors of survival and costs, such as age, sex, body surface area, body weight, and US-specific background mortality rates. To reflect the current SoC as outlined in the NCCN guidelines, a basket comparator was used, comprising cytotoxic chemotherapy (bendamustine), proteasome inhibitors (bortezomib), immunomodulatory drugs (lenalidomide), Bcl-2 protein inhibitors (venetoclax), and BTK inhibitors (acalabrutinib, ibrutinib, zanubrutinib). These treatments were combined into a single basket (“SoC”) because there is no single standard of care for R/R MCL. The cost-effectiveness analysis was conducted from a US payer perspective, over a lifetime horizon with a cycle length of 1 month, and a 3% annual discount applied to costs (2020 US dollars) and health outcomes. The primary outcome of the model was the incremental cost-effectiveness ratio (ICER) of KTE-X19 vs SoC, expressed as cost per quality-adjusted life year (QALY). Additional outcomes were also presented, as well as the results from sensitivity analyses.

Model structure

A decision-analytic model (Figure 1) was developed, using a partitioned survival framework with an MCM methodology to estimate how patients transition through the pre-progression, post-progression, and death health states. The model structure mirrors the data on PFS and OS commonly reported in clinical trials, and was designed to capture the course of the disease easily with a limited number of health states. Previous studies investigating the effectiveness of CAR T therapies have identified a strong response dichotomy (“cured” and “non-cured”). These groups are latent and require the survival model to estimate a “cure fraction” to distinguish the two groups. Subsequently, the MCM methodology can be used to capture whether the overall trial survival can be explained as a function of these two groups. This means that the survival of the “cured” proportion is
assumed to be based on sex- and age-matched background mortality, while survival curves using standard parametric distributions are fitted to the “non-cured” proportion. The model estimated the pre-progression health state based on PFS. This included patients who responded completely or partially to treatment, as well as those who remained in a stable disease state. It was assumed that patients who survived and whose disease had not progressed after 5 years would experience “long-term remission”. This assumption was based on similar assumptions in previous CAR T publications in other indications. The post-progression state was estimated as the difference between PFS and OS and reflects the proportion of patients who have experienced disease progression but remain alive. The death state included all patients who have died from either R/R MCL or other causes and was estimated by OS (1 minus OS). OS was corrected for background mortality, meaning that the OS of patients in the model could not exceed that of the general population. Additionally, as advised during interviews with two external clinical experts, patients who experienced long-term remission were associated with sex- and age-matched background mortality, adjusted with a hazard ratio of 1.09 as published by Maurer et al. to account for the impact of prior treatment on survival. This implied that patients with long-term remission had a slightly higher mortality than the general population.

Survival

KTE-X19

The efficacy of KTE-X19 was based on estimates from the first data reported (24 July 2019) for the safety population \( n = 68 \), i.e. the population who received infusion, in the ZUMA-2 trial (Supplementary Figures S1 and S2). MCM methodology was used based on expert opinion, goodness of fit, their acceptance in other CAR T therapies, and recently available data indicating that a proportion of the population may be cured after treatment with KTE-X19. Standard parametric models were fitted to the data. With the exception of the generalized gamma model, the different standard parametric models demonstrated a similar model fit in terms of Akaike information criterion (AIC). The generalized gamma model did not pass face validity as the median time for PFS was greater than that for OS. The cure fractions were consistent across the other standard parametric models, as well as between OS and PFS, which increased the confidence around the validity of the models. For the base case, the exponential curve, which minimized the AIC for both OS and PFS and requires the smallest number of parameters, was selected and extrapolated over a lifetime horizon.

Standard of care

The survival of SoC was estimated through a meta-analysis, which was based on a systematic literature review. The systematic literature review was conducted in February 2019 and updated in January 2020, to identify available evidence of the efficacy and safety of NCCN guideline-recommended treatments for adult patients with R/R MCL. After a feasibility assessment was performed, the results of the review were combined in a Bayesian meta-analysis to estimate parameters for the standard parametric survival curves for PFS and OS (data on file). All standard parametric survival curves, except for the generalized gamma, were fitted. The generalized gamma was excluded as it does not allow for robust estimation when synthesizing the three parameters in a multivariate meta-analysis. As a result, the Gompertz distribution for OS and the log-normal distribution for PFS were the best fitting models based on minimizing AIC for both OS and PFS and were used for the present analysis.

Cost and resource use

KTE-X19 conditioning, infusion, and related costs and resource use

KTE-X19 consists of a single infusion of CAR transduced autologous T-cells administered intravenously at the target dose of \( 2 \times 10^6 \) anti-CD19 CAR T cells/kg. The cost of KTE-X19 was based on the manufacturer’s list price ($373,000), to which administration and associated hospitalization costs were added. Based on the ZUMA-2 trial, a mean hospitalization stay of 21.2 days was applied. Prior to receiving KTE-X19, patients underwent leukapheresis and conditioning chemotherapy, consisting of cyclophosphamide (30 mg/m² intravenous (IV)) and fludarabine (500 mg/m² IV). Acquisition and administration costs associated with these procedures were included in the model. Conditioning chemotherapy was assumed to require a non-elective hospital stay. Conjointly with leukapheresis, 36.8% of patients received bridging therapy with rituximab, bendamustine, and cytarabine for one cycle. Additionally, based on observations in the ZUMA-2 trial, the model allowed for the retreatment of patients with KTE-X19, and associated pre-treatment with leukapheresis and conditioning chemotherapy. Only 2.9% of patients in the trial received retreatment. Table 1 provides an overview of the included parameters in the model, including KTE-X19 related costs and resource use.

Standard of care and related costs and resource use

Table 1 outlines the treatment distributions used for SoC. The distribution of SoC treatments was based on data on current treatment patterns for patients with MCL in the second and third line treatment settings obtained through a survey of hematologist-oncologists in the US (data on file). The costs of each of the treatments were derived from the Red Book Online using average wholesale cost and the Centers for Medicare & Medicaid Services’ (CMS) Average Sale Price Drug Pricing file (July 2020). The treatment duration and dose of these treatments reflect the approved regimen of the respective treatment. An additional cost parameter for IV administration was included, while no additional administration costs were assumed for oral therapies. No dispensing costs were considered. Additional details showing the share of costs contributing to the total SoC
| Model parameter                                      | Value           | Reference                  |
|------------------------------------------------------|-----------------|----------------------------|
| **KTE-X19 treatment costs ($)**                      | $373,000        | Kite Pharma List Price     |
| Leukapheresis                                        | $1,437.30       | CMS (HCPCS Codes 36511 APC S242) |
| Fludarabine (conditioning chemotherapy, $/admin)     | $50.74          | CMS (HCPCS J9185)         |
| Cyclophosphamide (conditioning chemotherapy, $/admin)| $345.66         | CMS (HCPCS J9070)         |
| Rituximab (bridging therapy, $/admin)                | $2,341.50       | CMS (HCPCS J9036)         |
| Bendamustine (bridging therapy, $/admin)             | $3,089.30       | CMS (HCPCS J9036)         |
| Cytarabine (bridging therapy, $/admin)               | $11.57          | CMS (HCPCS J9100)         |
| **Standard of care treatment distributions**         |                 |                            |
| Rituximab                                           | 33.6%           | Data on file               |
| B-cell lymphoma 2 inhibitors                         | 13.1%           | Data on file               |
| Cytotoxic chemotherapy                               |                 |                            |
| Bendamustine                                        | 3.2%            | Data on file               |
| Proteasome inhibitors                                |                 |                            |
| Bortezomib                                          | 5.5%            | Data on file               |
| Immunomodulatory drugs                               |                 |                            |
| Lenalidomide                                        | 9.0%            | Data on file               |
| **Standard of care costs ($/admin)**                 |                 |                            |
| Rituximab                                           | $2,341.50       | CMS (HCPCS J9312)         |
| B-cell lymphoma 2 inhibitors                         |                 |                            |
| Venetoclax (per dose)                                | $20.49 per 20 mg administered | Red Book Online |
| Cytotoxic chemotherapy                               |                 |                            |
| Bendamustine                                        | $3,089.30       | CMS (HCPCS J9036)         |
| Proteasome inhibitors                                |                 |                            |
| Bortezomib                                          | $682.84         | CMS (HCPCS J9044)         |
| Immunomodulatory drugs                               |                 |                            |
| Lenalidomide                                        | $763.01         | Red Book Online            |
| **Bruton Tyrosine Kinase inhibitors**                |                 |                            |
| Acalabrutinib                                       | $234.40         | Red Book Online            |
| Ibrutinib                                           | $463.07         | Red Book Online            |
| Zanubrutinib                                        | $215.38         | Red Book Online            |
| **Administrative costs ($/admin)**                   |                 |                            |
| KTE-X19                                              | $113.68         | CMS (CPT code 38241)      |
| Conditioning chemotherapy                            | $7,948.11       | Assumption: inpatient non-ICU stay of 3 days |
| Intravenous                                          | $142.55         | CMS (HCPCS 96413)         |
| **Hospitalization**                                 |                 |                            |
| KTE-X19: Intensive care unit (%)                    | 22.7%           | Wang et al.                |
| KTE-X19: Non-intensive care unit (%)                | 77.3%           | Wang et al.                |
| KTE-X19: Hospitalization duration (days)            | 21.2            | Wang et al.                |
| **Hospitalization costs ($)**                       |                 |                            |
| Intensive care unit                                  | $6,675.72       | Halpern et al.             |
| Non-intensive care unit                              | $2,649.37       | Kaiser Family Foundation   |
| Health state costs ($ per cycle)                    | $1,400          | Model calculations         |
| Pre-progression                                      | $25             | Model calculations         |
| Pre-progression (long-term remission)               | $25             | Model calculations         |
| Post-progression                                     | $6,960          | Model calculations         |
| **End-of-life**                                     |                 |                            |
| Palliative care days                                 | 37              | Bennett et al.             |
| Palliative care cost per day                         | $195.00         | CMS                        |
| **Adverse event costs ($)**                         |                 |                            |
| KTE-X19                                              | $72,297         | Model calculations         |
| **Health state utility values**                      |                 |                            |
| Pre-progression                                      | 0.843           | ZUMA-2                     |
| Pre-progression (long-term remission)               | 0.843           | ZUMA-2                     |
| Post-progression                                     | 0.743           | ZUMA-2                     |

**The treatment distributions for SoC sum to more than 100% as patients can be given combination treatment. *Model calculations are outlined in Supplementary Table S2.**

a One dose every 4-week cycle until progression or maximum six cycles.
b Daily dose of venetoclax until progression, starting at 20 mg daily and ramping up weekly to 750 mg by week 713.
c Two doses every 4-week cycle until progression or maximum six cycles.
d Four doses every 3-week cycle for nine cycles or until progression.
e Daily dose for 3 weeks every 4-week cycle until progression.
f One capsule twice daily until progression.
g One tablet daily until progression.
costs for each drug in the regimen are shown in Supplementary Table S3.

Adverse events
Grade 3/4 adverse events with an incidence of at least 5%, as well as grade 2 and higher cytokine release syndrome (CRS) events associated with KTE-X19 treatment as reported in ZUMA-2 were included in the model (Supplementary Table S1). Pyrexia, hypoxia, hypophosphatemia, hyponatremia, alanine and aspartate aminotransferase increase, hypokalemia, hypocalcemia, confusional state, and hyperglycemia were assumed to occur during KTE-X19 treatment and its associated hospital stay and therefore not costed separately. The remainder of adverse events were costed using the published literature and are outlined in Supplementary Table S1. For SoC, limited safety data was identified through the meta-analysis. While adverse events do occur in the treatments included as part of SoC, the conservative assumption was made to include costs related to adverse events only for KTE-X19 and not SoC.

Disease management costs and resource use
Due to the relatively rare incidence of MCL, it was not possible to collect reliable, US-specific healthcare resource utilization (HCRU) data during the ZUMA-2 trial, nor was other US-specific published data available. Estimates of HCRU were derived from the National Institute for Health and Care Excellence (NICE) technology appraisal for ibrutinib for R/R MCL (TA502). This technology appraisal determined HCRU by surveying active practicing hematologists and oncologists in the UK’s national health services. The results of the survey were validated by UK hematologic experts. The health state costs were estimated using published literature as well as data from CMS. Health state related costs were assumed equal regardless of treatment arm and applied until the patient experienced long-term remission or died. The cost per cycle was $1,400 in the pre-progression health state and $6,960 in the post-progression health state. The costs for patients with long-term remission were assumed to consist of an office visit twice a year priced at $148.81 per visit, corresponding to $25 per cycle (Supplementary Table S2). Disease management costs and resource use were validated by US clinical experts. Pre- and post-progression HCRU and costs are outlined in Table 1.

End-of-life costs
At the moment of death, end-of-life costs were applied to capture the resources used. This cost was applied for all patients, irrespective of cause of death. The median duration of palliative care was estimated to be 37 days at a cost of $195 per day. End-of-life costs were included in the model as the product of length of palliative care and cost per day.

Utilities
To estimate the utilities of R/R MCL patients in the model, EQ-5D-5L data collected in the ZUMA-2 trial was used. The trial data was combined with the US tariff to estimate the pre-progression utility value (0.843). The long-term remission utility was assumed to be the same as the pre-progression utility value (0.843). Due to a lack of data, the post-progression utility could not be estimated directly using the ZUMA-2 trial data. To derive the post-progression utility, the difference between the pre- and post-progression utilities was obtained from the NICE ibrutinib submission for R/R MCL (0.780 – 0.680 = 0.100). This difference was applied to the pre-progression utility estimated based on the ZUMA-2 trial, resulting in a post-progression utility estimate of 0.743. Subsequently, QALYs were derived by multiplying the utility associated with each health state by the time spent in the health state.

Utility decrements and duration of the included adverse events were based on the ZUMA-1 patient level data analysis for axicabtagene ciloleucel (axi-cel) (Supplementary Table S1). All utility decrements were multiplied with the adverse event’s incidence and applied during the model’s first cycle.

Outcomes
The model estimated OS, expected life years (LYs), QALYs, and total costs for KTE-X19 and SoC strategies. Based on these, incremental costs and effects were derived, which were used to establish the ICER comparing KTE-X19 to SoC. All results were presented as discounted over a lifetime horizon.

Sensitivity analyses
Both univariate and probabilistic sensitivity analyses were conducted. Inputs were varied using the standard error (SE) reported in the associated publication. If no SE was reported, an SE of 20% was applied. Additionally, a scenario analysis for CRS, included in the sensitivity analyses, assumed that CRS-associated hospitalization costs did not include tocilizumab treatment, thereby resulting in the costs associated with tocilizumab being added separately. Results from the univariate sensitivity analyses were presented in tornado diagrams, outlining the ten most influential model inputs on costs and effects, respectively. The incremental results of the probabilistic sensitivity analysis were plotted on a cost-effectiveness plane (CEP) and the probability that each treatment is cost-effective at different levels of willingness-to-pay (WTP) per QALY was presented using a cost-effectiveness acceptability curve. Specifically, the thresholds suggested and applied in previous analyses of CAR T therapies by the Institute for Clinical and Cost-Effectiveness Research ($100,000–$150,000 per QALY) were investigated.

Results

Base case results
Table 2 outlines discounted base case results. The model estimated that OS at 5 and 10 years was 57.7% and 49.7% for KTE-X19 and 30.4% and 20.0% for SoC, respectively.
Median survival was 9.71 years for KTE-X19 and 2.13 for SoC. Total discounted LYSs over the modeled time horizon were higher for KTE-X19 than SoC, at 8.99 vs 4.47 years, respectively. A similar difference was observed in terms of QALYs (7.39 vs 3.65 QALYs, respectively). For both treatments, the majority of LYSs and QALYs were accrued in the pre-progression health state. Total discounted costs were higher for KTE-X19 ($693,832) than SoC ($574,263). Treatment-related costs were the main cost drivers, contributing to 68% and 86% of KTE-X19 and SoC total costs, respectively. These values translated to a cost per LY gained of $26,479 for KTE-X19 vs SoC, and a cost per QALY of $31,985.

### Sensitivity analyses

The univariate sensitivity analysis indicated that the incremental cost results were most sensitive towards the drug acquisition costs of KTE-X19, the non-intensive care unit (ICU) and ICU day costs, and the hospitalization costs associated with the adverse event CRS (Figure 2). The addition of tocilizumab costs separately for the treatment of CRS resulted in a minimal increase of the ICER from $31,985 to $32,562 per QALY gained. The main driver of the incremental utilities was the pre-progression utility for patients with long-term remission, followed by the utility for post-progression and pre-progression prior to long-term remission (Figure 3).

### Table 2. Base case results (discounted).

|                      | KTE-X19 | Standard of care | Incremental difference |
|----------------------|---------|------------------|------------------------|
| **Total life years** | 8.99    | 4.47             | 4.52                   |
| Pre-progression      | 7.86    | 4.00             | 3.87                   |
| Post-progression     | 1.13    | 0.48             | 0.65                   |
| **Total quality-adjusted life years** | 7.39 | 3.65 | 3.74 |
| Pre-progression      | 6.63    | 3.30             | 3.33                   |
| Post-progression     | 0.81    | 0.35             | 0.46                   |
| Adverse events       | –0.05   | 0.00             | –0.05                  |
| **Total costs**      | $693,832| $574,263         | $119,562               |
| **Treatment-related costs** |  |  |  |
| Drug acquisition     | $383,971| $493,540         | –$109,569              |
| Apheresis            | $1,437  | $0               | $1,437                 |
| Drug administration  | $114    | $691             | –$577                 |
| Conditioning chemotherapy | $9,406 | $0 | $9,406 |
| Bridging therapy     | $3,460  | $0               | $3,460                 |
| Hospitalization      | $75,543 | $0               | $75,543                |
| **Disease management costs** |  |  |  |
| Pre-progression      | $48,177 | $34,192         | $13,985                |
| Post-progression     | $94,035 | $39,764         | $54,270                |
| **Other costs**      |  |  |  |
| End of life care     | $5,394  | $6,354           | –$960                 |
| Adverse events       | $72,297 | $0              | $72,297                |
| Cost per life years  | $26,479 | –                | –                      |
| Cost per quality-adjusted life years | $31,985 | – | – |

### Figure 2. Univariate sensitivity analyses: costs (Tornado Diagram).
The incremental results of the probabilistic sensitivity analysis are shown in Figure 4. For a WTP below the ICER (i.e. $31,985 per QALY gained), SoC was cost-effective, while for a WTP above this ICER KTE-X19 was cost-effective (Figure 5). At a WTP threshold of $100,000 and $150,000 per QALY, the probability that KTE-X19 was cost-effective was 94% and 99%, respectively.

**Discussion**

The treatment of patients with R/R MCL remains a therapeutic challenge, with the currently available treatments only offering transient responses. The ZUMA-2 trial has demonstrated that KTE-X19 is a promising treatment option for this group of patients, providing a significant clinical response and likely offering long-term disease-free survival. However, limited information is currently available on the cost-effectiveness of CAR T therapy in general and KTE-X19 specifically. The present study demonstrated that at various WTP thresholds commonly used for assessment in the US, KTE-X19 is a cost-effective treatment option in comparison to SoC in the treatment of patients with R/R MCL.

In this cost-effectiveness analysis, approximately 4.5 years of discounted life were projected to be gained with KTE-X19.
in comparison to SoC (8.99 vs 4.47 LYs, respectively) over a lifetime horizon. This additional survival translated to an incremental QALY gain of 3.74 for KTE-X19 compared to SoC (7.39 vs 3.65 QALYs, respectively). In the base case analysis, the incremental cost of KTE-X19 in comparison to SoC was $119,569, with the acquisition cost of KTE-X19 being the main cost driver. These values translated to a cost of $26,479 per LY gained and $31,985 per QALY gained. This falls well below the suggested Institute for Clinical and Cost-Effectiveness Research thresholds in the US ($100,000–$150,000 per QALY)\(^2\),\(^4\). Specifically, at a WTP threshold of $100,000 and $150,000 per QALY, the probability of KTE-X19 being cost-effective in comparison to SoC was estimated at 94\% and 99\%, respectively. In the US, these results suggest that treating patients with KTE-X19 may be a valuable distribution of the healthcare budget, while simultaneously providing patients with a meaningful new treatment option which may significantly extend survival.

The univariate sensitivity analyses demonstrated that the model outcomes were relatively stable to changes to inputs and assumptions. In terms of cost, KTE-X19 acquisition costs, initial non-ICU and ICU costs, as well as CRS-associated hospitalization costs had the largest impact. KTE-X19 acquisition costs were expected to have a substantial impact, given the cost level. The costs of (non-)ICU hospitalization can be attributed to the non-elective hospital stay associated with KTE-X19. Moreover, the uncertainty of these costs, with a standard error of 20\%, contribute to their high position on the tornado diagram. Additionally, the finding that CRS-associated hospitalization costs are a driver can be attributed to the substantial proportion of patients on KTE-X19 experiencing CRS (grade 2 and higher). Given that the cost of inpatient admissions in the US typically includes the cost of all services provided, the base case did not add CRS-associated tocilizumab costs separately. The more conservative scenario analysis in which CRS-associated tocilizumab cost was included separately resulted in only a minimal change of the ICER. Furthermore, the utility of patients with long-term remission was found to be a key driver of the incremental QALYs. This can be attributed to the moment of long-term remission being set at 5 years in the base case. At the moment of long-term remission, a large majority of patients receiving SoC will have died or progressed, while more than half of the patients receiving KTE-X19 will still be alive, and predominately progression free. As a result, any change in these utilities will directly affect the incremental QALYs.

CAR T therapies have been appraised in the literature\(^2\),\(^20\),\(^42\)–\(^44\) and by the Institute for Clinical and Cost-Effectiveness Research\(^2\),\(^1\), a US-based, private non-profit organization performing independent cost-effectiveness analyses. Nonetheless, this is the first cost-effectiveness analysis of a CAR T therapy in MCL. Previous studies consistently identified that CAR T therapies offered a substantial survival gain to patients, which on its turn has seen positive impacts on the ICERs. For example, the study by Roth et al.\(^20\) evaluated the cost-effectiveness of the CAR T therapy axi-cel in adult patients with R/R Large B-Cell Lymphoma (LBCL) following two or more prior therapies. In comparison to salvage chemotherapy, the SoC for R/R LBCL, patients receiving axi-cel had an incremental LY gain of 6.90 and QALY gain of 6.54. Nonetheless, at $55,128 per LY and $58,146 per QALY, the ICERs were higher than those observed in the present study. This was partially due to the positioning of therapy, i.e. after two or more prior therapies, but also due to the substantially lower treatment costs of salvage chemotherapy in R/R LBCL. In contrast, with R/R MCL SoC comprising several relatively new and expensive treatments, KTE-X19 is associated with an incremental gain of 3.74 QALYs. Additionally, similar to the present study, the study by Roth et al.\(^20\) and the review of the Institute for Clinical and Cost-Effectiveness Research\(^2\) both assumed that patients receiving CAR T therapy would revert to mortality rates of the age-

![Figure 5. Cost-effectiveness acceptability curve.](image-url)
and sex-matched general population if they were still alive at 5 years. This, along with updated data recently published on the ZUMA-2 outcomes suggesting a durable response for patients who respond to treatment with a minimum of 12 months follow-up, further supports the assumption made in the present study that patients who are alive at 5 years can be assumed to have long-term remission. Similarly, the modeling methodology used, the MCM methodology, has been assessed for appropriateness previously. In addition, the survival estimates from the MCM methodology were found to fit the data the best on the basis of AICs and was supported by experts. These studies and the data suggest that this methodology is more appropriate and sensitive to capturing the long-term effects and benefits of patients who experience long-term remission.

In terms of limitations, a number of assumptions have been identified that impact the model results. The most important limitation is related to uncertainty around the estimation of survival associated with KTE-X19. The model estimated long-term survival, whereas the data on which the survival estimates were based related to a relatively small sample size with a minimum follow-up of 7 months and a maximum follow-up of 36 months. Data with a minimum follow-up of 12 months for the ZUMA-2 population has recently been published which found that response continued to be substantial and durable and are in line with previous trials in CAR T-cell therapy. The model's time horizon was based on the extrapolated data and associated uncertainty and results should be interpreted in light of this. A second limitation relates to the ZUMA-2 trial being a single arm study. Such studies do not provide a comparator to allow for a direct assessment to other comparators and are subject to selection bias. Without such data, it was necessary to model the survival based on previously reported studies. Differences in survival between KTE-X19 and SoC may be due to differences in the populations studied and not the treatment effect directly. Nonetheless, patients enrolled in ZUMA-2 were generally of higher risk than SoC patients, given their higher number of prior therapies, with all patients having previously been treated with one or more BTK inhibitors, and overrepresentation of high-risk features such as TP53 mutation and Ki-67 proliferation index. Next, the definition of long-term remission used in the model is another limitation. While there is no clear and widely accepted definition for long-term remission, a publication by Maurer et al. suggested that event-free survival at 24 months after the completion of treatment should be considered a robust end point for disease-related outcomes in frontline diffuse LBCL (DLBCL). However, through interviews with clinical experts, it was determined that the 2-year long-term remission assumption for DLBCL would not be transferable to MCL due to late relapses. Based on this, the moment of long-term remission was set to 5 years in the base case of the model. In association with this, the univariate sensitivity analysis highlighted that the utility values of the long-term remission population was a main driver of the model, although the absolute impact was small. A fourth limitation of the model was the reliance on the NICE ibrutinib submission for HCRU and post-progression utilities. While the HCRU inputs were validated by UK hematologic experts, their transferability and use in an analysis from the US perspective may be questioned. However, given the lack of resource use evidence available for R/R MCL, this is currently the best available data. Further insights could be provided by hospital chart reviews and real-world evidence studies. In terms of utilities, the NICE ibrutinib submission was used to infer post-progression utilities, given these could not be obtained from the ZUMA-2 trial. No UK-specific utilities were applied. The lack of clarity surrounding the impact of long-term remission on resource utilization forms a fifth limitation. Similar to the previous limitation, further insights could be provided by hospital chart reviews or real-world evidence studies. A sixth limitation encompasses the population analyzed. The trial originally enrolled 74 patients, of which 68, the safety population, received treatment and were analyzed in this cost-effectiveness analysis. The safety population, rather than the full population, was chosen for this analysis because it provides a more accurate comparison of KTE-X19 vs SoC. Specifically, of the six patients who were enrolled but not treated, three patients were associated with manufacturing failure, two died before receiving the product, and one was found to be ineligible after conditioning chemotherapy. The three patients who had manufacturing failure continued with standard of care, highlighting that manufacturing failure does not stand in the way of patients receiving active treatment. Finally, a number of conservative assumptions were made, including the retreatment of patients with KTE-X19, though this is expected to rarely occur in a real-life setting, this was in line with the ZUMA-2 trial. Similarly, the separate costing of adverse events which may more commonly occur during KTE-X19 associated hospitalization, and the omission of adverse events for patients treated with SoC, given a lack of reported data. Each of these assumptions were deemed conservative given that they favor the comparator, SoC, by inflating costs associated with KTE-X19.

Conclusion

The treatment of R/R MCL with KTE-X19 presents a potentially cost-effective alternative to SoC, deriving its value from incremental survival and health-related quality-of-life benefits. From the US healthcare perspective at a WTP threshold of $150,000 per QALY gained, KTE-X19 is a cost-effective treatment option for adults with R/R MCL. In light of the findings from this cost-effectiveness analysis, future studies should focus on the long-term outcomes associated with KTE-X19 to validate the present study's findings.

Transparency

Declaration of funding

This study was funded by Kite, a Gilead Company.

Declaration of financial/other interests

CLS is employed by Pharmerit – an OPEN Health Company and is a consultant for or has consulted for Kite, a Gilead Company, Galderma, PTC therapeutics, Takeda, Bristol Myers Squibb, EMD Serono, and AbbVie in the past 2 years. DM is a consultant for or has consulted for Novartis,
Strategic Therapeutics and Sarepta in the past 2 years, has received honoraria from Novartis, Regeneron, Sanofi, Biomarin, and Pfizer. MW is a consultant for or has consulted for Pharmacyclics, Celgene, Janssen, AstraZeneca, MoreHealth, Pulse Biosciences, Nobel Insights, Guidepoint Global, Kite Pharma, Juno, Loxo Oncology, InnoCare, Oncentral, VelosBio in the past 2 years, has received research funding from Janssen, AstraZeneca, Acerta Pharma, Pharmacyclics, Juno Therapeutics, Celgene, Kite Pharma, Loxo Oncology, VelosBio, Verastem, Dava Oncology, Beijing Medical Award Foundation, Lu Daepei Medical Group, Genentech, has received travel accommodations/expenses from Janssen, Pharmacyclics, Celgene, Kite Pharma, AstraZeneca. GAM is an employee of Kite, a Gilead Company, was previously employed by Bristol Myers Squibb, has received research funding from Kite, a Gilead Company and Bristol Myers Squibb, has received a speaker’s honorarium from Bristol-Myers Squibb and is a stockholder of Gilead, Bristol Myers Squibb, and Amgen. TI is employed by Phamarit, an OPEN Health Company, and is a consultant for or has consulted for Kite, a Gilead Company, Takeda, Pfizer, AstraZeneca, Ferring, Resmed, Mallinckrodt, Insmed, and Indivior in the past 2 years. SWW is employed by Wade Outcomes Research and Consulting and is a consultant for or has consulted for Kite, a Gilead Company, AbbVie, and Amgen in the past 2 years. CB is employed by Phamarit, an OPEN Health Company, and is a consultant for or has consulted for Kite, a Gilead Company, AbbVie, Amgen, TEVA, Takeda, PTC therapeutics, Galderm, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Tesaro, Gilead, and Otsuka in the past 2 years. BS is an employee of Moffitt Cancer Center, is the vice-chair of the National Comprehensive Cancer Network’s Acute Lymphoblastic Leukemia Working Group, has received honoraria from Kite/Gilead, Celgene/Juno/BMS, Novartis, Pfizer, Amgen, Spectrum/Acrotech, Precision Biosciences, Beigene, AstraZeneca, Pharmacyclics/Jansen, Adaptive, and has received travel accommodations/expenses from Kite/ Gilead, Precision Biosciences, Novartis, and AstraZeneca, and has received research funding from Kite, a Gilead company, Jazz, and Incyte.

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