KTE-X19 versus Standard of Care for Relapsed/Refractory Mantle Cell Lymphoma Previously Treated with Bruton Tyrosine Kinase Inhibitors: Real-World Evidence from Europe

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INTRODUCTION

- Based on the current treatment patterns in Europe, there is no standard therapeutic process for patients with relapsed or refractory Mantle Cell Lymphoma (R/R MCL)
- Bruton tyrosine kinase inhibitor (BTKi) therapy is an option for patients with relapsed MCL; however, outcomes are poor for patients who experience disease progression, following BTKi therapy. The median Overall Survival (OS) for these patients ranges from 5.8 to 12.2 months, indicating an unmet need for the treatment of R/R MCL in the post-BTKi setting[1,2]

OBJECTIVES

- To compare the OS of post-BTKi R/R MCL patients who received KTE-X19 in the ZUMA-2 clinical trial with the OS of patients who received currently available standard of care (SOC) in a real-world setting in Europe (SCHOLAR-2)

METHODS

Data Sources

- ZUMA-2, a phase II, multi-center, single arm clinical trial, evaluated KTE-X19, an autologous anti-CD19 chimeric antigen receptor T cell therapy, in patients with R/R MCL who received 1–5 prior therapies including a BTKi[3]. Individual patient data (IPD) from the ZUMA-2 clinical trial was used to estimate the clinical efficacy of KTE-X19, using n = 60 from the inferential set (with sensitivity analysis using the safety set, n = 68, and ITT set n = 74) [3]
- SCHOLAR-2 was a retrospective, observational, multi-center patient chart review study, designed to collect data on patients with R/R MCL across 24 centers in Europe (UK, France, Germany, Spain, Italy, Denmark and Sweden)
- IPD from SCHOLAR-2 was used to form a SOC cohort (n = 59), which closely matched ZUMA-2 patients (i.e., ECOG 0–1 and a minimum of 12-month potential follow-up from initiation of active therapy post-BTKi)

Statistical Analysis

- Propensity scores (PS) were used to balance the baseline characteristics of the study populations, and to derive weights for SCHOLAR-2 patients. The PS model used key prognostic factors with non-missing data, including duration of and response rate (i.e., objective response rate) to prior BTKi therapy, number of prior therapy lines, and prior autologous stem cell transplant (SCT) (Table 1)
- A naïve (unadjusted) comparison was performed as a benchmark, followed by three separate comparisons using inverse probability weighting (IPW), multivariable regression (MVR), and doubly robust methods designed to adjust for residual imbalances in prognostic factors across the two non-randomized populations
- Survival times were summarized using Kaplan-Meier curves
- Cox proportional hazards models were used to estimate the effect of KTE-X19 relative to SOC, with outcomes presented as hazard ratios (HRs), along with the 95% confidence intervals (CIs)
- All analyses were performed in R version 3.6.3 (http://www.r-project.org/)

DISCLOSURE

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RESULTS

Table 1: Patient Baseline Characteristics (ZUMA-2 vs. SCHOLAR-2 Comparison)

Baseline characteristics		SCHOLAR-2: N=59	ZUMA-2; N=60	P-value
Index date (start of OS measurement)		At initiation of first post-BTKi therapy	At start of KTE-X19 infusion	--
Prior autologous SCT	Yes, n (%)	21 (35.6)	26 (43.3)	0.50[a]
Number of prior therapies	1 prior, n (%)	3 (5.1)	0 (0.0)	0.08[b]
	2 prior, n (%)	21 (35.6)	12 (20.0)	
	3 prior, n (%)	19 (32.2)	28 (46.7)	
	4+ prior, n (%)	16 (27.1)	20 (33.3)	
Duration of prior BTKi therapy	Median (IQR), months	7.3 (0.4, 52.5)	7.0 (0.03, 49.7)	0.98[b]
Response to prior BTKi therapy	ORR, n (%)	23/57 (40.4)	22 (36.7)	0.83[a]
Age	Median (IQR), years	63 (45, 88)	65 (38, 79)	0.52[b]
Sex	Male, n (%)	43 (72.9)	51 (85.0)	0.16[a]
ECOG performance score	0, n (%)	27 (45.8)	39 (65.0)	0.05[a]
	1, n (%)	32 (54.2)	21 (35.0)	
Disease stage	I–II, n (%)	9/49 (18.4)	2 (3.3)	0.02[c]
	III–IV, n (%)	40/49 (81.6)	58 (96.7)	

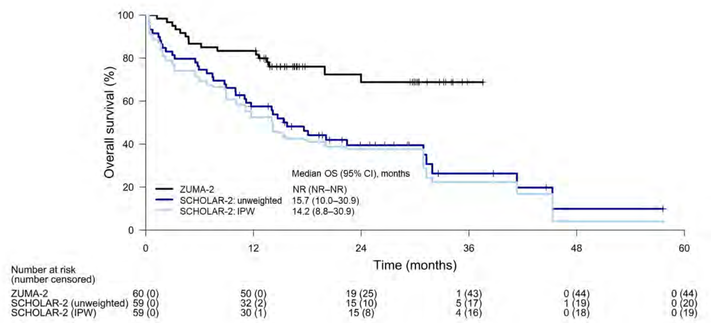
Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ORR, objective response rate; SCT, stem cell transplantation; OS, overall survival
[a]Chi-square test. [b]Kruskal-Wallis test. [c]Fisher's exact.

Table 2: Indirect Comparison of OS in ZUMA-2 and SCHOLAR-2 Patient Populations

Model	OS HR (95% CI) KTE-X19 vs SOC		
	ZUMA-2 ITT (n=74)	ZUMA-2 inferential (n=60)	ZUMA-2 safety (n=68)
Naïve, unadjusted	0.46 (0.27, 0.78) p=0.004	0.37 (0.20, 0.66) p<0.001	0.39 (0.22, 0.68) p=0.001
Inverse probability weighting (IPW)	0.41 (0.24, 0.71) p=0.001	0.33 (0.18, 0.59) p<0.001	0.35 (0.19, 0.62) p<0.001
Multivariable regression (MVR)	0.49 (0.29, 0.82) p=0.007	0.40 (0.22, 0.71) p=0.002	0.41 (0.23, 0.73) p=0.002
Doubly robust (DR)	0.42 (0.25, 0.73) p=0.002	0.32 (0.18, 0.58) p<0.001	0.32 (0.18, 0.58) p<0.001

***Notes:** All values are statistically significant at p-value <0.05. **Abbreviations:** CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; SOC, standard of care*

Figure 1. Kaplan-Meier curves: Indirect Comparison of OS in ZUMA-2 and SCHOLAR-2



Notes: Figure shows the observed OS KM curve for ZUMA-2 KTE-X19 (n=60 patients) as well as the observed and IPW-adjusted OS KM curves for SCHOLAR-2 SOC (n=59 patients); SOC included single-agent therapies (targeted therapy [n=8], immunotherapy [n=2], immunomodulator [n=4], chemotherapy [n=2], and radiotherapy [n=2]) and combination therapies (immunotherapy/immunodulator [n=6], immunochemotherapies [n=26], immunotherapy/targeted therapy [n=3], immunotherapies [n=3]; immunomodulators [n=1], targeted therapies [n=1], and chemotherapies [n=1]). Abbreviations: CI, confidence interval; DR, doubly robust; HR, hazard ratio; IPW, inverse probability weighting; KM, Kaplan-Meier; MVR, multivariable regression; OS, overall survival; SOC, standard of care

RESULTS CONTINUED

- In the naïve comparison, KTE-X19 was superior to SOC, with an OS HR of 0.37 (95% CI: 0.20–0.66; p<0.001). The IPW-adjusted median OS in SCHOLAR-2 was 14.2 (95% CI: 8.8–30.9) months. With the IPW approach (base-case), the HR was 0.33 (95% CI: 0.18–0.59; p<0.001), consistent with the naïve analysis. The HR estimates were also consistent across sensitivity analyses using the MVR and doubly robust models (Table 2 and Figure 1)

STRENGTHS AND LIMITATIONS

- SCHOLAR-2 provides data on survival outcomes of patients who receive current real-world SOC in Europe
- In this indirect treatment comparison of ZUMA-2 and SCHOLAR-2, three different adjustment methods (IPW, MVR and doubly robust) were used, per the National Institute for Health and Care Excellence (NICE) TSD 174 recommendation
- The OS estimates of the adjusted and unadjusted analysis were relatively consistent across the adjustment methods used
- Residual confounding may still exist in this non-randomized study

CONCLUSIONS

- This analysis suggests that KTE-X19 can improve survival over current active SOC in Europe for the treatment of R/R MCL in patients who have previously received BTKi therapy

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