Poster #491

An Updated Comparison of Overall Survival with Brexucabtagene Autoleucel (Brexu-cel) CAR T-Cell Therapy (ZUMA-2) Versus Standard of Care (SCHOLAR-2) in Patients with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Previously Treated with a Covalent Bruton Tyrosine Kinase Inhibitor (BTKi)

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BACKGROUND

- Patients with MCL typically require multiple lines of therapy and have poor prognosis, especially after having failed a covalent BTKi therapy;[1]
- Limited published survival data for patients with R/R MCL in the post-BTKi setting based on small retrospective studies have reported median overall survival (OS) ranging from 5.8 to 12.5 months in this population.[2–6]
- SCHOLAR-2 is a retrospective, observational study reporting OS among 240 patients with R/R MCL who received covalent BTKi therapy between July 2012–July 2018 in 7 European countries (Denmark, France, Germany, Italy, Spain, Sweden, and the UK) and either had disease progression while on BTKi therapy or discontinued BTKi therapy due to intolerance.[7]
- SCHOLAR-2 data reflects recent clinical practice (prior to chimeric antigen receptor [CAR] T-cell therapies), thus providing a benchmark for indirect comparisons of newer agents to non-CAR T-cell standard of care (SOC).

OBJECTIVES

- To compare the efficacy, in terms of OS, of brexu-cel (an anti-CD19 CAR T-cell therapy, formerly known as KTE-X19) versus non-CAR T-cell SOC in patients with R/R MCL post-BTKi using individual patient data (IPD) from both ZUMA-2 and SCHOLAR-2. Results from this updated comparison based on longer follow-up data from ZUMA-2 are presented.[8]

METHODS

DATA SOURCES

- ZUMA-2 (NCT02601313) is a multicenter, single-arm, phase 2 trial of brexu-cel in patients with R/R MCL who had 1–5 prior therapies, including a BTKi; updated clinical efficacy results based on 4-year follow-up at data cut-off date of July 23, 2022 (N=68 treated patients) were used for this analysis.[8]
- Real-world evidence on the effectiveness of SOC was based on a subset of the SCHOLAR-2 population that better resembled the ZUMA-2 patients.

STATISTICAL ANALYSIS

- Indirect treatment comparisons were conducted using three different statistical methods which adjusted for imbalances in prognostic factors between the two non-randomized study populations: 1) inverse probability weighting (IPW) with ZUMA-2 as the target population, 2) multivariable regression (MVR), and 3) doubly robust (DR) method.
- For the IPW analysis, weights were generated from the model among all possible propensity score models which provided i) an absolute standardized difference of <10% for the four pre-specified prognostic factors (bolded in **Table 1**) and ii) the minimum sum of absolute standardized differences (referred to as base-case analysis).
- For the MVR and DR method sensitivity analyses, univariate Cox models were first performed to identify potential confounders for OS (P<0.3) and backward elimination was then performed to build a parsimonious model based on the Akaike Information Criterion.
- OS was measured from the date of brexu-cel infusion in ZUMA-2 and the date of initiation of the first post-BTKi therapy (i.e., index SOC treatment) in SCHOLAR-2.
- As there was no strong evidence of a violation in the proportional hazards assumption based on Schoenfeld residuals and visual inspection of plots of the log cumulative hazards, relative treatment effects were estimated from Cox models and summarized as hazard ratios (HRs) with 95% confidence intervals (CIs).

RESULTS

EVIDENCE BASE

- Prior to the analyses, key eligibility criteria from the ZUMA-2 trial, i.e., Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1 and a minimum of 12-month potential follow-up from initiation of active therapy post-BTKi, were first applied to the SCHOLAR-2 population to construct an SOC cohort (n=60 patients) that closely matched the patients eligible for ZUMA-2.
- Index SOC treatments received by the SCHOLAR-2 SOC cohort included:
  - BTKi regimens (n=2), bendamustine + rituximab (n=11), rituximab + bendamustine + cytarabine (R-BAC, n=5), other cytarabine-containing regimens (n=4), other chemotherapy ± antibodies (n=5), lenalidomide-containing regimens (n=12), bortezomib-containing regimens (n=7), other targeted therapy ± antibodies (n=12), and radiotherapy (n=2).
- At baseline, both study populations were broadly balanced in terms of response to prior BTKi and duration on prior BTKi (**Table 1**); mean number of prior lines of therapy was 3.3 in ZUMA-2 and 3.0 in SCHOLAR-2.
  - The proportions of patients with prior autologous stem cell transplantation (SCT), male sex, stage IV disease, and ECOG PS of 0 were relatively higher in ZUMA-2 compared to SCHOLAR-2; ZUMA-2 consisted of a slightly younger population.
- Median OS follow-up times estimated using the reverse Kaplan-Meier curve method were 46.1 months for brexu-cel and 27.6 months for SOC.

INDIRECT COMPARISONS – OVERALL SURVIVAL

Naïve (unadjusted) analysis

- A naïve (unadjusted) comparison was first performed as a benchmark.
- Median OS was 46.4 (95% CI: 24.9, 58.7) months for brexu-cel and 15.4 (95% CI: 10.0, 30.9) months for SOC, with a 4-year OS estimate of 43.1% and 9.7% respectively.
- The unadjusted analysis suggested that brexu-cel was more effective compared to SOC with an OS HR of 0.43 (95% CI: 0.26, 0.69; P<0.001).

IPW base-case analysis

- All the key prognostic factors were well-balanced between the two populations after weighting (**Table 1**); the following covariates were included in the final propensity score model: response to prior BTKi, number of prior lines of therapy, duration on prior BTKi, prior autologous SCT, and stage IV disease.
- With IPW, the adjusted OS Kaplan-Meier curve for SOC shifted slightly downward; the median OS was 14.0 (95% CI: 6.8, 30.9) months and the 4-year OS estimate was 3.0% (**Figure 1**).
- Consistent with the unadjusted results, the IPW-adjusted OS HR of 0.38 (95% CI: 0.24, 0.62; P<0.001) suggested that brexu-cel reduced the risk of death relative to SOC.

Table 1. Baseline characteristics before and after applying weights

Variables	ZUMA-2, n=68	SCHOLAR-2: unadjusted, n=60	SCHOLAR-2: IPW-adjusted, ESS=45.7
Response to prior BTKi (ORR, %)	38.2	39.7	38.0
Mean number of prior lines of therapy	3.3	3.0	3.4
Mean duration on prior BTKi (months)	11.4	11.8	11.1
Prior autologous SCT (%)	42.6	36.7	42.2
Mean age (years)	63.2	69.5	68.7
Male sex (%)	83.8	71.7	68.4
Stage IV disease (%)	85.3	63.3	82.7
ECOG PS 1 (%)	35.3	55.0	54.8

Notes: *Variables in bold represents key prognostic factors and/or effect modifiers of highest relevance to be balanced between populations.* ***Abbreviations****: BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IPW, inverse probability weighting; ORR, objective response rate; SCT, stem cell transplantation*

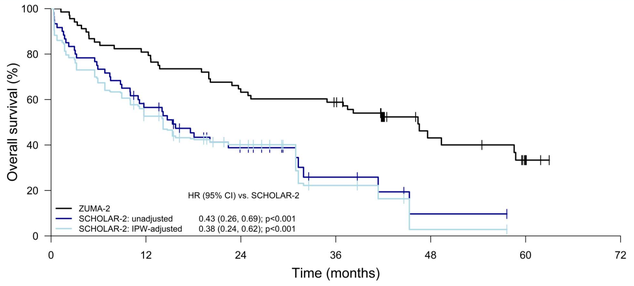
Multivariable regression sensitivity analysis

- The final MVR model included treatment (brexu-cel or SOC), duration on prior BTKi, and ECOG PS.
- The estimated OS HR of 0.46 (95% CI: 0.28, 0.74; P=0.001) suggested that brexu-cel reduced the risk of death relative to SOC.

Doubly robust sensitivity analysis

- The final DR model included treatment (brexu-cel or SOC), number of prior lines of therapy, duration on prior BTKi, and ECOG PS.
- Again, the estimated OS HR of 0.38 (95% CI: 0.24, 0.60; P<0.001) suggested that brexu-cel reduced the risk of death relative to SOC.

Figure 1. Kaplan-Meier estimates of overall survival with brexu-cel (ZUMA-2) and SOC (SCHOLAR-2); IPW base-case analysis



Time-points (months)	Overall survival rate, % (95% CI)		
	ZUMA-2	SCHOLAR-2: unadjusted	SCHOLAR-2: IPW-adjusted
6	85.3 (74.4, 91.8)	73.3 (60.2, 82.7)	67.4 (51.6, 79.0)
12	80.9 (69.4, 88.4)	56.5 (43.1, 68.0)	51.2 (35.9, 64.5)
18	73.5 (61.3, 82.4)	45.4 (32.2, 57.6)	42.0 (27.7, 55.6)
24	63.2 (50.6, 73.4)	38.8 (25.9, 51.5)	38.1 (24.1, 51.9)
30	60.3 (47.7, 70.8)	38.8 (25.9, 51.5)	38.1 (24.1, 51.9)
36	58.8 (46.2, 69.4)	25.9 (12.7, 41.2)	21.8 (8.5, 38.8)
42	52.4 (39.8, 63.5)	19.4 (6.9, 36.6)	16.0 (4.5, 33.9)
48	43.1 (29.3, 56.2)	9.7 (1.0, 30.9)	3.0 (0.1, 15.6)

Note: *The weights for 'SCHOLAR-2: IPW' patients were standardized so that the rescaled weights are relative to the original unit weights of each SCHOLAR-2 patient; as such, the numbers at risk for both 'SCHOLAR-2: unadjusted' and 'SCHOLAR-2: IPW-adjusted' are the same at time=0. In the actual analysis, the unscaled conventional weights were used.* ***Abbreviation:*** *CI, confidence HR, hazard ratio; IPW, inverse probability weighting; SOC, standard of care*

STRENGTHS/LIMITATIONS

- Findings were robust across the three different adjustment methods and show superiority with brexu-cel over SOC in terms of OS.
- While SCHOLAR-2 was exclusively conducted in Europe, the majority (91%) of patients in ZUMA-2 were from the United States. Consequently, the adjusted OS in SCHOLAR-2 may not be fully representative of patients undergoing treatment in the United States or other non-European countries, attributable to the possible variations in non-CAR T-cell SOC regimens received and distinct clinical management approaches adopted across different countries and regions.
- The methods used in the current analyses aligned with guidance from the National Institute for Health and Care Excellence on controlling for confounding effects introduced by study design when dealing with single-arm or observational evidence for which there is access to IPD.[9]
- As with any analysis of single-arm or non-comparative studies, there will, however, always be uncertainty regarding any unknown or unmeasured prognostic factors and/or treatment effect modifiers that are not captured in the chosen model which may influence the outcome of interest.
- Despite our efforts to ensure the most appropriate models were used, it is important to acknowledge that the models still rely on the assumptions, and as such cannot be considered as valid as having randomized controlled trials for the interventions of interest.

CONCLUSIONS

- Despite the inherent limitations of an unanchored indirect treatment comparison, these updated results continue to suggest significant OS benefit with brexu-cel versus non-CAR T-cell SOC in patients with R/R MCL post-BTKi and may help inform treatment choices in this high unmet need population.

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DISCLOSURES
Author disclosures are available on the conference website.

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