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ELEVENTH ANNUAL MEETING

# UNMET NEED IN RELAPSED/REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL) POST-BRUTON TYROSINE KINASE INHIBITOR (BTKI): A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

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## INTRODUCTION

- BTKis have become the mainstay treatment for R/R MCL, an aggressive type of B-cell non-Hodgkin's lymphoma;[1-5] however, impactful and reliable standard therapies, once the only available standard of care following BTKi failure, remain limited.[6]
- We sought to characterize and quantify the unmet clinical need of patients with R/R MCL in the post-BTKi setting.
- Brexucabtagene autoleucel (brexu-cel), a chimeric antigen receptor (CAR) T-cell therapy, has become a standard of care in this therapeutic space with demonstrated efficacy and effectiveness in both trial and real-world settings.[7,8]

## AIM

The objectives of this systematic literature review and meta-analysis are to:

- **Characterize and quantify** the unmet clinical need of patients with R/R MCL who receive a non-CAR T-cell standard therapy post-BTKi;
- **Contrast** the outcomes of standard therapy with the outcomes of patients who receive brexu-cel post-BTKi.

## METHOD

### Systematic literature review

- A systematic search of MEDLINE, Embase, CENTRAL, and relevant conferences was conducted to identify trials and observational studies (prospective or retrospective) of adult patients with R/R MCL who were receiving a post-BTKi standard therapy or brexu-cel.
- The list of eligible interventions extended to any non-experimental systemic therapy, with or without concomitant interventions such as radiotherapy.
- Outcomes of interest included overall survival (OS), progression-free survival (PFS), response (objective [ORR], complete [CR]), and duration of response (DOR).
- Study selection, data extraction, and critical appraisal steps were completed by two reviewers working independently and in duplicate.

### Meta-analysis

- Where published Kaplan-Meier curves were available, time-to-event outcomes (OS, PFS) were synthesized using multivariate meta-analyses of survival function parameters on pseudo-individual patient data (IPD) generated from digitized curves.[9-10]
- The goodness-of-fit of alternative survival distributions (Weibull, log-normal, log-logistic, Gompertz, exponential) was evaluated based on statistical and visual inspection.
- Dichotomous response outcomes (ORR) were meta-analyzed to generate a pooled proportion with 95% confidence interval (CI).

## RESULTS

### Summary of the literature review

- The database searches (26 October 2022) returned 1460 records.
- Following screening and supplemental hand searching, **52 publications (26 studies)** were included:
  - 19 standard therapy studies (N = 1238);
  - 7 brexu-cel studies (N = 607).

### Summary of the evidence base

- While most evidence (23/26) came from retrospective observational studies, 2 trials reporting standard therapy outcomes (MCL-3001; VALERIA) and 1 single-arm trial (ZUMA-2) reporting outcomes from patients receiving brexu-cel were also identified.
- 12/19 standard therapy studies reported downstream outcomes (post-BTKi) after initial enrollment for treatment with a BTKi.
- Studies of standard therapy typically reported outcomes from multiple interventions in a single estimate.
- Critical appraisals did not reveal any methodological concerns.

### Summary of the meta-analysis

***Patients treated with a post-BTKi standard therapy***

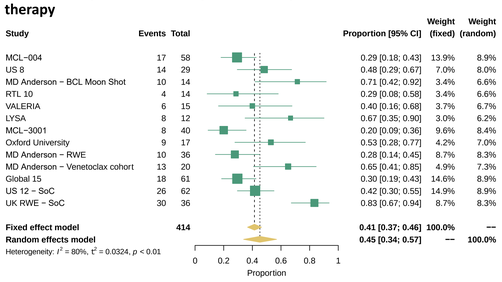
- The estimated ORR, based on 13 studies, was 45.3% (95% CI: 33.9 – 56.9, n = 414; $I^2$: 80%; **Fig 1A**).
- Median OS was reported in 14 studies (n = 1080), with observations varying from 2.5 to 19.4 months.
- Across 10 studies where KM curves for OS were available, the estimated median OS was 9.1 months (95% CI: 7.3 – 11.3; n = 669; **Fig 2A**).
- Median PFS was reported in 5 studies (n = 169), with observations varying from 1.9 to 10.1 months.
- The estimated median PFS, based on 3 studies with published KM curves, was 7.6 months (95% CI: 3.9 – 14.6; n = 80; **Fig 2B**).

***Patients treated with brexu-cel***

- The estimated ORR, based on 7 studies, was 88.6% (95% CI: 85.7 – 91.2, n = 546; $I^2$: 0%; **Fig 1B**).
- OS outcomes were reported in 6 studies (n = 560). Observed 6-month survivals varied from 79% to 93% (n = 5 studies).
- The estimated median OS, from 5 studies with published KM curves, was 32.1 months (95% CI: 25.2 – 41.2; n = 371; **Fig 2C**).
- From 6/7 studies reporting PFS, 6-month PFS varied from 58% to 83%.
- Based on 6 studies with published KM curves, the estimated median PFS was 14.9 months (95% CI: 10.5 – 20.9; n = 418; **Fig 2D**).

**Figure 1**

**A: Meta-analysis of overall response rate in patients treated with standard therapy**




**B: Meta-analysis of overall response rate in patients treated with brexu-cel**

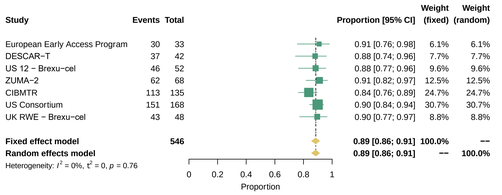
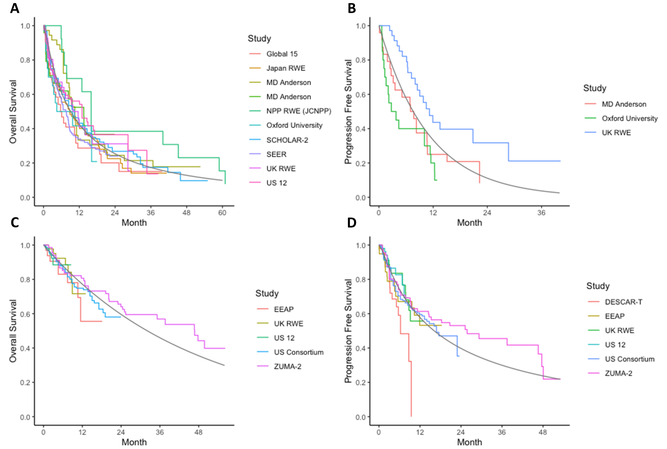



**Figure 2**




**A:** Meta-analysis of overall survival outcomes from studies of non-CAR T-cell standard therapy, summary curve based on a log-normal distribution; **B:** Meta-analysis of progression-free survival outcomes from studies of non-CAR T-cell standard therapy, summary curve based on an exponential distribution; **C:** Meta-analysis of overall survival outcomes from studies of brexucabtagene autoleucel, summary curve based on an exponential distribution; **D:** Meta-analysis of progression-free survival outcomes from studies of brexucabtagene autoleucel, summary curve based on a log-normal distribution

## CONCLUSIONS

- Although the treatment landscape for post-BTKi R/R MCL standard therapy is composed of several intervention strategies and significant heterogeneity, the outcomes of patients treated in this setting are consistently defined by an **unmet clinical need.**
- In contrast, clinical outcomes with brexu-cel are robust, with high rates and durations of response as well as extended survival compared to non-CAR T-cell standard therapy.
- Consistent demonstration of these patterns in both real-world and trial settings reinforce these findings.

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A list of references for the publications included through the systematic literature review is available upon request.

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