Pirtobrutinib-First vs. Brexucabtagene Autoleucel-First Sequencing Post-covalent BTK Inhibitor Failure in Mantle Cell Lymphoma

A Propensity-Matched Real-World Analysis

Shankar Biswas, MD[1]; Suhail Sapkota[2]; Kumar Anmol[3]; Aditya Anand[4]; Arashdeep Singh[5]; Dhiraj Kumar Das[6]; Archit Srivastava[7]; Yashasvi Srivastava[1]; Gagan Gupta[8]; Rahul Falodia[9]

Kumar Anmol, MD — PRESENTING AUTHOR | dr.kumar.anmol@outlook.com

[1]Ivano-Frankivsk National Medical University, Ukraine • [2]University of Michigan Health Sparrow, USA • [3]Baptist Memorial Hospital–North Mississippi, USA
[4]Jacobi Medical Center/Albert Einstein College of Medicine, NY • [5]Allegheny General Hospital, PA • [6]Universal College of Medical Sciences, Nepal
[7]Boston Medical Center Health System, USA • [8]ESI Model Hospital, Basaidarapur, India • [9]All India Institute of Medical Sciences, India

BACKGROUND & OBJECTIVE

Following covalent BTK inhibitor (cBTKi) failure in mantle cell lymphoma (MCL), both pirtobrutinib and brexucabtagene autoleucel (brexu-cel) have FDA approval. No head-to-head prospective or real-world study has directly guided their optimal sequence.

STUDY OBJECTIVE

To determine whether pirtobrutinib-first versus brexu-cel-first treatment after cBTKi cessation affects overall survival in MCL.

METHODS

DESIGN & SETTING

Retrospective cohort study using the TriNetX Research Network (112 healthcare organizations).

ELIGIBILITY

- Adults aged ≥18 years with MCL (ICD-10 C83.1; ≥2 encounters)
- Prior ibrutinib, acalabrutinib, or zanubrutinib
- Pirtobrutinib index: Jan 27, 2023; brexu-cel index: Jul 24, 2020
- No prior exposure to the comparator agent

OUTCOME & FOLLOW-UP

All-cause mortality from day 1 after the index therapy through available follow-up.

ANALYSIS

- Kaplan–Meier survival and log-rank test
- 1:1 propensity score matching on 25 demographic, clinical, medication, and laboratory characteristics
- Cox proportional hazards models before and after covariate adjustment

COHORT SELECTION AND MATCHING

Pirtobrutinib first
n = 200

Brexu-cel first
n = 74

↓ **1:1 propensity matching** ↓

66 patients per group

Proportional-hazards assumption was not violated in the matched analysis (p=0.612). The discordance between matched and multivariable estimates highlights the sensitivity of this observational comparison to model choice and measured covariates.

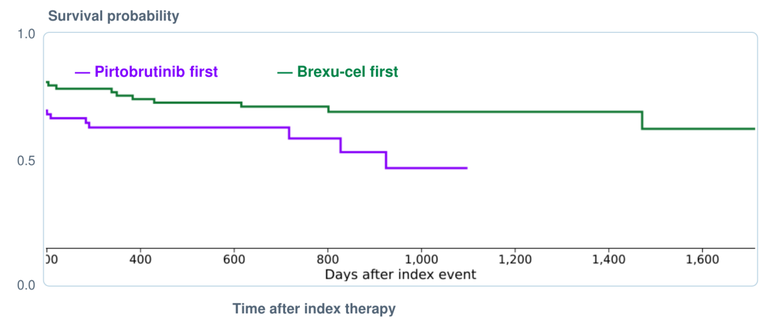
RESULTS

Before matching, pirtobrutinib-first patients were older at index and important imbalances remained. Matching reduced most differences, though residual imbalance persisted for hemoglobin and bendamustine exposure.

Characteristic	Pirto-first	Brexu-cel-first	Std. diff.
Age at index, mean y	67.6	67.7	0.012
Male	87.9%	81.8%	0.170
CKD	21.2%	22.7%	0.037
Prior ibrutinib	36.4%	34.8%	0.032
Prior zanubrutinib	33.3%	33.3%	<0.001
Hemoglobin, mean g/dL	11.5	10.7	0.315
LDH, mean U/L	336	273	0.132

Selected matched characteristics; n=66 per group.

MATCHED KAPLAN–MEIER ANALYSIS



1.82
Matched hazard ratio
95% CI 1.03–3.24; log-rank p=0.038

828 days
Median survival
Pirto-first; not reached for brexu-cel

- Brexu-cel may provide durable benefit in appropriately selected, fit patients
- The adjusted result cautions against interpreting sequencing as causal
- Access, referral timing, comorbidity, and disease biology should guide individualized decisions

SURVIVAL ANALYSES

HR 2.02
Unadjusted Cox model
95% CI 1.26–3.22; p=0.003 | Median OS: 718 d vs NR; 12-mo survival: 38.6% vs 59.5%

HR 1.82
Propensity-matched KM analysis
95% CI 1.03–3.24; p=0.038

aHR 1.25
Multivariable Cox model
95% CI 0.78–2.01; p=0.355

Interpretation
The survival difference attenuated after covariate adjustment, suggesting substantial confounding by patient selection and disease severity.

INDEPENDENT MORTALITY PREDICTORS

Covariate	aHR	95% CI
Sepsis	**4.21**	2.83–6.26
Male sex	**2.39**	1.44–3.98
CKD	**1.68**	1.12–2.52
Age (per year)	**1.02**	1.00–1.05
Hemoglobin (per g/dL)	**0.70**	0.63–0.76

CONCLUSIONS & LIMITATIONS

Among patients with post-cBTKi MCL, brexu-cel-first was associated with better OS than pirtobrutinib-first. After adjustment for fitness indicators, including hemoglobin and infection history, the OS advantage became non-significant. This highlights favorable selection of fitter patients for CAR-T therapy and should be considered when sequencing treatment.

LIMITATIONS

- Retrospective EHR-based design and residual confounding
- Small brexu-cel cohort and potential selection/immortal-time bias
- No granular data on performance status, MIPI, TP53, disease response, or toxicity
- Treatment availability and referral patterns may influence sequencing

TAKE-HOME MESSAGE

Brexu-cel-first favored survival after matching, but not after multivariable adjustment; sequencing should remain individualized pending prospective data.

SOHO 2026

Acknowledgment: Data were obtained from the TriNetX Research Network. | Presenting author: Kumar Anmol, MD | dr.kumar.anmol@outlook.com