FAVORABLE RESPONSES TO BTKI BASED REGIMENS IN RELAPSE/REFRACTORY MANTLE CELL LYMPHOMA (MCL): A PROSPECTIVE REVIEW FROM THE MER AND LION COHORTS

Katelin Baird, BS, PharmD Candidate[1,2], Ashley A. McCook-Veal, MPH[3], Jeff Switchenko, PhD[3], Yazeed Sawalha, MD[4], Greg Kirkpatrick[5], Eric Mou[5], Umar Farooq[5], Melissa C. Larson[6], Melissa Kives, MS[1], Yucai Wang, MD, PhD[6], Javier Pinilla-Ibarz, MD, PhD[7], Narendranath Epperla, MD, MS[8], Harsh R. Shah, DO[8], Allison Bock[8], Craig Portell[9], Joanna M. Rhodes, MD[10], Jonathon B. Cohen, MD, MS[1], David Bond, MD[4]

1 Emory University Winship Cancer Institute, 2 Lipscomb University College of Pharmacy, 3.Departments of Biostatistics and Bioinformatics, Emory University , 4 The Ohio State University the James Cancer Hospital , 5 University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer, 6 Mayo Clinic Comprehensive Cancer Center , 7 Moffitt Cancer Center , 8 Huntsman Cancer Institute, University of Utah , 9 UVA Comprehensive Cancer Center , 10 Rutgers Cancer Institute

Background

- Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy characterized by frequent relapse and declining survival with successive lines of therapy[1-5].
- Over the past decade, Bruton tyrosine kinase inhibitors (BTKis) have transformed MCL management and are increasingly used across treatment lines.
- BTK inhibitors disrupt B-cell receptor signaling by inhibiting Bruton tyrosine kinase, thereby reducing downstream pathways (ex. NF-κB and PI3K/AKT) critical for malignant B-cell survival, with activity achieved through either covalent or non-covalent binding.
- 4 BTKi are FDA approved to treat MCL including ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib[11-14].
- Since BTKis are high-cost oral agents dispensed through specialty pharmacies, prior authorization requirements may delay treatment initiation.

BTKi	FDA Approval for MCL	Dose	Generation	Reversible?	Approx. Cost (U.S.)
Ibrutinib	**Nov 2013**	560 mg once daily (280 mg tablets)	1st	Irreversible (covalent)	~ $725.68 per tablet ($21,770.40 per month)[11]
Acalabrutinib	**Oct 2017**	100 mg BID (100 mg tablets)	2nd	Irreversible (covalent)	~ $316.58 per tablet ($18,994.8 per month)[12]
Zanubrutinib	**Nov 2019**	160 mg BID or 320 mg once daily (160 mg tablets)	2nd	Irreversible (covalent)	~$314.88 per tablet ($18,892.80 per month)[13]
Pirtobrutinib	**Jan 2023**	200 mg once daily (100 mg tablets)	Next-gen	Reversible (non-covalent)	~$460.85 per tablet ($27,651 per month)[14]

Methods

This study assesses outcomes using combined data from the MER (Molecular Epidemiology Resource) and LION (Lymphoma Innovations ORIEN Network) cohorts. Survival outcomes were analyzed using Kaplan-Meier methods, with overall survival (OS) defined as time from initiation of treatment to death from any cause, and event-free survival (EFS) defined as time from initiation of treatment to start of new treatment or death. Survival curves were compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated.

Results

- A total of 409 patients (n=191 from the MER Cohrt and n=218 from the LION Cohort) with MCL; median age 67 years old (IQR 59-72) were treated and included in the combined data analysis. A majority self-reported being white (96.7%).
- In this combined cohort, 159 (39%) patients received BTKis.
- Of patients who received a 2nd line therapy, **112 (27.7%) patients received 2L BTKi including Ibrutinib n=60; Acalabrutinib n=31; Zanubrutinib n=20; Pirtobrutinib n=1.**
- Of patients who received a 3rd line therapy **85 (31.2%) received 3L BTKi including Ibrutinib n=41; Acalabrutinib n=27; Zanubrutinib n=10; Pirtobrutinib n=1.**
- 49% percent of patients in this cohort had an early release within 1 year of diagnosis.

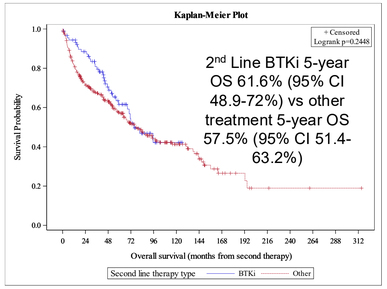

Figure 1. 2nd Line Treatment Overall Survival (OS).

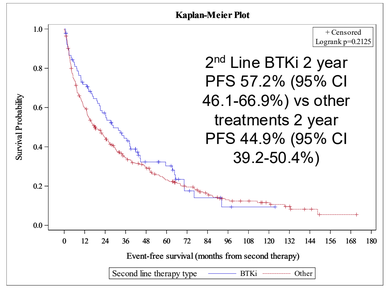

Figure 2. 2nd Line Treatment Progression Free Survival (PFS)

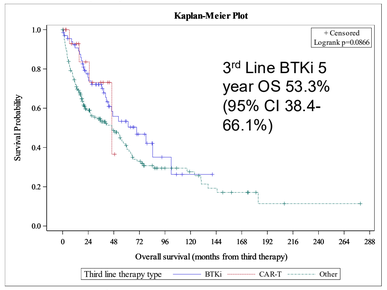

Figure 3. 3rd Line Treatment Overall Survival (OS).

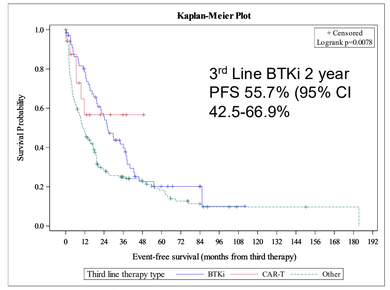

Figure 4. 3rd Line Treatment Progression Free Survival (PFS)

Discussion

- Use of BTK inhibitors (BTKi) demonstrated favorable survival outcomes when incorporated 2L and 3L therapies.
- The 1-year and 5-year OS for those who received 2L BTKi was 94.4% (95% CI 87.0%-97.6%) and 61.6% (95% CI 48.9-72.0%) compared to 81.4% (95% CI 76.5-85.4%) and 57.5% (95% CI 51.4 - 63.2%), respectively for non-BTKi based approaches.
- The 1-year and 5-year OS for those who received 3L BTKi was 90.7% (95% CI 80.5- 95.7%) and 53.3% (95% CI 38.4 - 66.1%).
- For patients who received 2L BTKi, the 12-month PFS was reported as 71.8% (61.1-80.0%) and the 5-year PFS was reported as 30.3% (20.1 - 41.1%).
- For patients who received 3L BTKi, the 12-month PFS was reported as 78.5% (66.3-86.6%) and the 5-year PFS was reported as 20.1% (10.3 - 32.3%).
- Side effects were not assessed in this study.

Conclusions

- These prospective observational data demonstrate favorable survival for 2L and 3L BTKi use for MCL, supporting ongoing clinical use in both settings.
- While survival outcomes remain favorable over time, decreasing long-term PFS highlights ongoing disease progression risk and underscores the need for effective subsequent treatment strategies. Optimal treatment for MCL remains an area for needed research.

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Contact: kbaird2@emory.edu