CO147

Novel therapies for relapsed/refractory mantle cell lymphoma post Bruton's tyrosine kinase inhibitor: A targeted literature review

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Background

- Mantle cell lymphoma (MCL) is a subtype of B-cell lymphoma that arises from B lymphocytes in the mantle zone of lymph node follicles, with an annual incidence of 1 case per 200,000 people.[1,2]
- MCL is characterized by a progressive shortening of response durations with each successive relapse.[2,3]
- As the use of covalent Bruton's tyrosine kinase inhibitors (BTKis) continues to shift into earlier lines of therapy, the post-BTKi patient population is steadily expanding.
- Patients who become relapsed/refractory (R/R) to BTKis face a historically poor prognosis
  - In early, heavily pretreated cohorts (median of 3 prior lines of therapy [LoT]), post-ibrutinib median progression-free survival (PFS) and overall survival (OS) were 1.9 and 2.9 months, respectively, underscoring the severe unmet need in this setting.[4]

Objective

- We identified therapies evaluated in adults with R/R MCL post-BTKi to assess the emerging clinical research.

Methods: Targeted literature review

Search

- The search was conducted via PubMed, Cochrane, and Embase from January 2016 to November 2025, and from September 2023 to November 2025 for conference abstracts.
- 12 databases were searched.
- Keywords comprised: "Mantle Cell Lymphoma", "Relapsed", "Refractory", and "BTKi".

Inclusion Criteria

- Studies of adults with R/R MCL who previously received a BTKi.
- United States (US) or global clinical trials.

Exclusion Criteria

- Studies that do not report outcomes for the post-BTKi population.
- Pre-clinical studies.
- Non-English language.

Review Process

- Screening and data extraction were performed by a single reviewer using an artificial intelligence systematic review tool, AutoLit (Nested Knowledge), validated by human review.

Data Extraction

- The following data were extracted:
  - Study characteristics: phase, location, and number of participants
  - Patient characteristics: age, sex, prognostic indicators (prior LoT, Mantle Cell Lymphoma International Prognostic Index [MIPI], tumor protein 53 [TP53] mutation, Ki-67), and follow-up
  - Interventions and comparators
  - Efficacy outcomes: objective response rate (ORR), complete response (CR), duration of response (DoR), PFS, and OS.
- Missing data were addressed as not reported (NR) in the extraction tables.

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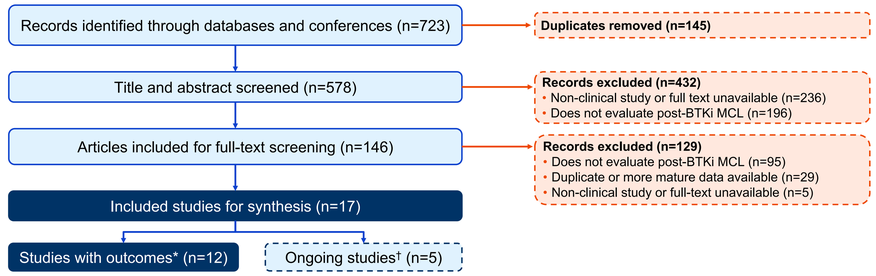
Results

- The PRISMA flow diagram is shown in **Figure 1**.

Figure 1. PRISMA flow diagram



*Twelve studies meeting all criteria were included for outcomes extraction. †Five ongoing studies had no results reported.

- From the search results, all studies with outcomes investigating novel therapies in post-BTKi MCL were phase II trials conducted in the US or globally (**Table 1**)
  - In general, the patients recruited for these trials were older males, had a high number of previous lines of therapy, and had varying high-risk characteristics (MIPI, TP53 mutations, and Ki-67)
  - Notably, the populations for these trials were small, limiting interpretability
  - Studies evaluated single- or multi-targeted therapies to bypass BTKi-resistance.

Table 1. Study characteristics

Author, year	Intervention	Category	Location	n†	Median age (range)	Male	Median prior LoT (range)	MIPI (risk)	TP53 mutation	Ki-67 (cutoff)
Glimelius, 2024[5]	Zilovertamab vedotin	ADC	US and global	40	68 (42–86)	70%	4 (2–9)	40% (H)	18%	55% (≥30%)
Yang, 2024[6]	Polatuzumab vedotin + obinutuzumab ± chemotherapy	ADC	China	9	NR (44–73)	75%	4 (2–9)	NR	67%	78% (≥50%)
Budde, 2024[7]	Mosunetuzumab	BsAb	US and global	25	70 (50–89)	NR	3 (2–6)	84% (H¶)	NR	NR
Phillips, 2024[8]	Glofitamab	BsAb	US and global	31	70 (41–84)	74%	3 (1–5)	23% (H¶)	16%	52% (≥30%)
Mato, 2021[9]	Pirtobrutinib	ncBTKi	US and global	52	69 (IQR: 63–75)§	77%§	3 (IQR: 2–4)§	NR	NR	NR
Liu, 2025[10]	Pirtobrutinib	ncBTKi	China	35	66 (47–75)	66%	3 (1–9)	69% (I/H)	NR	NR
Palomba, 2024[11]	Liso-cel	CAR-T	US	83	NR	NR	NR	NR	NR	NR
Minson, 2024[12]	Tisa-cel + ibrutinib	CAR-T	Australia	10	69 (41–74)	80%	3 (2–5)	70% (I/H)	50%	29% (≥30%)
Wang, 2020[13] 2024[14]	Brexu-cel	CAR-T	US and global	60‡	65 (38–79)	84%	3 (1–5)	56% (I/H)	17%	82% (≥30%)
Cavallo, 2024[15]*	KRD	PI	Italy	16	69 (53–79)	81%	NR	NR	NR	NR
Wang, 2025[16]	Mosun-Pola	Multi-target	US and global	42	68 (44–82)	NR	3 (2–9)	48% (H¶)	31%	67% (≥50%)
Melani, 2024[17]	ViPOR	Multi-target	US	8	67 (41–82)§	69%§	3 (1–7)§	33% (H)§	32%§	37% (>30%)§

Prognostic indicators (prior LoT, MIPI, TP53 mutation, Ki-67) are included to establish baseline severity and quantify the heavily pretreated, treatment-resistant phenotype defining this high-risk post-covalent BTKi cohort. *Trial terminated prematurely due to failure to meet specified efficacy endpoints and unacceptable toxicity at the planned interim analysis. †Denotes the number of patients in the post-BTKi efficacy cohort. ‡Denotes metrics derived from the n=68 all-treated population. §Denotes baseline covariates extracted from the broader overall population. Isolated post-covalent BTKi subgroup demographics were not published. ¶MIPI ≥6. ADC, antibody-drug conjugate; brexu-cel, brexucabtagene autoleucel; BsAb, bispecific antibody; CAR-T, chimeric antigen receptor T cell; H, high; I/H, intermediate/high; IQR, interquartile range; KRD, carfilzomib plus lenalidomide and dexamethasone; liso-cel, lisocabtagene maraleucel; Mosun-Pola, mosunetuzumab plus polatuzumab vedotin; ncBTKi, non-covalent Bruton's tyrosine kinase inhibitor; PI, proteasome inhibitor; tisa-cel, tisagenlecleucel; ViPOR, venetoclax plus ibrutinib, prednisone, obinutuzumab and lenalidomide.

- Single- and multi-targeted therapies show heterogeneous efficacy results in general and within drug classes (**Table 2**)
  - Notably, some survival outcomes are not estimable due to the duration of follow-up; longer trial durations may be needed to see the full benefit of these therapies
  - Additionally, not all outcomes were reported for each drug class, further limiting comparison.

Table 2. Efficacy results

Intervention	n†	ORR, % (95% CI)	CR, % (95% CI)	Median DoR, mo (CI)	Median PFS, mo (CI)	Median OS, mo (CI)	Median follow-up, mo
Zilovertamab vedotin[5]	40	40 (25–57)	13 (NR)	3 (range: 0–9)¶	3 (3–5) [6-mo: 26%]	9 (7–NE) [6-mo: 67%]	12 (range: 7–20)
Polatuzumab vedotin + obinutuzumab ± chemotherapy[6]	9	67 (NR)§	11 (NR)	NR	NR	NR	NR
Mosunetuzumab[7]	25	44 (NR)	24 (NR)	10 (2–20)	4 (1–6)	7 (4–26)	55‡‡ (NR)
Glofitamab[8]	31	74 (55–88)	71 (52–86)	13 (7–NE)	9 (3–16)	NR	20 (range: 0–39)
Pirtobrutinib[9]	52	52 (38–66)	NR	NR	NR	NR	6 (IQR: 3–9)
Pirtobrutinib[10]	35	63 (45–79)	11 (NR)	NE (5–NE) [12-mo: 60%]	7 (5–NE) [12-mo: 44%]	16 (10–NE) [12-mo: 62%]	12–16§§
Liso-cel[11]	83	83 (NR)	72 (NR)	16 (6–24)	15 (7–25)	18 (13–36)	16 (range: 0–61)
Tisa-cel + ibrutinib[12]	10	70 (NR)	70 (NR)	NR	NE [12-mo: 60%]	NE [12-mo: 100%]	13 (range: 3–21)
Brexu-cel[13,14]	60‡	93 (84–98)	67 (53–78)	37 (18–49)**	25 (13–47)**††	47 (25–60)**††	68** (range: 58–89)
KRD[15]*	16	19 (4–46)	6 (0–30)	NR	NR	NR [12-mo: 13%]	2 (95% CI: 1–6)
Mosun-Pola[16]	42	88 (74–96)	79 (63–90)	NR	19 (14–NE)	21 (17–NE)	16 (range: 0–41)
ViPOR[17]	8	≥88 (NR)	≥88 (NR)	NR	NE [24-mo TTP: 80%]	NR	24 (NR)

*Trial terminated prematurely due to failure to meet specified efficacy endpoints and unacceptable toxicity at the planned interim analysis. †Denotes the number of patients in the post-BTKi efficacy cohort. ‡Denotes metrics derived from the n=68 all-treated population. §Composite best ORR was not explicitly reported; outcomes reflect a cross-sectional 56% partial response rate at interim cycle 2 and an 11% CR rate at cycle 6. ¶Denotes ongoing responses at data cutoff. **Denotes mature longitudinal survival outcomes extracted from 5-year follow-up data (Wang 2024), structurally linked to the primary response rates established in the original trial publication (Wang 2020). ††Survival endpoints reflect the n=68 all-treated population (efficacy n=60). ‡‡Follow-up reported for OS only. §§Follow-up duration varied by the specific clinical endpoint reported (e.g., 12 mo [IQR: 9–15] for DoR, 14 mo [IQR: 9–17] for PFS, and 16 mo [IQR: 13–25] for OS).
CI, confidence interval; mo, months; NE, not estimable; TTP, time to progression.

- Ongoing phase II and III trials studying R/R MCL are currently investigating BsAb,[18–20] ncBTKi,[21] B-cell lymphoma-2 inhibitors,[20] and PIs[22] but have not reported results.

Limitations

- Data extraction was performed by a single reviewer.
- Interpretation of results is limited by phase II trials with small population sizes, short duration of follow-up, heterogeneous populations, and differences in study design.
- There was no formal assessment of the analysis of safety outcomes, publication quality, publication bias, sensitivity analysis, or heterogeneity, further limiting cross-trial interpretability.
- Due to the lack of data synthesis, outcomes are descriptive only.

Conclusions

- Novel therapeutic modalities, including ADC, BsAb, CAR-T, PI, and multi-target therapies, are actively being evaluated to biologically bypass the pathways driving covalent BTKi resistance.
- Patients with R/R MCL in the post-BTKi setting have generally been studied as part of a larger study, with inconsistent reporting of outcomes in this specific patient population.
- As BTKis move into earlier lines of therapy, these inconsistencies highlight the need for fully powered randomized trials which enroll patients with R/R MCL as the primary cohort
  - To our knowledge, the GLOBRYTE trial (NCT06084936), which evaluates glofitamab (CD20xCD3 bispecific antibody) monotherapy, is the only randomized phase III study actively investigating this population.
- Long-term follow-up and comprehensive reporting will be essential to demonstrate efficacy in this area of expanding unmet need.

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References

1. National Comprehensive Cancer Network. NCCN Guidelines for Patients. 2021.
2. Lynch DT, et al. StatPearls. 2023.
3. Kumar A, et al. Blood Cancer J. 2019;9(6):50.
4. Martin P, et al. Blood. 2016;127(12):1559–63.
5. Glimelius I, et al. Blood. 2024;144(Suppl 1):4405.
6. Yang P, et al. Blood. 2024;144(Suppl 1):6303.
7. Budde LE, et al. Blood. 2024;144(Suppl 1):1646.
8. Phillips TJ, et al. J Clin Oncol. 2024;43:318–28.
9. Mato AR, et al. Lancet. 2021;397(10277):892–901.
10. Liu Y, et al. Int J Cancer. 2025;156(11):2158–68.
11. Palomba ML, et al. J Clin Oncol. 2024;42(16_suppl):7016.
12. Minson A, et al. Blood. 2024;143(8):673–84.
13. Wang M, et al. N Engl J Med. 2020;382(14):1331–42.
14. Wang M, et al. Blood. 2024;144(Suppl 1):4388–90.
15. Cavallo F, et al. Br J Haematol. 2024;205(4):1404–10.
16. Wang ML, et al. Blood. 2023;142(Suppl 1):734.
17. Melani C, et al. Blood. 2024;144(Suppl 1):750.
18. Cho SG, et al. Blood. 2024;144(Suppl 1):6302.
19. Phillips T, et al. Clin Lymphoma Myeloma Leuk. 2024;24(Suppl 1):S515.
20. ClinicalTrials.gov. Identifier: NCT06558604.
21. ClinicalTrials.gov. Identifier: NCT05716087.
22. ClinicalTrials.gov. Identifier: NCT03323151.

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Disclosures

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AL-R: employment: Genentech, Inc.; current holder of stock options in a privately-held company: Roche.
C-WL: employment: Genentech, Inc.; current holder of stock options in a privately-held company: Roche.
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