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Title: Treatment landscape and survival outcomes among patients treated for Mantle Cell Lymphoma in real-world practice

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Introduction: Mantle cell lymphoma (MCL) is a rare, aggressive and incurable B-cell non-Hodgkin lymphoma. Although chemoimmunnotherapy (CIT) remains common frontline treatment (tx), use of covalent Bruton kinase inhibitors (cBTKis) has increased substantially. Despite these advances, outcomes after cBTKi discontinuation remain suboptimal and subsequent tx options are limited. This study examined real-world tx patterns across multiple lines of therapy (LOTs) and assessed clinical outcomes in patients (pts) with MCL.

Methods: This retrospective cohort study used the electronic health record-derived, deidentified Flatiron Health Research Database and included adults diagnosed with MCL who initiated 1L between 2016-2025. Pts were followed from 1L initiation until last activity, death, or study end (03/31/2026). Tx patterns were summarized by LOT (1-4L) overall and by 1L subgroup (aggressive [cytarabine-containing] vs less aggressive induction tx per NCCN guidelines). Real-world time to next tx (rwTTNT) and overall survival (rwOS), were assessed using Kaplan-Meier methods for 1L overall, by 1L subgroup, and in the post-cBTKi subgroup.

Results: A total of 4674 pts were included (median age at 1L: 70 years [IQR: 63-77]; 72% male); 2490 pts had stage IV MCL (53%); *TP53* mutations via NGS were tested in 19% (n=906) before 1L, with 25% (n=222) positive among those tested. 3171 pts (68%) had Ki67 data before 1L, with 48% (n=1513) had Ki67 ≥30% among those tested. Median follow-up was 27 months (IQR: 9-54). 491 (11%) received aggressive 1L therapy (median age at 1L: 61 years [IQR: 55-66]), 3125 (67%) received less aggressive 1L therapy (71 years [IQR: 64-77]). Remaining pts received clinical study drug (4%), lenalidomide +/- rituximab (3%), anti-CD20 monotherapy (8.9%), or other therapy (3.5%).

In 1L, CIT was the most frequent tx (67%), predominantly bendamustine and rituximab (BR; 45% of all 1L), followed by cBTKi-based regimens (13%). Rituximab maintenance was administered to 37% of pts treated with 1L BR. In later lines (2L+), cBTKi monotherapy was the

most common regimen (31% in 2L, 20% in 3L, and 13% in 4L), followed by CIT (21%, 15%, and 11%, respectively). Venetoclax-based, pirtobrutinib, and CAR –T-cell therapies were used more frequently in 3-4L (range 5-10%). Autologous stem cell transplant as consolidation after 1L was received by 9% and was more common among those receiving aggressive 1L therapy (38% vs 6%). Tx patterns were similar across 2-4L regardless of 1L intensity.

Overall median rwTTNT was 20 months (95% confidence interval [CI]: 19-22) from 1L. Median rwTTNT was 27 months (95% CI: 20-37) in pts treated with aggressive 1L therapy, and 24 months (95% CI: 22-27) in pts with less aggressive 1L therapy. Overall median rwOS was 71 months (95% CI: 67-75), with 24-months OS rates of 76% (74-77%). Median rwOS was 112 months (95% CI: 107-NR) among pts who received aggressive 1L therapy, and 68 months (95% CI: 64-74) for those with less aggressive 1L therapy.

In the post-cBTKi subgroup (n=839), median age at post-cBTKi therapy start was 71 years (IQR: 63-78); 71% male and 63% were treated in community care. *TP53* was tested in 33% pts (n=275), with 42% positive among pts tested; 74% pts (n=625) had Ki67 results, with 20% had Ki67 30-49% and 44% had Ki67 ≥50%. Median follow-up from initiation of post-cBTKi therapy was 10 months (IQR: 3-26). Post-cBTKi therapy occurred in 3L for 50% (n=421) of pts, 2L for 31% (n=261), and 4L for 14% (n=119). The most common post-cBTKi therapies were cBTKi-containing regimens (36%), mainly with anti-CD20 therapy (19%) or BCL2 inhibitors (12%). CIT was used in 15%, pirtobrutinib-containing regimens in 11%, and CAR T-cell therapy in 8%. Median rwTTNT was 6 months (95% CI: 6-7), and median rwOS was 27 months (95% CI: 23-31). Outcomes decreased as index line increased (rwTTNT: 8 months at 2L; 6 months at 3L; rwOS: 37 months at 2L; 23 months at 3L).

Conclusions: In this real-world analysis, 1L tx of MCL remained dominated by BR and approximately one-third of pts received rituximab maintenance. The use of cBTKis in 1L is increasing and continues to be widely used across subsequent LOT. Longer survival with intensive frontline therapy likely reflects favorable baseline characteristics. Despite outcomes that compare favorably with historical post-BTKi benchmarks, therapeutic options following cBTKi exposure remained limited, highlighting an unmet need for effective txs.