# Mantle Cell Lymphoma: Optimal Treatment With Bruton Tyrosine Kinase–Targeted Approaches

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## ABSTRACT

Mantle cell lymphoma (MCL) represents a relatively uncommon, heterogeneous lymphoma associated with limited overall survival. Targeting of the B-cell receptor pathway in relapsed disease with covalent Bruton tyrosine kinase (cBTK) inhibition has been demonstrated to be highly effective with cBTK inhibitor monotherapy, an established standard of care in relapsed MCL. This review summarizes the recent data strongly suggesting a role for the integration of covalent BTK inhibition in the first-line treatment setting, after the recent presentation and publication of multiple phase II and randomized phase II/III clinical trials demonstrating benefit for the addition of cBTK inhibitors first line. The authors discuss herein the strength and quality of the evidence for therapeutic strategies integrating cBTK inhibitors first line and proposal treatment algorithms on the basis of assumed future availability of this highly active small molecules first line in the near future.

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## INTRODUCTION

Mantle cell lymphoma (MCL) remains an aggressive, uncommon, and heterogeneous B-cell malignancy, which shortens the relative overall survival (OS) of those affected. It is characterized by increasing genomic instability over lines of therapy, worsening disease kinetics, and resistance to therapy. Survival outcomes substantially worsen across lines of therapy,[1] and optimizing first-line therapy across all patient groups is the best strategy to improve patient outcome and survival. Within this clinical review, we focus on the new developments within the Bruton tyrosine kinase inhibitor (BTKi) class—arguably the most potent single-agent class available in the MCL therapeutic armamentarium. We track BTKi development in relapsed MCL to the first-line setting where highly encouraging data suggest that it now should form part of standard first-line treatment across a wide spectrum of patients and will form the backbone of nonchemotherapy combinations in the future.

## BTK INHIBITION IN RELAPSED/REFRACTORY MCL

BTK inhibition has been developed as a key therapeutic target in patients with relapsed or refractory (R/R) MCL.[2] Ibrutinib, acalabrutinib, and zanubrutinib are all licensed as covalent[3] BTKi (cBTKi) monotherapy in different geographies in R/R MCL following phase II trials[4-6] and the subsequent randomized confirmatory RAY trial of ibrutinib versus temsirolimus.[7] These three oral cBTKis are generally well tolerated and demonstrate clear efficacy with overall response rates (ORRs) between 70% and 80% and median progression-free survival (PFS) between 14 and 33 months depending on the risk of the patient population studied. Pooled trial data from patients receiving ibrutinib monotherapy suggest that the best outcomes in terms of response depth and survival are seen at first relapse compared with subsequent relapses,[8] and their dominant use is at this time point.[9] There are currently no head-to-head comparisons of these three agents specifically in MCL. Although no randomized trials exist of BTK inhibition versus immunochemotherapy, international nontrial series demonstrate improved efficacy of cBTK inhibition in patients with early relapse (progression of disease within 24 months [POD24],[10] late relapse [non-POD24],[11] and CNS relapse[12]) compared with immunochemotherapy.

There have been multiple attempts focused on improving response rates and survival in R/R MCL using a cBTK inhibitor backbone. Combination partners include proteasome inhibitors,[13] immunomodulatory agents,[14] and most successfully B-cell lymphoma-2 (BCL2) inhibitors.[15,16] The SYMPATICO trial[17] demonstrated an improvement of complete response rate (CRR), ORR, and PFS of ibrutinib-venetoclax versus ibrutinib monotherapy in R/R MCL, although this combination is yet to be approved and no OS benefit has been seen with current follow- up. Ibrutinib-venetoclax increases hematotoxicity and infection risk and requires careful monitoring and risk assessment for tumor lysis syndrome. The optimum utility of ibrutinib-venetoclax in R/R MCL remains incompletely defined. Studies of cBTKi-BCL2i combinations in R/R MCL have, however, paved the way for their development in first line.

**TABLE 1.** Covalent BTKi and anti-CD20 Monoclonal Antibody Combination Phase II Trials in First-Line Mantle Cell Lymphoma

| Reference | Jain et al[18] | Gine et al[19] | Jerkeman et al[20] | Jain et al[21] |
|---|---|---|---|---|
| Study group | MD Anderson | GELTAMO | NORDIC | MD Anderson |
| cBTKi | Ibrutinib | Ibrutinib | Acalabrutinib | Acalabrutinib |
| Anti-CD20 | Rituximab | Rituximab | Rituximab | Rituximab |
| Target population | Elderly | Indolent | Elderly | Elderly |
| Number of patients | 50 | 50 | 81 | 50 |
| Follow-up, months | 45 | 36 | 19.3 | 17 |
| Age, years (range) | 71 (69-76) | 65 (40-85) | 75 (63-92) | 69 (65-81) |
| Treatment duration | Until PD | 2 years | Until PD | Until PD |
| MRD-driven stopping rules | No | At 2 years if MRD negative (Euro-MRD) | At 1 year if MRD negative for low risk only (Euro-MRD) | No |
| MIPI high | 69% | 38% | 69% | 22% |
| Ki67 >30% | 25% | 5% | 24.5% | 31% |
| *TP53* alterations | 17% (del 17p) | 15% | 23.5% | 28% |
| Blastoid/pleomorphic variants | 0% | 0% | 11.1% | 8% |
| ORR | 84% | 84% | 76% | 94% (best) |
| CRR | 71% | 80% | 51% | 90% (best) |
| uMRD at cycle 12 | Not applicable | 40/46, 87%[a] | 37/59, 63%[a] | 20/28, 73%[a] |
| PFS | 3 years 87% | 3 years 93% | 2 years 75% | 2 years 94% |
| OS | 3 years 94% | 3 years 92% | 2 years 84% | 2 years 96% |

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; CRR, complete response rate; MIPI, mantle cell lymphoma international prognostic index; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; uMRD, undetected minimal residual disease.
[a]Among patients with evaluable MRD, data at the end of cycle 12.



## BTK PLUS ANTI-CD20 MONOCLONAL ANTIBODY COMBINATION IN FIRST-LINE MCL

Several phase II trials have assessed the efficacy of cBTKi and anti-CD20 monoclonal antibody combinations in the first-line setting of MCL (Table 1). They were initially conducted in older patients, those ineligible for high-dose therapy, and/or patients with low-risk features, and subsequently in all comers. In the GELTAMO study,[19] indolent asymptomatic MCL, defined as nonblastoid, with a Ki67 <30% and no tumor mass >3 cm were eligible. Of the 50 treated patients with ibrutinib-rituximab (IR), the ORR after 12 cycles was 84%, including 80% CRR and 87% of patients achieving minimal residual disease (MRD)-negative status in peripheral blood (PB). After a median follow-up of 36 months, the estimated 3-year PFS was 93%. Among the 35 patients who obtained MRD-negative status, 24 (69%) discontinued ibrutinib: five subsequently converted to detectable MRD (between 3 and 20 months from discontinuation) and one clinical relapse was observed. Importantly, the MCL International Prognostic Index (MIPI) and *TP53* status demonstrated a significant impact on PFS, although numbers were low. At a similar time, Jain et al[18] reported the results of the IR regimen (applied until progression or unacceptable toxicity) in patients aged 65 years and older and without blastoid morphology or high Ki67. Of the 50 patients treated, the best ORR was 84% (71% CRR). The 3-year PFS and OS estimates were 87% and 94%, respectively. It was notable that 21 patients discontinued ibrutinib because of adverse events (AEs), including 22% experiencing grade 3 or worse atrial fibrillation, highlighting the necessity to perform full baseline evaluation for cardiovascular risks before receiving this combination. Patients with partial response had tumors enriched in *KMT2D*, *FAT4*, *ROS1*, *CARD11*, *ATM*, *NOTCH1*, *CCND1*, and *FAT1* genetic mutations, as well as gain in *SMARCA4*, or deletion in *KMT2C* and upregulation of the B-cell receptor pathway in gene expression profiling. A couple of years later, the Nordic group initiated a similar study in an older population of patients aged 60 years and older with the second-generation cBTKi acalabrutinib combined with rituximab (AR) with the exception that there were no exclusion criteria on the basis of risk factors. Results including a synthetic chemo-treated arm for comparison were recently presented.[20] AR performed equally well to IR in terms of response in these older patients (ORR, 95%, CRR, 90%). For the low-risk patients (ie, nonblastoid morphology, absence of *TP53* mutation: 74% of the population), an inbuilt MRD-directed stopping rule allowed to stop treatment after 1 year in those patients achieving MRD negativity, which was observed in 56% of low-risk patients. High-risk patients (26% of all enrolled patients) were planned to continue AR until progression or unacceptable toxicity. When high Ki67 was added to the high-risk group, there was a markedly inferior 2-year PFS of 38% compared with 96% for the patients with a low-risk MCL. In comparison with a synthetic control arm treated with rituximab-chemotherapy

and matched on MIPI and sex, AR seemed to improve PFS and OS, although there were limitations with this cross-population analysis. In a separate phase II trial investigating AR with acalabrutinib delivered until progression or unacceptable toxicity in the older fit and generally lower risk patient cohort. Patients had cardiac clearance on the basis of in-depth cardiac assessment at enrollment. The 2-year PFS was 92%, without impact of traditional high-risk features.[21] Differences in baseline characteristics of the patients recruited in these studies might explain these observed differences in outcomes.

Overall, these trials suggest that a risk stratification approach is very important when considering a doublet regimen based on cBTKi and anti-CD20 for first-line MCL with lower risk patients clearly benefiting. Moreover, these patients with low-risk MCL may benefit from a time-limited strategy with MRD stopping rules, although this approach requires further refinement. Patients with high-risk features such as blastoid morphology, high Ki67, or *TP53* mutation did not benefit sufficiently from this doublet combination and are likely to require an alternative approach.

## cBTKI-BCL2i PLUS ANTI-CD20 MONOCLONAL ANTIBODY AND OTHER TRIPLET COMBINATIONS IN FIRST-LINE MCL

Several phase II studies of novel triplet combinations have been evaluated in first-line MCL to enhance therapeutic synergy, depth, and durability of response (Table 2). The addition of agents, such as venetoclax, to cBTKi therapy has shown evidence of synergy in preclinical models and in clinical studies in R/R MCL, such as AIM and SYMPATICO, thus providing strong rationale for triplet combinations in treatment-naïve MCL.[27,28]

OASIS I was a phase I/II trial of the triplet ibrutinib, obinutuzumab, and venetoclax in relapsed and treatment-naïve MCL.[15] In Cohort C, 15 treatment-naïve patients received the triplet, including patients with high-risk features such as *TP53* aberrancy (n = 8) and pleomorphic variant (n = 1). ORR after six cycles was 93% (CRR 87%), with 73% (n = 11) attaining PB uMRD by allele-specific oligonucleotide polymerase chain reaction (PCR). With a median follow-up of 14 months, 1-year PFS for the cohort was 93.3% with a 1-year OS of 100%.[15] Long-term data reported 5-year PFS and OS estimates of 80% and 93%, respectively, reflecting durable remissions.[22]

Acalabrutinib, venetoclax, and rituximab[24] demonstrated a 100% ORR in 21 treatment-naïve patients, with a CRR of 71% and 91% by positron emission tomography-computed tomography (PET-CT). At 28-month follow-up, the 2-year PFS and OS were 63% and 75%, respectively. Survival outcomes were adversely affected by COVID-19–related deaths (n = 5) among unvaccinated patients early in the COVID-19 pandemic.

Zanubrutinib, venetoclax, and obinutuzumab (BOVen) was studied specifically in untreated MCL patients with *TP53* mutation using a MRD-driven cessation approach.[25] In 25 patients, the best ORR was 96% (CRR 88%). The 2-year PFS and OS were 72% and 75%, respectively, which compared favorably with historical outcomes with chemo-immunotherapy in this high-risk subgroup. Among the 18 patients completing 24 cycles, 11 achieved uMRD (ClonoSEQ, $10^{-6}$ sensitivity) and remain in remission with limited follow-up. Further follow-up is required to evaluate the durability of clinical and molecular remissions in these high-risk patients.

An alternative chemo-free triplet in untreated MCL is the ALR regimen (acalabrutinib, lenalidomide, and rituximab) incorporating the immunomodulator lenalidomide, applying MRD-driven treatment discontinuation for oral agents after 2 years and rituximab after 3 years.[26] High rates of grade 3 rash were observed. The best ORR and complete response rates were 100% and 83%, respectively. The 3-year PFS and OS were 87.5% and 95.7%, respectively, with a trend toward inferior PFS outcome among *TP53*-mutant patients.

When comparing two-drug versus three-drug non-chemotherapy cBTKi combinations, the OASIS II randomized phase II trial provides important comparative data.[23] It evaluated ibrutinib and anti-CD20 (rituximab or obinutuzumab; arm A) versus ibrutinib, anti-CD20 (rituximab or obinutuzumab), and venetoclax (arm B). The addition of venetoclax enhanced therapeutic activity with a significantly higher uMRD rate by digital droplet PCR after cycle 6 in arm B (82%) versus arm A (54%). However, it remains unclear at present whether this will translate to long-term PFS and OS benefits, as these results were not reported separately in the first futility analysis and follow-up remains short. Arm B was tolerable, but showed increased toxicity compared with Arm A, including higher rates of diarrhea (predominantly low-grade), cardiac events, and grade ≥3 neutropenia. While triplet regimens show enhanced therapeutic activity, their increased toxicity may limit their use in frail or older patients, where two-drug combinations may be sufficient. Triplet combinations may, however, emerge as the standard for high-risk subgroups, such as *TP53*-mutated patients, and may more effectively facilitate MRD-driven, time-limited approaches.

## FIRST-LINE RANDOMIZED PHASE II/III TRIALS INCORPORATING COVALENT BTK INHIBITORS

Four recent large phase III trials have addressed different questions in the evaluation of cBTKis in first-line treatment of patients with MCL (Table 3). In patients considered ineligible for autologous stem-cell transplantation (ASCT), two studies evaluated different cBTKis given until progression or unacceptable toxicity (ibrutinib in SHINE[33] and acalabrutinib in ECHO[34]) and used similar designs. Both demonstrated that the addition of continuous cBTKi to bendamustine-rituximab (BR) followed by rituximab maintenance significantly prolonged PFS, but not OS. Both were designed with a primary end point of PFS, and both met their primary end point. Neither study was specifically

**TABLE 2.** BTKi-Based Triplet Nonchemotherapy Combinations From Phase II Trials in First-Line Mantle Cell Lymphoma

| Reference | Le Gouill et al[15] and Tessoulin et al[22] | Le Gouill et al[23] | Wang et al[24] | Kumar et al[25] | Ruan et al[26] |
|---|---|---|---|---|---|
| Study group | OASIS I | OASIS II | AVR | BOVEN | ALR |
| cBTKi | Ibrutinib | Ibrutinib | Acalabrutinib | Zanubrutinib | Acalabrutinib |
| Anti-CD20 | Obinutuzumab | Obinutuzumab or rituximab | Rituximab | Obinutuzumab | Rituximab |
| Third novel agent | Venetoclax | Venetoclax | Venetoclax | Venetoclax | Lenalidomide |
| Number of agents | 3 | 2 (arm A), 3 (arm B) | 3 | 3 | 3 |
| Target population | Unselected | Unselected | Unselected | *TP53*-mutant | Unselected |
| Number of patients | 15 (cohort C) | 51 in each arm | 21 | 25 | 24 |
| Follow-up, months | 61 | 27 | 28 | 28.2 | 41 |
| Age, years (range) | 65 (51-77) | Arm A: median 65<br>Arm B: median 66 | 66 (51-85) | 68 (29, 82) | 64 (35-77) |
| Treatment duration | Obin until C23, Ibr + VEN for 2 years or until PD | Obin or rituximab for 42 cycles, Ibr ± VEN for 24 cycles | Ritux until PD or capped at 15 cycles in patients with CR/PR, Acala until PD, VEN until C25 | Obin ×8 cycles, Zanu and VEN for at least 2 years | ALR induction ×12 cycles, then ALR maintenance from C13 to POD. If uMRD CR after 24 cycles, can stop oral agents. Ritux maintenance for at least 3 years |
| MRD driven stopping rules | No | No | No | Discontinue Zanu-VEN at 2 years if uMRD CR | Discontinue Acala-Len at 2 years if uMRD CR, Ritux at 3 years |
| MIPI high | 27% | Arm A: 29%<br>Arm B: 28% | 19% | 68% | 21% |
| Ki67 >30% | NA | Arm A: 34%<br>Arm B: 48% | 48% | 52% | 29% |
| *TP53* alterations | 13% (mutation n = 2)<br>40% (17p deletion n = 6) | Data not presented | Not collected | 100% | 25% *TP53* mutation |
| Blastoid variants | 7% (n = 1) | Arm A: 2%<br>Arm B: 6% | 5% | 20% | 0% |
| ORR | 93% | Arm A: 78.5%<br>Arm B: 80% | 100% | 96% | 100% |
| CRR | 87% | Arm A: 56.9%<br>Arm B: 64% | 71% by Lugano, 91% by PET/CT | 88% | 83% |
| MRD assay | ASO-qPCR | ddPCR | Adaptive clonoSEQ | Adaptive clonoSEQ | Adaptive clonoSEQ |
| MRD results in PB | At C6, uMRD 73% (n = 11) | Planned MRD analysis in 39 pts in each arm after C6<br>Arm A, uMRD 54%<br>Arm B, uMRD 82% | At C6, uMRD 57% (n = 12)<br>At C12, uMRD 52% (n = 11) | At C13, uMRD5 72% (n = 18) and uMRD6 64% (n = 16) | At C6, uMRD6 50%. At C12, uMRD6 67%<br>At C24, uMRD6 76% |
| PFS | 5-year 80% | 2-year 88% (arm A and B combined) | 2-year 63.2% | 2-year 72% | 3-year 87.5% |
| OS | 5-year 93% | 2-year 92% (arm A and B combined) | 2-year 75.2% | 2-year 76% | 3-year 95.7% |

Abbreviations: Acala, acalabrutinib; ASO-qPCR, allele-specific oligonucleotide polymerase chain reaction; AVR, acalabrutinib, venetoclax, rituximab; C, cycle; cBTKi, covalent Bruton tyrosine kinase inhibitor; CR, complete response; CRR, complete response rate; ddPCR, digital droplet polymerase chain reaction; Ibr, ibrutinib; Len, lenalidomide; MIPI, Mantle Cell Lymphoma International Prognostic Index; NA, not applicable; Obin, obinutuzumab; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD, progressive disease; PET/CT, positron emission tomography-computed tomography; PFS, progression-free survival; POD, progression of disease; PR, partial response; Ritux, rituximab; uMRD, undetected minimal residual disease; VEN, venetoclax; Zanu, zanubrutinib.

**TABLE 3.** Summary of Design and Outcomes of First-Line Randomized Trials Including a Covalent BTKi in Mantle Cell Lymphoma

| TRIALS | ASCT Eligible? | BTKi | Design | Treatment | Crossover | n | Age, Years, Median | mFU, Months | mPFS (experimental *v* SOC) | OS |
|---|---|---|---|---|---|---|---|---|---|---|
| SHINE (NCT01776840)[33] | No | Ibrutinib | III | BR followed by R maintenance 2 years ± ibrutinib until PD | No | 523 | 71 | 84.7 | 80.6 months *v* 52.9 months (*P* = .011) | HR 1.07 (95% CI, 0.81 to 1.40) |
| ECHO (NCT02972840)[34] | No | Acalabrutinib | III | BR followed by R maintenance 2 years ± acalabrutinib until PD | Yes | 598 | 71 | 44.9 | 66.4 months *v* 49.6 months (*P* = .0160) | HR 0.86 (95% CI, 0.65 to 1.13) |
| ENRICH (NCT11038174)[39] | No | Ibrutinib | II/III | R-chemo (R-CHOP or BR) versus Ibrutinib-R | No | 397 | 74 | 47.9 | 65.3 months *v* 42.4 months (*P* = .003) | HR 0.87 (95% CI, 0.64 to 1.18) |
| TRIANGLE (NCT02858258)[31,37] | Yes | Ibrutinib | III | Group A: R-CHOP/R-DHAP followed by ASCT ± R maintenance per local practice<br>Group A + I: per A + ibrutinib<br>Group I: per A + I without ASCT | No | 870 | 57 | 31 | 4 year FFS:<br>A + I *v* A: 82% *v* 70%, *P* = .0026<br>A *v* I: 70% *v* 81%; *P* = .99<br>A + I *v* I: 82% *v* 81% *P* = .21 | 4 year OS:<br>A: 81%<br>A + I: 88%<br>I: 90% |
| ECOG-ACRIN EA4181 (NCT04115631)[29] | Yes | Acalabrutinib | II | BR/cytarabine-R (control arm)<br>BR/cytarabine R-acalabrutinib<br>BR-acalabrutinib | No | 359 | 61 | 27.9 | 12 months PFS 86% *v* 89% *v* 87% | 12 months OS 94% *v* 98% *v* 95% |

Abbreviations: A or ASCT, autologous stem-cell transplantation; BR, bendamustine-rituximab; BTKi, Bruton tyrosine kinase inhibitor; FFS, failure-free survival; HR, hazard ratio; I, ibrutinib; mPFS, median progression-free survival; MRD, minimal residual disease; OS, overall survival; PD, progressive disease; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; SOC, standard of care.

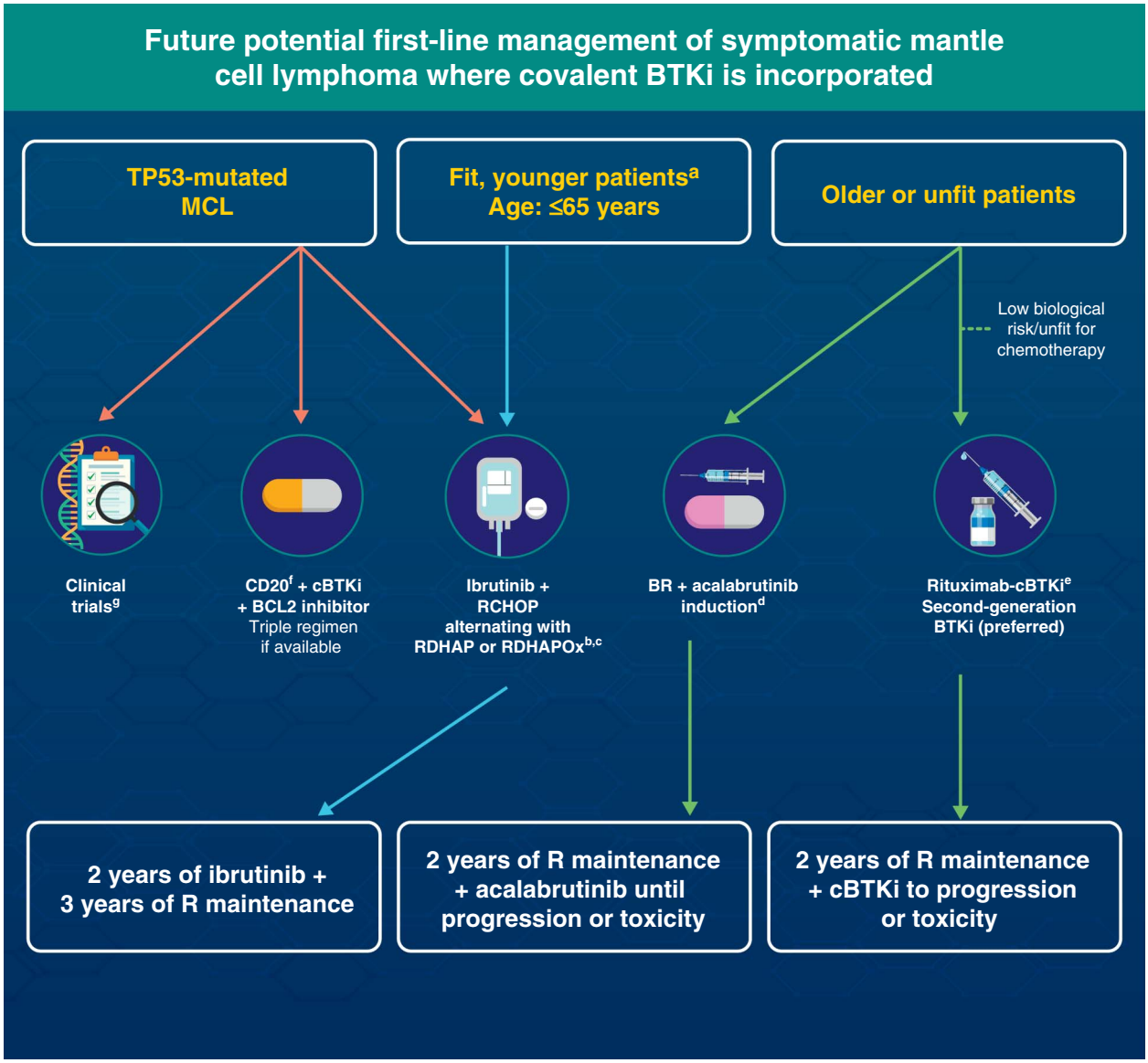


**FIG 1.** "How I would like to treat first line MCL." [a]Patients typically aged 65 years and younger. [b]Ibrutinib alongside R-CHOP but not R-DHAP or R-DHAOx (rituximab, dexamethasone, cytarabine, oxaliplatin alongside rituximab maintenance). Allows safe omission of ASCT. Other cBTKis considered dependent on availability and preference. [c]Author's preference is for R-DHAOx given improved safety profile (this is acknowledged on the basis of nonrandomized data). [d]Consider in higher risk older patients, for example, blastoid/pleomorphic, Ki-67 ≥30%, acknowledging data of possible benefit is subgroup analysis from RCT. Consider in younger patients based on the results of the ECOG-ACRIN EA4181. [e]Evidence from RCTs currently with IR and phase II trials with AR and IR. [f]Consider obinutuzumab in place of rituximab when available and clinically appropriate. [g]Clinical trials are appropriate for all patients, particularly those with high-risk genetic abnormalities. AR, acalabrutinib-rituximab; ASCT, autologous stem-cell transplantation; BR, bendamustine-rituximab; cBTKi, covalent Bruton tyrosine kinase inhibitor; ICT, immunochemotherapy; IR, ibrutinib-rituximab; MCL, mantle cell lymphoma; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RCT, randomized controlled trials; RDHAP, rituximab, dexamethasone, cytarabine, cisplatin; RDHAPOx, rituximab, dexamethasone, cytarabine, oxaliplatin.

designed or powered for OS. In SHINE, there was a trend toward inferior OS in the ibrutinib arm, attributed to a higher number of deaths due to toxicity. The same trend was not observed in ECHO, because of improvements in disease control, and despite crossover from placebo to acalabrutinib being permitted (a key design difference), there was no difference in OS. The US Food and Drug Administration (FDA) has recently approved (January 2025) BR-acalabrutinib for patients with previously untreated MCL unsuitable for ASCT. In contrast to SHINE, there was a trend toward OS benefit in the experimental arm, which was stronger when a prespecified COVID-19 sensitivity analysis was performed. A key question raised by both studies is whether sequential therapy with chemoimmunotherapy

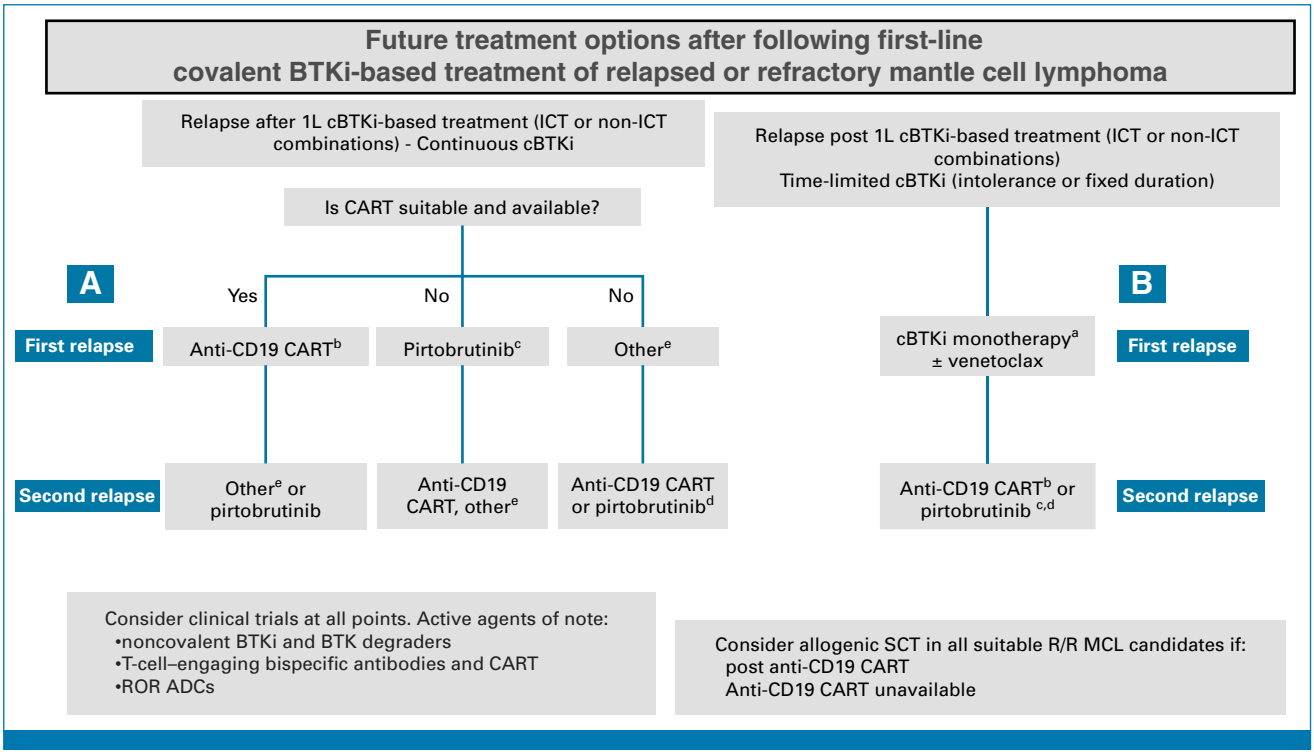


**FIG 2.** "How I would like to treat relapsed MCL." (A) Ibrutinib-venetoclax choice dictated by patient fitness and MCL biology. Consider cBTKi rechallenge if prior intolerance only or prior fixed-duration cBTKi in patients achieving an adequate initial remission. All options described in pathway A are also valid for patients progressing after fixed-duration covalent BTKi in the absence of a clear evidence base. (B) CART considered if second line available for patients. Brexucabtagene autoleucel licensed second line in the United States and third line in Europe. (C) Pirtobrutinib depending on availability and patient preference. Pirtobrutinib licensed second line in Europe and third line in the United States. (D) Third-line pirtobrutinib or CART choice according to patient fitness, disease kinetics, patient choice, CART suitability, and availability. (E) Other options include rituximab-lenalidomide, immunochemotherapy, and bortezomib-rituximab. CART, chimeric antigen receptor T-cell therapy; cBTKi, covalent Bruton tyrosine kinase inhibitor; ICT, immunochemotherapy; MCL, mantle cell lymphoma; R/R, relapsed/refractory; SCT, stem-cell transplantation.

followed by cBTKi at relapse is a sufficient approach. Neither study was specifically designed to address this question, but 69% of patients randomly assigned to the control arm in ECHO received a cBTKi at disease progression. Some observational data sets may inform these decisions. Around 7% of patents with MCL died of lymphoma before being able to receive second-line therapy in an Australian series,[35] which constitutes an argument to incorporate cBTKi into initial therapy. By contrast, a large Mayo Clinic–led US consortium analyzed event-free survival 2 (EFS2) in 491 patients with MCL who received first-line BR followed by a second-line cBTKi.[36] The median EFS2 using this approach was 68.1 months, which appears broadly similar to the median PFS of 66.4 months for the BR-acalabrutinib arm in ECHO. This comparison between a prospective trial cohort and retrospective data set is subject to inherent limitations, the impact of COVID-19 events in ECHO, and differences in baseline characteristics. However, the observational data set had more patients with simplified MIPI (s-MIPI) high risk (40 *v* 24%) and similar rates of *TP53* mutation (11 *v* 7%) and blastoid/pleomorphic histology (13%). As expected, combining cBTKi with BR increased the incidence of AEs in both studies, with the most frequent AEs in both studies being neutropenia and diarrhea. The addition of ibrutinib resulted in higher rates of atrial fibrillation, with 13.9% for BR-ibrutinib in SHINE compared with 6.7% for BR-acalabrutinib in ECHO. Hypertension, bleeding, and arthralgia were similar in both studies. SHINE was largely performed before the COVID-19 pandemic, and there were minimal differences in COVID-19–related deaths between the ibrutinib-BR and BR arms (3 *v* 2 deaths). By contrast, ECHO was conducted during the pandemic, and there were more all-grade, grade ≥3, and grade 5 COVID-19 events in the acalabrutinib arm compared with placebo (41% *v* 30%, 20% *v* 17%, and 9.4% *v* 6.7%, respectively). In older populations, the increased cardiovascular risks and immunosuppression resulting from both bendamustine and a cBTKi should be carefully considered when choosing a first-line treatment.

The benefit of combining a cBTKi with immunochemotherapy is also evident in transplant-eligible patients. In TRIANGLE, 870 patients were randomly assigned to one of three arms: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP)/rituximab, dexamethasone, high-dose cytarabine, cisplatin (R-DHAP), followed

by ASCT (arm A); R-CHOP + ibrutinib/R-DHAP followed by ASCT, followed by 2 years of ibrutinib maintenance (arm A + I); or R-CHOP + ibrutinib/R-DHAP with no ASCT, followed by 2 years of ibrutinib maintenance (arm I).[37] After the results of the LYMA trial[32,38] confirmed an OS benefit for rituximab maintenance after ASCT, patients in all arms were permitted to have rituximab maintenance according to investigator discretion. In the primary analysis, after 31-month median follow-up, both ibrutinib-containing arms resulted in improvements in the ORR and failure-free survival (FFS) over the control arm. With the 4-year follow-up, TRIANGLE confirmed an OS benefit for both ibrutinib-containing arms over the control arm.[31] Among certain high-risk subgroups (Ki-67 >30%, high p53 expression, and blastoid histology) there was a nonsignificant trend toward superiority in FFS for the A + I arm over arm I. Thus, while we cannot exclude a potential benefit from ASCT for a minority, it is known to increase toxicity and the overall results of TRIANGLE suggest that ASCT can be omitted when ibrutinib is available in this setting and the authors suggest arm I can be considered the new standard of care in this younger patient population. It is important to highlight that ibrutinib cannot be combined with high-dose cytarabine in induction because of increased toxicity.

All three studies were conducted in different populations including cBTKi plus rituximab maintenance. cBTKi maintenance, with or without ASCT, seems tolerable and enhances duration of disease control. The optimal duration of cBTKi maintenance remains undetermined.

ENRICH[39] is the first trial so far that compares a first-line chemotherapy-free strategy with IR to immunochemotherapy (investigator choice BR or R-CHOP). The investigators demonstrated that IR prolonged PFS without improving OS. It is worth noting that the benefit of the experimental arm was observed exclusively in comparison with the R-CHOP subgroup and not the BR subgroup. The lower incidence of grade 3-4 neutropenia and the faster improvement in quality-of-life measure also favor IR, although it was more cardiotoxic (22% all-grade and 6% grade ≥3 atrial fibrillation). ENRICH thus positions anti-CD20 plus cBTKi (ibrutinib) without chemotherapy as a relevant option in the first-line setting, paving the way for a chemotherapy-free first-line era.

Although a phase II design (rather than phase III), ECOG-ACRIN EA4181 randomly assigned patients with MCL younger than 70 years to one of three arms: BR with high-dose cytarabine and rituximab (BR/HDAC), BR/HDAC with a fixed-duration acalabrutinib (BR/HDAC-A), and BR with fixed-duration acalabrutinib (BR-A).[29] The primary end point was a composite of PET-complete metabolic response (CMR) and PB uMRD rate by ClonoSeq (<1 in $10^{-5}$). The primary analysis set comprised 260 patients with baseline clonal sequence identified and end-of-treatment MRD result. The BR-A arm was closed early because of lack of superiority. The PET CMR/uMRD rates were high in all arms, and although the addition of acalabrutinib did not improve efficacy, it did result in greater toxicity (hematologic and febrile neutropenia) when combined with cytarabine. This contrasts with the TRIANGLE outcomes in which ibrutinib was paused during high-dose cytarabine, highlighting the importance of this dosing strategy. The relatively short median follow-up of 28 months and study design (permitting consolidation approaches per investigator discretion) make it challenging to draw firm conclusions regarding the impact of fixed-duration acalabrutinib on PFS and OS, although they seemed similar at the 12-month landmark. Whether younger patients (ie, ≤65 years) can reasonably receive BR-A in place of a TRIANGLE approach remains unclear, and at present, the TRIANGLE-based approach is the only treatment to demonstrate a superior PFS and OS over the standard-of-care approach in a large, randomized trial. However, for younger patients where anthracycline or platinum-based therapy may be inadvisable, BR-A represents a possible induction option.

With the limitation of subgroup analyses, none of these four phase III studies identifies a clear subgroup of patients with MCL benefiting more (or less) from the addition of a cBTKi, suggesting that all patients, regardless of their profile, derive an advantage from the addition of a first-line cBTKi.

## ALTERNATIVE BTK TARGETING IN R/R MCL AFTER COVALENT BTK INHIBITION

The success of cBTK inhibitors in the initial treatment of patients with MCL has led to the need to develop agents active in patients developing resistance to these agents. Although fixed-duration application of cBTKi as in TRIANGLE may afford the opportunity for re-treatment, most patients with MCL will eventually experience disease progression after these agents. The reversible, noncovalent BTK (ncBTK) inhibitor pirtobrutinib[30] was developed to overcome the C481S mutation, responsible for many instances of acquired resistance in patients with chronic lymphatic leukemia (CLL) treated with ibrutinib.[40] Although most patients with MCL who develop cBTKi resistance do so by using non-C481S dependent mechanisms,[41] the BRUIN investigators demonstrated pirtobrutinib to be highly effective in this setting. In the phase II MCL cohort of BRUIN, the primary efficacy cohort comprised the first 90 patients treated in either phase I/II who had received a prior cBTKi.[42] The median age was 70 years, and patients had a median of three prior lines of therapy, with 78% of patients with an intermediate-risk or high-risk s-MIPI score. The ORR was 58% (20% complete response) in the primary publication; in a more recent update with a larger data set of 152 patients, more information regarding high-risk subgroups was available: Although subgroups were modest, the ORR was similar in those with blastoid (6/15, 40%) or pleomorphic (8/17, 47%) histology, *TP53* mutation (13/30, 43%), and Ki-67 ≥ 30% (20/45, 44%).[43] Similarly, there was no ORR differences according to the prior cBTKi used: ibrutinib (n = 59; ORR 59%), acalabrutinib (n = 31, ORR 58%), or zanubrutinib

(n = 6, ORR 50%). The 13 patients treated with prior chimeric antigen receptor (CAR) T-cell therapy had a numerically lower ORR (38%), which seemed similar in observational data sets recently presented from a US academic consortium (n = 13, ORR 31%).[44] Pirtobrutinib is being compared with physician's choice of cBTKi in BTKi-naïve R/R MCL in the phase III randomized BRUIN-321 study.[45] The primary end point is PFS, with the primary efficacy analysis expected in the near future.

The other reversible ncBTKi nemtabrutinib is also being evaluated in MCL after cBTKi failure as monotherapy in BELLWAVE-003 (ClinicalTrials.gov identifier: NCT04728893), for which no results are currently available, and cohort C of the phase Ib WAVELINE-006 study in combination with the ROR1 antibody-drug conjugate zilovertamab vedotin.[46] Among 28 patients treated, the ORR is 64% (CRR 32%) to date, but the single-agent activity of nemtabrutinib remains unclear until data from the monotherapy study are presented.

BTK protein degraders are a novel class of agent that reduces BTK protein levels through binding to both BTK and E3 ligase, leading to ternary complex formation, polyubiquitination, and degradation. The most clinically advanced agents in this class are BGB-16673, NX-5948, and ABBV-101. The initial data from the phase I CaDAnCe study of BGB-16673 included four patients with post-cBTKi MCL,[47] with 1 response observed. The study is ongoing and seems to result in promising activity in other disease subtypes including CLL,[47] indolent B-cell lymphoma,[48] and Waldenström macroglobulinemia.[49] Of note, patients with prior treatment lines including covalent and ncBTK inhibitors have had responses and the safety profile similar to other BTK inhibitors, with bruising the most common AE. Enrollment to the study is ongoing, and data from a larger number of patients with MCL is anticipated. Early data from the phase I study of NX-5948, which shares a similar mechanism of action, also seem promising, with encouraging preliminary efficacy in the CLL cohort.[50] Enrollment to the study includes patients with MCL and is ongoing. The phase I study evaluating ABBV-101 is ongoing, with no data available currently.[51]

## FUTURE PARADIGM

On the basis of the recent data generated in the context of prospective clinical trials incorporating BTKi first line, the authors present in Figure 1 a potential future first-line management algorithm of symptomatic MCL, while recognizing the limitations of BTKi availability depending on the geographies, reimbursement, and access. Although the results of TRIANGLE have made ASCT consolidation outdated, the young/fit versus older/less fit paradigm remains broadly valid, as most of the prospective trials were designed on the basis of this dichotomy. For young patients, the OS benefit observed in TRIANGLE with the two ibrutinib-containing arms (I and A + I) combined with the excess of toxicity of the A + I arm favor the R-CHOP-ibrutinib/R-DHAP/Ox induction followed by ibrutinib and rituximab maintenance, with the safe omission of ASCT. Other less toxic second-generation cBTKis may be considered in place of ibrutinib depending on availability and preference. For older or less fit patients, the positive results of the registrational ECHO trial has led to the FDA approval of BR-A, providing a new standard-of-care option for chemotherapy-eligible patients. More recent evidence from the randomized ENRICH and phase II ALTAMIRA trials suggest that rituximab and cBTKi combinations provide a safe and highly effective option for patients with a lower biological risk disease (defined as without *TP53* abnormalities, classical morphology, and low Ki67 <30%), as well as for those unfit for full-dose immunochemotherapy. In both strategies, maintenance should be applied with 2 years of rituximab and cBTKi until progression or toxicity until strong evidence suggests otherwise. Importantly, for *TP53*-mutated patients, the authors highlight the absence of a clear standard of care and consider all patients for clinical trials or the anti CD20-cBTKi-BCL2i triplet regimen if available (on the basis of BOVEN and OASIS I data).

As first-line treatments evolve to incorporate continuous and fixed-duration cBTKi therapy, future treatment approaches for R/R MCL will leverage new therapeutic tools including CD19-directed CAR T-cell therapy, ncBTK inhibition, and other therapies currently under investigation such as bispecific antibodies,[52,53] BTK degraders, and ROR1 antibody-drug conjugates.[54] In Figure 2, we present a potential future management approach with available therapies for patients with R/R MCL after first-line cBTKi–based treatment. For patients achieving a response and adequate remission with initial time-limited cBTKi, retreatment with cBTKi with or without venetoclax should be considered at first relapse.[55] Limited data on cBTKi retreatment highlight the need for future studies to identify optimal candidates on the basis of clinical and molecular features. For patients progressing on continuous first-line cBTKi therapy, we recommend CD19-directed CAR T-cell therapy, such as brexucabtagene autoleucel, given the high efficacy with best ORR 91%, CRR 68%, and median PFS 25.8 months reported in ZUMA-2,[56,57] although few patients were treated in the second-line setting. If CAR T-cell therapy is not appropriate or available, then the noncovalent BTKi pirtobrutinib is a well-tolerated and broadly applicable oral option. BRUIN demonstrated ORR 58%, CRR 20%, and a median PFS of 7.4 months with pirtobrutinib in patients previously treated with cBTKi.[42] For younger, fit patients with high-risk features and a suitable donor, allogeneic SCT remains a potentially curative option for selected patients with R/R MCL.[58] Other historically available treatments such as non–cross-resistant chemoimmunotherapy, rituximab and lenalidomide have shown modest efficacy after cBTKi treatment.[59-61] This underscores the urgent need for clinical trial enrollment to define novel therapies and refine treatment strategies after cBTKi therapy for R/R MCL.

In conclusion, the management of MCL is transforming rapidly, with improvements seen for many of our patients with the advent of novel nonchemotherapeutics. cBTK inhibitors have been the most prominent example of this over recent years and as outlined in this article, the direction of travel to integrate their use in the first line is clear. What remains unanswered is which combination strategies, leveraging potentially either chemotherapy or nonchemotherapeutic approaches, will optimally benefit which patient groups. An improved understanding and study of biological risk, optimal time length of therapy, MRD utility and kinetics, and toxicity of combinations is necessary to keep moving the needle forward to further improve survival for our patients with MCL.


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## REFERENCES


1. Kumar A, Sha F, Toure A, et al: Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: Progressive shortening in response duration and survival after each relapse. Blood Cancer J 9:50, 2019
2. Eyre TA, Cheah CY, Wang ML: Therapeutic options for relapsed/refractory mantle cell lymphoma. Blood 139:666-677, 2022
3. Boike L, Henning NJ, Nomura DK: Advances in covalent drug discovery. Nat Rev Drug Discov 21:881-898, 2022
4. Song Y, Zhou K, Zou D, et al: Zanubrutinib in relapsed/refractory mantle cell lymphoma: Long-term efficacy and safety results from a phase 2 study. Blood 139:3148-3158, 2022
5. Wang M, Rule S, Zinzani PL, et al: Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): A single-arm, multicentre, phase 2 trial. Lancet 391:659-667, 2018
6. Wang ML, Rule S, Martin P, et al: Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 369:507-516, 2013
7. Rule S, Jurczak W, Jerkeman M, et al: Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study. Leukemia 32:1799-1803, 2018
8. Rule S, Dreyling M, Goy A, et al: Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: Extended 3.5-year follow up from a pooled analysis. Haematologica 104:e211-e214, 2019
9. McCulloch R, Lewis D, Crosbie N, et al: Ibrutinib for mantle cell lymphoma at first relapse: A United Kingdom real-world analysis of outcomes in 211 patients. Br J Haematol 193:290-298, 2021
10. Visco C, Di Rocco A, Evangelista A, et al: Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: Results from the MANTLE-FIRST study. Leukemia 35:787-795, 2021
11. Malinverni C, Bernardelli A, Glimelius I, et al: Outcomes of younger patients with mantle cell lymphoma experiencing late relapse (>24 months): The LATE-POD study. Blood 144:1001-1009, 2024
12. Rusconi C, Cheah CY, Eyre TA, et al: Ibrutinib improves survival compared with chemotherapy in mantle cell lymphoma with central nervous system relapse. Blood 140:1907-1916, 2022
13. Novak U, Fehr M, Schär S, et al: Combined therapy with ibrutinib and bortezomib followed by ibrutinib maintenance in relapsed or refractory mantle cell lymphoma and high-risk features: A phase 1/2 trial of the European MCL network (SAKK 36/13). EClinicalMedicine 64:102221, 2023
14. Jerkeman M, Eskelund CW, Hutchings M, et al: Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): A multicentre, open-label, single-arm, phase 2 trial. Lancet Haematol 5:e109-e116, 2018
15. Le Gouill S, Morschhauser F, Chiron D, et al: Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: A phase 1/2 trial. Blood 137:877-887, 2021
16. Handunnetti SM, Anderson MA, Burbury K, et al: Seven-year outcomes of venetoclax-ibrutinib therapy in mantle cell lymphoma: Durable responses and treatment-free remissions. Blood 144:867-872, 2024
17. Wang M, Jurczak W, Trněný M, et al: Ibrutinib combined with venetoclax in patients with relapsed/refractory mantle cell lymphoma: Primary analysis results from the randomized phase 3 Sympatico study. Blood 142:LBA-2, 2023
18. Jain P, Zhao S, Lee HJ, et al: Ibrutinib with rituximab in first-line treatment of older patients with mantle cell lymphoma. J Clin Oncol 40:202-212, 2022
19. Giné E, de La Cruz F, Jiménez Ubieto A, et al: Ibrutinib in combination with rituximab for indolent clinical forms of mantle cell lymphoma (IMCL-2015): A multicenter, open-label, single-arm, phase II trial. J Clin Oncol 40:1196-1205, 2022
20. Jerkeman M, Wader KF, Glimelius I, et al: Acalabrutinib and rituximab in elderly patients with newly diagnosed mantle cell lymphoma including a matched population-based external comparator-the Nordic Lymphoma Group NLG-MCL8 (ALTAMIRA) phase II trial. Blood 144:747, 2024
21. Jain P, Chi Young C, Nastoupil LJ, et al: Acalabrutinib with rituximab as first-line therapy for older patients with mantle cell lymphoma—A phase II clinical trial. Blood 142:3036, 2023
22. Tessoulin B, Morschhauser F, Chiron D, et al: 5-y follow-up of combination of ibrutinib, obinutuzumab and venetoclax for patients with newly diagnosed mantle cell lymphoma, the oasis trial. Blood 144:1657, 2024
23. Le Gouill S, de Wilde V, Eyre TA, et al: Ibrutinib, venetoclax plus CD20 monoclonal ab provides very high MRD negativity in previously untreated MCL patients, initial results of OASIS II, a randomized phase 2 trial. Blood 144:745, 2024
24. Wang M, Robak T, Maddocks KJ, et al: Acalabrutinib plus venetoclax and rituximab in treatment-naive mantle cell lymphoma: 2-year safety and efficacy analysis. Blood Adv 8:4539-4548, 2024
25. Kumar A, Soumerai J, Abramson JS, et al: Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a TP53 mutation. Blood 145:497-507, 2025
26. Ruan J, Bond DA, Shah BD, et al: MRD-driven time-limited therapy of acalabrutinib and lenalidomide plus rituximab (ALR) or obinutuzumab (ALO) in patients with treatment-naïve mantle cell lymphoma: Phase 2 trial outcomes with MRD and cfDNA analyses. Blood 144:746, 2024
27. Zhao X, Bodo J, Sun D, et al: Combination of ibrutinib with ABT-199: Synergistic effects on proliferation inhibition and apoptosis in mantle cell lymphoma cells through perturbation of BTK, AKT and BCL2 pathways. Br J Haematol 168:765-768, 2015
28. Tam CS, Anderson MA, Pott C, et al: Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. N Engl J Med 378:1211-1223, 2018
29. Wagner-Johnston N, Jegede O, Spurgeon SE, et al: Addition or substitution of acalabrutinib in intensive frontline chemoimmunotherapy for patients ≤ 70 years old with mantle cell lymphoma: Outcomes of the 3-arm randomized phase II intergroup trial ECOG-ACRIN EA4181. Blood 144:236, 2024
30. Mato AR, Shah NN, Jurczak W, et al: Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): A phase 1/2 study. Lancet 397:892-901, 2021

31. Dreyling M, Doorduijn JK, Gine E, et al: Role of autologous stem cell transplantation in the context of ibrutinib-containing first-line treatment in younger patients with mantle cell lymphoma: Results from the randomized triangle trial by the European MCL network. Blood 144:240, 2024
32. Le Gouill S, Thieblemont C, Oberic L, et al: Rituximab after autologous stem-cell transplantation in mantle-cell lymphoma. N Engl J Med 377:1250-1260, 2017
33. Wang ML, Jurczak W, Jerkeman M, et al: Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma. N Engl J Med 386:2482-2494, 2022
34. Wang M, Salek D, Belada D, et al: Acalabrutinib plus bendamustine-rituximab in untreated mantle cell lymphoma. J Clin Oncol 43:2276-2284, 2025
35. Minson A, Hamad N, Di Ciaccio P, et al: Death from mantle cell lymphoma limits sequential therapy, particularly after first relapse: Patterns of care and outcomes in a series from Australia and the United Kingdom. Br J Haematol 204:548-554, 2024
36. Wang Y, Larson MC, Hwang SR, et al: Multicenter study of mantle cell lymphoma outcomes following first-line bendamustine-rituximab and second-line Bruton's tyrosine kinase inhibitor therapy. Blood 142:300, 2023
37. Dreyling M, Doorduijn J, Giné E, et al: Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): A three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. Lancet 403:2293-2306, 2024
38. Sarkozy C, Thieblemont C, Oberic L, et al: Long-term follow-up of rituximab maintenance in young patients with mantle-cell lymphoma included in the LYMA trial: A LYSA study. J Clin Oncol 42: 769-773, 2024
39. Lewis DJ, Jerkeman M, Sorrell L, et al: Ibrutinib-rituximab is superior to rituximab-chemotherapy in previously untreated older mantle cell lymphoma patients: Results from the International Randomised Controlled Trial, Enrich. Blood 144:235, 2024
40. Woyach JA, Furman RR, Liu T-M, et al: Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med 370:2286-2294, 2014
41. Hershkovitz-Rokah O, Pulver D, Lenz G, et al: Ibrutinib resistance in mantle cell lymphoma: Clinical, molecular and treatment aspects. Br J Haematol 181:306-319, 2018
42. Wang ML, Jurczak W, Zinzani PL, et al: Pirtobrutinib in covalent Bruton tyrosine kinase inhibitor pretreated mantle-cell lymphoma. J Clin Oncol 41:3988-3997, 2023
43. Cohen JB, Shah NN, Jurczak W, et al: Pirtobrutinib in relapsed/refractory (R/R) mantle cell lymphoma (MCL) patients with prior cBTKi: Safety and efficacy including high-risk subgroup analyses from the phase 1/2 BRUIN study. Blood 142:981, 2023
44. Epstein-Peterson ZD, Lionel AC, Joseph A, et al: Treatment patterns and outcomes following progression of disease post-CAR-T therapy in relapsed or refractory mantle cell lymphoma: A multicenter analysis. Blood 144:238, 2024
45. Eyre TA, Shah NN, Dreyling M, et al: BRUIN MCL-321: Phase III study of pirtobrutinib versus investigator choice of BTK inhibitor in BTK inhibitor naive mantle cell lymphoma. Future Oncol 18: 3961-3969, 2022
46. Paszkiewicz-Kozik E, Moreira C, Turgut M, et al: Zilovertamab vedotin in combination with nemtabrutinib for patients with relapsed or refractory mantle cell lymphoma: Cohort C of the open-label, phase 2 Waveline-006 study. Blood 144:3025, 2024
47. Seymour JF, Cheah CY, Parrondo R, et al: First results from a phase 1, first-in-human study of the Bruton's tyrosine kinase (BTK) degrader Bgb-16673 in patients (Pts) with relapsed or refractory (R/R) B-cell malignancies (BGB-16673-101). Blood 142:4401, 2023
48. Tam CS, Frustaci AM, Bijou F, et al: Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory (R/R) indolent NHL: Results from the phase 1 CaDAnCe-101 study. Blood 144:1649, 2024
49. Seymour JF, Tam CS, Cheah CY, et al: Preliminary efficacy and safety of the Bruton tyrosine kinase degrader BGB-16673 in patients with relapsed or refractory Waldenström macroglobulinemia: Results from the phase 1 CaDAnCe-101 study. Blood 144:860, 2024
50. Shah NN, Omer Z, Collins GP, et al: Efficacy and safety of the Bruton's tyrosine kinase (BTK) degrader NX-5948 in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL): Updated results from an ongoing phase 1a/b study. Blood 144:884, 2024
51. Chong EA, Yuda J, Izutsu K, et al: A first-in-human study of the potent and highly selective BTK degrader ABBV-101 in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 42, 2024 (suppl 16; abstr TPS7091)
52. Phillips TJ, Matasar M, Eyre TA, et al: GLOBRYTE: A phase III, open-label, multicenter, randomized trial evaluating glofitamab monotherapy in patients with relapsed or refractory mantle cell lymphoma. Blood 142:3052, 2023
53. Phillips TJ, Carlo-Stella C, Morschhauser F, et al: Glofitamab in relapsed/refractory mantle cell lymphoma: Results from a phase I/II study. J Clin Oncol 43:318-328, 2024
54. Wang ML, Barrientos JC, Furman RR, et al: Zilovertamab vedotin targeting of ROR1 as therapy for lymphoid cancers. NEJM Evid 1:EVIDoa2100001, 2022
55. Wierda WG, Jacobs R, Barr PM, et al: Outcomes in high-risk subgroups after fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Up to 5.5 years of follow-up in the phase 2 CAPTIVATE study. J Clin Oncol 42, 2024 (suppl 16; abstr 7009)
56. Wang M, Munoz J, Goy A, et al: Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. J Clin Oncol 41: 555-567, 2023
57. Wang M, Munoz J, Goy A, et al: KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med 382:1331-1342, 2020
58. Munshi PN, Hamadani M, Kumar A, et al: ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma. Bone Marrow Transplant 56: 2911-2921, 2021
59. Wang M, Schuster SJ, Phillips T, et al: Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004). J Hematol Oncol 10:171, 2017
60. Wang M, Fayad L, Wagner-Bartak N, et al: Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: A phase 1/2 clinical trial. Lancet Oncol 13: 716-723, 2012
61. McCulloch R, Visco C, Eyre TA, et al: Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. Br J Haematol 189:684-688, 2020

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Mantle Cell Lymphoma: Optimal Treatment With Bruton Tyrosine Kinase–Targeted Approaches**

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