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Mantle cell lymphoma: Evolving frontline treatment strategies

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Introduction

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for 3-10% of new NHL cases in Canada.[1] The clinical course of MCL is heterogeneous, ranging from indolent behavior that does not require therapy for years, to highly aggressive disease with limited prognosis.[2,3] As such, the 2022 International Consensus Classification (ICC) and World Health Organization (WHO) classifications subdivide MCL into two categories: 1) indolent MCL, which is characterized by blood involvement, splenomegaly without nodal involvement, or low-burden nodal involvement (mutated immunoglobulin heavy chain [IGHV], SOX11 negative, low Ki67 proliferative index); and 2) aggressive MCL, which is characterized by pleomorphic and blastoid morphologic appearance, *TP53* aberrancy, high Ki67, and unmutated IGHV.[4,5]

While traditionally, patients with MCL had a median overall survival (OS) of only 3 to 5 years, there has been significant improvement over the last two decades, owing to chemoimmunotherapy with rituximab, cytarabine-based induction regimens, addition of consolidative autologous stem cell transplant (ASCT), rituximab maintenance, and the advent of novel targeted therapies (including Bruton kinase inhibitors [BTKi], venetoclax, and lenalidomide) in the relapsed setting.[6] Despite these advances, MCL remains incurable even with aggressive therapy, and most patients will invariably relapse.[7] As such, prospective studies integrating novel therapies with either a chemotherapy backbone or evaluating chemotherapy-free regimens are ongoing, aiming to improve outcomes and reduce toxicities. This review summarizes the current understanding of disease prognostication, treatment options, and novel therapeutic strategies that will reshape the treatment paradigm of MCL in the near future.

Prognostic factors in the frontline setting

While several prognostic factors have been identified, including the mantle cell international prognostic index (MIPI-c)[8], Ki67 fraction[8], aberrant *TP53*[9,10], and other molecular aberrations, including gene expression profiling (e.g. *NOTCH, KMT2D,* and *MYC*)[11-13], SOX11 expression[14], and a complex karyotype[15], none have been investigated prospectively to guide treatment selection. The prognostic role of the most recent iteration of MIPI, the MIPI-c, which incorporates Ki67, has been validated predominantly in trial settings[8] and it is important to highlight that *TP53* mutation status is not included in this model.[9] While a *TP53* mutation appears to be a stronger prognostic marker than del17p, its role is limited by access to widespread *TP53* testing.[16] Studies are inconsistent regarding the correlation between p53 expression by immunohistochemistry and *TP53* mutation.[17-19] Due to current diagnostic limitations, both *TP53* mutation and p53 expression by immunohistochemistry have been recommended for risk assessment.[9]

Observation vs. initial treatment

Although most patients ultimately require treatment, patients with non-nodal MCL and a subset of patients with nodal MCL with indolent disease at presentation do not require immediate treatment and can be safely observed. Although there are no prospective studies for observation vs. immediate treatment, retrospective real-world data (RWD) suggest the safety (without impacting survival outcomes) of this approach for patients with asymptomatic disease, good performance status, non-nodal disease, normal lactate dehydrogenase (LDH), and low Ki67.[20-22] However, while there are currently no standardized selection criteria for identification of patients suitable for initial observation, an approach similar to follicular lymphoma presenting without symptoms and with low tumour burden that does not progress on short

interval (3-4 months) follow-up scans, is often taken.

Current standard-of-care approach in the frontline setting

A current treatment algorithm for frontline management of MCL is presented in **Figure 1.** Patients requiring treatment are broadly categorized into two cohorts: those undergoing intensive chemoimmunotherapy followed by consolidative ASCT; and those who are transplant-ineligible for whom less intensive chemoimmunotherapy regimens are appropriate. Although prospective studies have utilized a cut-off age of 65 years to determine ASCT eligibility, no definitive age limit exists, and individuals up to age 70, provided they are otherwise fit, may still be deemed suitable candidates for ASCT.

Transplant-eligible patients

ASCT has been the standard-of-care for younger patients requiring therapy at first remission.[23,24] The benefit of ASCT was established by the MCL European Network study, which randomized patients following CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without rituximab (R) to either ASCT or IFN-α maintenance treatment.[24] At a median follow-up of 14 years, an OS benefit emerged (median progression-free survival [PFS] 3.3 years vs. 1.5 years favouring ASCT; median OS 7.5 years vs. 4.8 years in all patients); however, this OS benefit was mainly observed in patients who did not receive rituximab, as confirmed by subgroup analysis,[25] suggesting that the induction regimen likely plays an important role in outcomes.

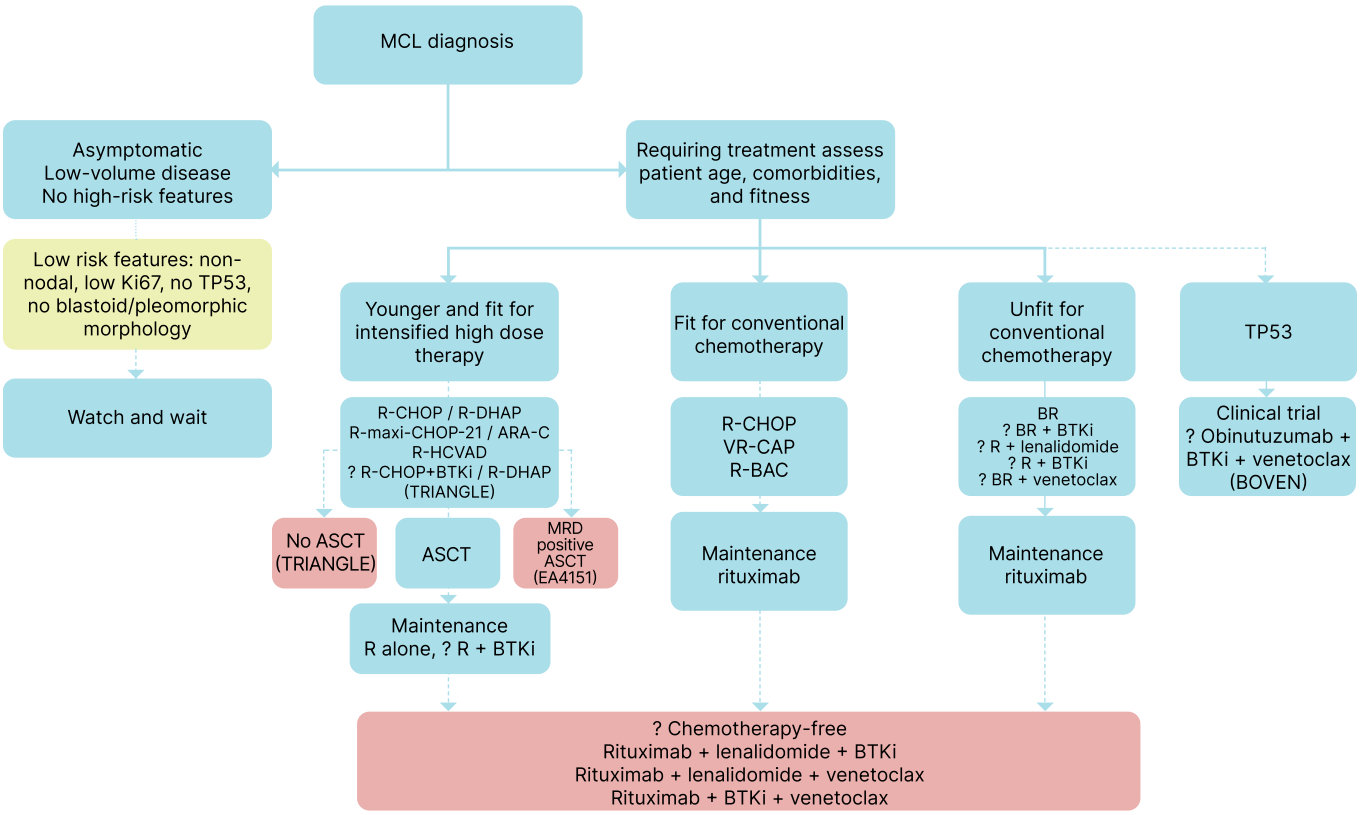


Figure 1. Flow chart reflecting the current treatment algorithm for frontline management of mantle cell lymphoma, with integration of the evolving treatment landscape with recent pivotal trials integrating novel targeted agents in the frontline setting. Dashed lines represent areas of uncertainty and ongoing areas of investigation. *Courtesy of Inna Y. Gong, MD. John Kuruvilla, MD and Michael Crump, MD*

Abbreviations: ASCT: autologous stem cell transplant; **BR:** bendamustine/rituximab; **BTKi:** Bruton tyrosine kinase inhibitor; **MCL:** mantle cell lymphoma; **R:** rituximab; **R-CHOP:** rituximab/cyclophosphamide/vincristine/doxorubicin/prednisone; **R-DHAP:** rituximab/dexamethasone/ARA-C/cisplatin; **R-HCVAD:** rituximab/cyclophosphamide/vincristine/doxorubicin/dexamethasone; **VR-CAP:** bortezomib/rituximab/cyclophosphamide/doxorubicin/prednisone; **R-BAC:** BR/lower dose cytarabine.

For young and fit patients, various intensive chemoimmunotherapy induction regimens have been studied, with cytarabine-based regimens being the preferred approach. The importance of cytarabine-based induction was established by the MCL YOUNGER trial, which compared R-CHOP with alternating R-CHOP and R-DHAP (rituximab, dexamethasone, ARA-C: i.e. high-dose cytarabine, cisplatin), followed by total body irradiation-based conditioning and ASCT. While R-CHOP/R-DHAP more than doubled the time-to-treatment failure (109 vs. 47 months) and OS, this was associated with increased grade 3-4 toxicity.[26] Long-term follow-up of the Nordic MCL2 trial evaluating alternating dose-intense CHOP and high-dose cytarabine prior to ASCT showed a median PFS of 8.5 years and OS of 12.7 years, suggesting long-term remissions in a subset of patients.[7,27] The R-hyper-CVAD regimen (hyperfractionated intense-dose cyclophosphamide, vincristine, continuous doxorubicin, and dexamethasone)[28], resulted in a complete response rate (CR) of 87%, median PFS of 4.8 years (5.5 years for those aged ≤65 years), and median OS of 6.8 years.[29]

As an alternative to multi-agent induction regimens often requiring inpatient administration, bendamustine-based therapies have been increasingly studied prior to ASCT. Bendamustine-rituximab (BR) was compared to R-hyper-CVAD in the randomized Phase II S1106 study, which was closed early due to a high rate of stem cell mobilization failure in the R-hyper-CVAD arm,[30,31] limiting the conclusions that can be drawn regarding the relative efficacy of BR in the pre-ASCT setting.

The role of rituximab maintenance (RM) treatment after ASCT for younger patients was uncertain until results of the Phase III LyMa trial were published, which showed a 4-year event-free survival (EFS) of 79% in the RM arm compared to 61% in the observation arm, and a 4-year OS of 89% and 80%, respectively.[32] The benefit of RM after ASCT has also been reported in observational studies,[33] and remains the standard-of-care.

Transplant-ineligible patients

For patients who are not candidates for intensive induction and ASCT, treatment involves the selection of one of several chemoimmunotherapy regimens, with or without RM. In the long-term follow-up of the MCL ELDERLY trial (median follow-up of 7.6 years), R-CHOP followed by RM was superior to FCR (fludarabine, cyclophosphamide, rituximab),[34] with a median OS of 6.4 and 3.9 years, respectively.[35] The LYM-3002 trial compared the substitution of bortezomib for vincristine (VR-CAP) to R-CHOP and has reported superiority of this regimen, with improved response rates and OS benefit (median OS of 90 months for VR-CAP compared to 55 months for R-CHOP).[36,37] However, its widespread use in this patient population has been limited in the Canadian context by funding constraints and the adoption in most provinces of BR as the preferred standard-of-care in this setting based on the BRIGHT and STiL trials. These randomized Phase III studies found a significant benefit for PFS and improved toxicity profile of BR over R-CHOP, which has been corroborated by findings from a recent population-based study in Ontario.[38,39] The addition of lower dose cytarabine to BR (R-BAC) showed excellent outcomes in older patients, with 7-year PFS and OS rates of 55% and 62%, respectively.[40,41] While these results are encouraging, the single-arm nature of the study limits its routine clinical adoption.

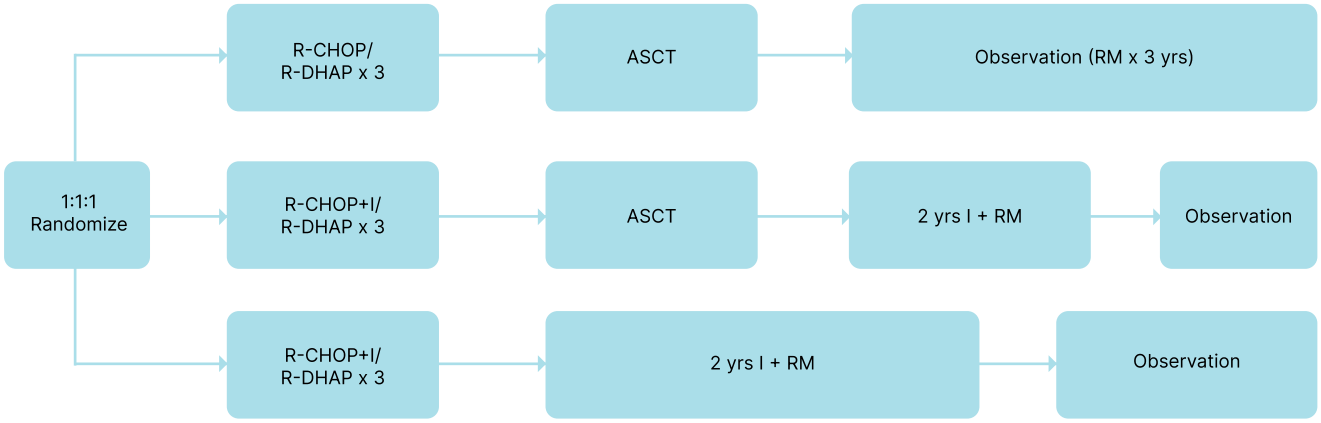
RM following chemoimmunotherapy is supported by the MCL ELDERLY trial, which compared RM with IFN-α maintenance. In patients who responded to R-CHOP, RM led to a longer median PFS (51 vs. 24 months) and OS (9.8 vs. 7.1 years).[35] Improved outcomes with RM have also been corroborated in retrospective RWD.[42,43] Despite a lack of prospective evidence for RM following BR, it is well accepted as standard-of-care practice across Canada.

The evolving frontline treatment landscape

Integration of targeted agents to chemoimmunotherapy

The integration of novel agents in the frontline setting to improve chemoimmunotherapy is being actively investigated. The TRIANGLE trial aimed to address whether the inclusion of ibrutinib for induction and maintenance treatment could replace ASCT. This trial by the European MCL Network randomized patients to one of three arms: R-CHOP/R-DHAP induction, followed by ASCT and 3 years of RM (cohort A); addition of the BTKi ibrutinib to induction pre-ASCT and first 2 years of maintenance (cohort B); and addition of ibrutinib to induction and maintenance with ASCT omission (cohort C) **Figure 2A**.[44] The recently published manuscript reported a 3-year failure-free survival (FFS) and OS rates of 72% and 86% in cohort A, 88% and 91% in cohort B, and 86% and 92% in cohort C, respectively. These results are provocative

A. Study schema of TRIANGLE



B. Study schema of EA4151

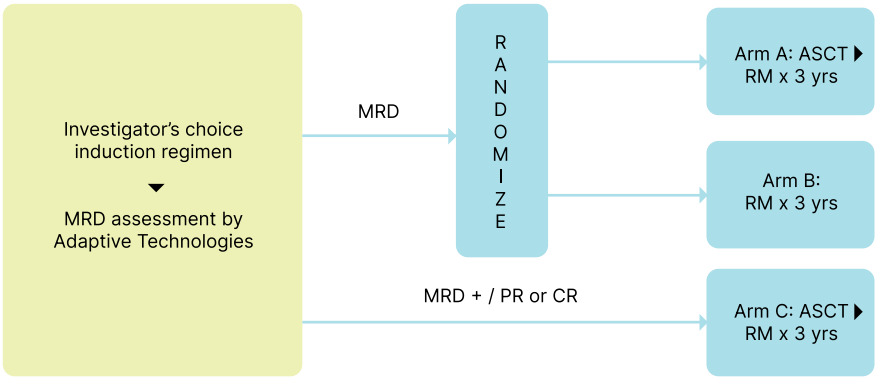


Figure 2. Simplified schema of the TRIANGLE trial integrating a Bruton tyrosine kinase inhibitor in the frontline setting and the EA4151 response-adapted trial evaluating the role of ASCT in patients achieving MRD-negativity post-induction. *Courtesy of Inna Y. Gong, MD. John Kuruvilla, MD and Michael Crump, MD*
Abbreviations: ASCT: ASCT, autologous stem cell transplant; **BR:** bendamustine/rituximab; **BTKi:** Bruton tyrosine kinase inhibitor; **CR:** complete remission; **I:** ibrutinib; **MCL:** mantle cell lymphoma; **MRD:** measurable residual disease; **PR:** partial remission; **R:** rituximab; **R-CHOP:** rituximab/cyclophosphamide/vincristine/doxorubicin/prednisone; **R-DHAP:** rituximab/dexamethasone/ARA-C/cisplatin; **RM:** rituximab maintenance; **YRS:** years

and show an improvement in 3-year PFS in the two arms that integrated BTKi in the frontline compared to arm A, which did not. Further support for integration of BTKi in the frontline setting comes from the RECTANGLE Phase II study (acalabrutinib to R-CHOP, followed by ASCT and maintenance with R and acalabrutinib for 2 years), which showed promising results with an objective response rate (ORR) of 100% (complete remission [CR] 91%) and PFS and OS of ~95%.[45] Taken together, the results of these studies may establish the role of BTKi in the frontline setting for younger patients.

The addition of ibrutinib has also been studied in transplant-ineligible patients. In the randomized Phase III SHINE trial, ibrutinib was added to BR, followed by RM in those who achieved partial or complete response, while patients with stable disease continued ibrutinib with rituximab.[46] While a PFS benefit was observed in the ibrutinib arm compared to BR alone (median PFS 81 months [6.8 years] vs. 53 months [4.4 years]), there was no survival benefit reported with a median follow-up of 85 months. The benefit was also limited to low- or intermediate-risk MIPI and unmutated TP53 in subgroup analyses. Notably, the ibrutinib arm had a higher incidence

of grade 3+ adverse events (AEs), namely atrial fibrillation and hypertension. Although there was a lower incidence of death due to disease progression in the ibrutinib arm, this was offset by the higher incidence of death due to AEs (11% vs. 6%) and death during follow-up (18% vs. 14%). Among deaths attributed to AEs, compared to BR, the ibrutinib arm had more infection-(9 vs. 5 patients, respectively) and COVID-19-related deaths (3 vs. 0 patients, respectively), followed by cardiovascular-related deaths (3 vs. 0 patients, respectively).

Several ongoing trials explore the addition of a second-generation BTKi to chemoimmunotherapy, which will inform whether a more selective BTKi could alleviate the toxicity observed in the SHINE trial. The EA4181 study (NCT04115631) is randomizing patients to one of three arms: 1) BR for 3 cycles followed by rituximab and cytarabine for 3 cycles; 2) addition of acalabrutinib with BR for 3 cycles followed by R-cytarabine; and 3) BR with acalabrutinib for 6 cycles. The ECHO study (NCT02972840) similarly compares the combination of acalabrutinib with BR to BR alone.

Chemotherapy-free approaches for MCL?

While outcomes have improved with intensive chemotherapy strategies, chemotherapy-free approaches in the relapsed and refractory setting have become the standard-of-care,[47,48] and their role in the frontline setting to improve outcomes is subject of ongoing investigation. These regimens include the combination of a BTKi (ibrutinib, acalabrutinib, or zanubrutinib) with an anti-CD20 monoclonal antibody (rituximab or obinutuzumab), lenalidomide with rituximab (R2), triple therapy with a BTKi, venetoclax, and an anti-CD20 antibody, or a T-cell therapy (chimeric antigen receptor [CAR] T-cell therapy or bispecific antibody treatment). While selected regimens are highlighted below, an in-depth review of all trials in this setting is outside the scope of this paper, and a summary of ongoing studies is provided in **Table 1**.

A Phase II study led by Jain *et al.* evaluating ibrutinib with rituximab for 2 years, followed by ibrutinib maintenance in patients with Ki67 <50% and without blastoid morphology, showed high response rates and the median PFS and OS was not yet reached.[49] Toxicity was also a concern as 42% of patients discontinued therapy due to toxicity. A large Phase III randomized trial of zanubrutinib with rituximab vs. BR is currently accruing.[50]

A Phase II trial of lenalidomide with rituximab (R2) induction for 12 months followed by indefinite lenalidomide treatment reported a 3-year PFS of 80%, but this was associated with grade 3+ neutropenia and rash.[51] However, lenalidomide is currently not widely available in Canada for the treatment of lymphomas. The triple combination of R2 with venetoclax is also being studied,[52] this approach has the potential advantage that BTKi could be reserved for the relapsed setting. Owing to the synergy between ibrutinib and venetoclax in the early phase setting,[53] triple therapy combinations with BTKi, venetoclax, and anti-CD20 antibodies are currently being investigated **Table 1**.

While these promising results of chemotherapy-free regimens are encouraging, comparative Phase III studies are needed before these novel combinations can be adopted as the standard-of-care. Moreover, MCL remains a remitting and relapsing lymphoma, and whether chemotherapy will be effective in the second-line setting after BTKi-based chemotherapy-free regimens has not been evaluated.

Can maintenance therapy be optimized?

Given that lenalidomide has shown activityin the relapsed/refractory setting,[54] a Phase III trial evaluated lenalidomide maintenance vs. investigator's choice following ASCT, and showed an improved 3-year PFS of 80% vs. 64%.[55] However, owing to the toxicity profile of lenalidomide, this maintenance strategy likely does not have a role in this setting. Maintenance treatment with ibrutinib rather than rituximab is also being explored, but in one small study in which 560 mg daily ibrutinib after chemoimmunotherapy was assessed, there was a high incidence of infection and 15/36 patients (42%) discontinued treatment due to toxicity.[56]

Currently, no definite conclusions can be made due to the heterogeneity of study designs, small sample sizes, and the single-arm nature of available studies. Given the possibility of ASCT omission, maintenance therapy is an important area for future investigation, and prospective randomized trials of maintenance strategies are required.

Risk-adapted studies

Given the significant heterogeneity in MCL's clinical course, current treatment approaches

Trial	Phase	Key inclusion criteria	Regimen details	No. patients	Primary endpoint	ORR	Outcomes	Key adverse events
ASCT-eligible patients								
TRIANGLE	III	Age ≤65 yrs, ASCT-eligible	A) R-CHOP/ R-DHAP → ASCT → RM B) R-CHOP + I/R-DHAP → ASCT + R/I maintenance x 2 years C) R-CHOP + I/R-DHAP (no ASCT) → R/I maintenance x 2 years	870	FFS	A) 94% (CR: 36%) B) and C) 98% (CR: 45%)	Median follow-up 31 months 3-year FFS: A) 72% B) 86% C) 88% 3-year OS: A) 86% B) 92% C) 91%	No difference during induction: grade 3+ neutropenia (47-49%), febrile neutropenia (9-12%), infection (9-12%) Maintenance arm A vs. B vs. C: Grade 3+ neutropenia (17%, 44%,23%), febrile neutropenia (3%, 6%, 3%), infections (13%, 25%,19%), cardiac (1%, 3%, 4%)
WINDOW-1[67]	II	Age ≤65 years	Part A: R + I induction Part B: If CR → R-HCVAD and R-HD-MTX-ARA-C alternating x 4 If PR/SD → R-HCVAD and R-HD-MTX-ARA-C alternating x 2 → reassess → R-HCVAD up to 8 cycles (stop if SD/ PD during R-HCVAD)	131	ORR	Part A: ORR 89% (CR 14%) Overall: ORR 98% (CR 87%) Part B ORR 90% (CR 89%)	3-year PFS 79% 3-year OS 95%	Grade 3+ Part A: lymphopenia 14%, rash 12%, infection 8% Part B: Lymphopenia (73%), neutropenia (19%), thrombocytopenia (30%), anemia (17%), myalgia (9%), elevated liver enzymes (9%)
ECOG-ACRIN EA4181	III	Age 18-70 years ASCT-eligible	A) BR + ARA-C B) BR + ARA-C + A C) BR + A	NA	PET-CT CR and PB MRD negativity	NA	NA	NA
BR + A followed by R+ A + ARA-C (preliminary)[68]	Pilot study	Age 18-70 years ASCT-eligible	BR + A cycle 1-3 → R + A+ ARA-C cycle 4-6 → apheresis	12	Mobilization success rate	ORR 83% (CR 75%)	9/12 completed treatment	Grade 3+ thrombocytopenia 100%, neutropenia 83%

Trial	Phase	Key inclusion criteria	Regimen details	No. patients	Primary endpoint	ORR	Outcomes	Key adverse events
ASCT-eligible patients								
BO + ven (preliminary)[69]	II	Age ≥18 years, planned transplant allowed	BO + ven for up to 6 cycles	23	CR at end of induction	86% (CR 81%)	NR	Grade 3+ neutropenia (26%), anemia (9%), thrombocytopenia (17%), tumour lysis (9%), infection(9%), infusion reaction (9%)
EA4151 (NCT03 267433)	III	Age 18-70 years, ASCT-eligible	RM vs. ASCT + RM in patients in MRD-negative CR after induction (investigator's choice)	Planned 689	OS PFS	NA	NA	NA
Rectangle[45]	II	Age 18+ years, ASCT-eligible	R-CHOP + A x maximum 6 cycles → ASCT → R + A x 2 yrs	54	CR	100% (CR 91%)	12-month PFS 94% 12-monthe OS 95%	Grade 3+ neutropenia (22%), lung infection (7%)
No transplant consolidation in ASCT-eligible patients								
ECOG-ACRIN E1411 BR +/- bortezomib (V) → R +/- len (preliminary)[70,71]	II	Age ≥18 years, ECOG PS 0-2	A) BR x 6 → RM x 2 yrs B) BR + V → RM C) BR → RM + len D) BR + V → RM + len	373	Induction PFS Consolidation PFS	BR 90% (CR 61%) BR + V 89% (CR 66%)	Induction PFS 64 months for BR or BR + V (did not meet primary endpoint) Consolidation 2-year PFS 78% for RM vs. 86% for RM + len (p=0.42)	Grade 3+ neutropenia (BR 21%, BR + V 285), neuropathy (BR 0%, BR + V 4%), rash (BR 6%, BR + V 5%)
R-CHOP + len, R-HiDAC, R + len[72]	II	Stage II-IV	A) R-CHOP + len x 4 B) R-HiDAC x 2 C) monthly R + len x 6	47	3-yr PFS	88% (CR 88%)	3-year PFS 63% 3-year OS 85% (TP53 had inferior PFS and OS)	Grade 3+ neutropenia (37% R-CHOP + len, 70% R-HiDAC, 42% R + len), thrombocytopenia (22%, 83%, 9%)

Trial	Phase	Key inclusion criteria	Regimen details	No. patients	Primary endpoint	ORR	Outcomes	Key adverse events
No transplant consolidation in ASCT-eligible patients								
R + A + ven (AVR) (NCT05951959)	II	≥18 yrs	AVR induction x 13 → CR after 13 cycles → randomized to A until PD vs. observation	Planned 100	CR, MRD negativity	NA	NA	NA
R2 + ven (VLR) (NCT03523975)	I	Age ≥18 years	Ven D8-28, len D1-21, R D1	30	ORR, MTD	NA	NA	NA
R2 + A (ALR) (NCT03863184)	II	Age ≥18 years	A continuous, len D1-21, R D1	35	CR, MRD negativity	NA	NA	NA
ASCT ineligible								
SHINE BR + I vs. BR[46]	III	Age ≥65 years, TI, ECOG PS 0-1	BR + I vs BR x 6 → RM x 2 years AND I or placebo until progression	523	PFS	BR+I: 90% BR: 89% (CR 66% vs. 58%, p=0.06)	Median PFS 81 months vs. 53 months 7-yr OS 55% vs. 57% (HR 1.1; 0.8-1.4)	BR+I vs. BR: Grade 3+ rash (12% vs. 1.9%), pneumonia (20% vs. 14%), AF (4% vs. 0.8%), death due to AE (11% vs. 6%)
BR + len[73]	I/II	Unable to tolerate intensive chemo, stage II-IV	BR + len (10 mg) x 6 → len cycles 7-13	50	Phase I: MTD Phase II: PFS	At 3 months: 88% (CR 48%)	At median follow-up of 31 months: median PFS 42 months Median OS 53 months 3-year OS 73%	Grade 3+ infection (42%), neutropenia (76%), secondary malignancy (16%)
BR + len + bortezomib (V)[74]	II	Age ≥65 years or <65 years if TI	BR + len + V + dex for up to 6 cycles	74	18-month PFS of > 65%	After 4 cycles: 87% (CR 76%)	24-month PFS 70% 4-year OS 71%	Grade 3+ neutropenia (51%), thrombocytopenia (35%), anemia (19%), fatigue (19%), neuropathy (15%)
BR + ven (preliminary)[75]	II	Age ≥60 years, TI	BR + ven x 6 cycles	33	CR	97% (CR 85%)	2-year PFS 70% 2-year OS 81%	NA

Trial	Phase	Key inclusion criteria	Regimen details	No. patients	Primary endpoint	ORR	Outcomes	Key adverse events
ASCT ineligible								
R + I (preliminary)[49]	II	Age ≥65 years, no blastoid or pleomorphic histology, Ki67 <50%	Cycle q28d: R weekly x 4 cycle 1 → every other cycle, I daily; for up to 2 years	50	ORR	96% (CR 71%)	3-year PFS 87% 3-year OS 94%	Grade 3+ atrial fibrillation (22%), fatigue (18%), diarrhea (14%), myalgias (14%), neutropenia (8%), anemia (4%), thrombocytopenia (2%)
R + len (R2)[51]	II	Unable to undergo chemo-therapy	Cycle q28d: R weekly x 4 cycle 1 → every other cycle, len 20 mg cycle 1 D1-21 → 15 mg cycle 2+ D1-21	38	ORR	92% (CR 64%)	5-year PFS 64% 5-year OS 77%	Grade 3+ neutropenia (42%), anemia (8%), thrombocytopenia (11%), rash (29%), tumour flare (11%)
ACE-LY-308 BR + A vs. BR[76]	III	Age ≥65 years, TI	A) BR + A B) BR + placebo	Planned 546	PFS	NA	NA	NA
Ongoing accrual								
BR vs R + zanu (NCT04002297)	III	Age >60 years, TI	BR x 6 vs. R + zanu 80 mg twice daily x 6	Planned 510	PFS	NA	NA	NA
ENRICH	III	Age >60 years, TI	BR/R-CHOP x 6-8 → RM x 2 yrs vs. R + I → I + R maintenance x 2 yrs	Planned 400	PFS	NA	NA	NA
ECHO	III	Age ≥65 years, TI	A)BR + A B)BR + placebo	635	PFS	NA	NA	NA

Table 1. Summary of key trials in frontline treatment of mantle cell lymphoma. *Courtesy of Inna Y. Gong, MD. John Kuruvilla, MD and Michael Crump, MD*

Abbreviations: A: acalabrutinib; **ARA-C:** high-dose cytarabine; **ASCT:** autologous stem cell transplant; **BO:** bendamustine/obinutuzumab; **BR:** bendamustine/rituximab; **CR:** complete response; **FFS:** failure-free survival; **I:** ibrutinib; **LEN:** lenalidomide; **MTD:** maximum tolerated dose; **NCT:** U.S. National Clinical Trials; **NA:** not available; **NR:** not reported; **ORR:** overall response rate; **OS:** overall survival; **PD:** progressive disease; **PFS:** progression-free survival; **PR:** partial response; **R:** rituximab; **RM:** rituximab maintenance; **R-CHOP:** rituximab/cyclophosphamide/vincristine/doxorubicin/prednisone; **R-DHAP:** rituximab/dexamethasone/ARA-C/cisplatin; **R-HCVAD:** rituximab/cyclophosphamide/vincristine/doxorubicin/dexamethasone; **R-HiDAC:** rituximab/ARA-C; **MRD:** minimal residual disease; **MTX:** methotrexate; **SD:** stable disease;
TI: transplant-ineligible; **VEN:** venetoclax; **ZANU:** zanubrutinib.

may lead to over- and undertreatment in certain patients with MCL. Risk-adapted trials are essential to address the intensity and duration of therapy. *TP53* aberrancy is observed in 11% of patients with MCL. The intensive regimens for younger patients with MCL do not overcome the dismal outcomes associated with *TP53* mutations, with a median OS of 1.8 years, compared to 12 years for *TP53*-unmutated cases.[16] The BOVEN trial represents the first dedicated study for patients with *TP53* mutations, evaluating zanubrutinib, venetoclax, and obinutuzumab with a measurable residual disease (MRD)-guided treatment duration.[57] In the WINDOW-2 study evaluating ibrutinib, venetoclax, and rituximab in young patients with MCL, patients will be assigned to consolidation vs. observation based on disease characteristics (Ki67 <30%, tumour size <3 cm, low MIPI, no *TP53*/del17p/blastoid or pleomorphic morphology).[58]

Although MRD is a potential biomarker in improving the predictive outcomes of patients with MCL,[59-62] its integration into routine clinical practice is presently limited. Constraints of MRD assessment in MCL include the challenge of reliably detecting residual disease at low levels, variability in techniques used for MRD measurement (real-time quantitative polymerase chain reaction [PCR], nested-PCR, double-droplet PCR, and next-generation sequencing [NGS]) and lack of a gold standard, lack of consensus on standardized cut-offs and interpretation of MRD data, and uncertainty regarding the optimal timing and frequency of MRD assessment during and after treatment. The prognostic significance of MRD in MCL remains an important area of ongoing investigation. Indeed, prospective studies evaluating its role in a risk-adapted approach are underway, which will address whether MRD could guide the intensification of therapy in patients at risk of relapse or de-escalation of therapy. The design of the EA4151 study integrating MRD-guided ASCT omission is shown in **Figure 2B**.

The future role of ASCT

For the past two decades, ASCT following intensive induction has been the cornerstone of treatment consolidation for younger, fit patients with MCL, with long-term outcomes from prospective clinical trials demonstrating excellent outcomes with PFS ranging 8-12 years, potentially achieving cure in a subset of patients.[7,26,32] However, the independent contribution of ASCT to favourable outcomes using intensive induction regimens (i.e. cytarabine-based) is uncertain. Several retrospective reports attempting to address this question have not yielded consistent findings. While the largest study by Flatiron RWD by Martin *et al.* indicated no PFS benefit using time-to-next treatment (a common surrogate for PFS in such datasets), Gerson *et al.* showed improved PFS (6 vs. 4 years) without OS benefit in adjusted analysis.[43,63]

The recent reconsideration of ASCT in the frontline management of MCL reflects the ongoing advancements in therapeutic approaches. The potential omission of ASCT is desirable, given the associated toxicity, as the field moves towards de-escalation and chemotherapy-free approaches, aiming to identify the most effective (short- and long-term) and least toxic treatment strategy.

First, the emergence of novel targeted therapies, particularly BTKis, can potentially change the treatment landscape for frontline MCL management, as their integration into the frontline setting is the subject of active investigation. As highlighted above, preliminary results from the TRIANGLE study showed that the addition of ibrutinib resulted in similar FFS without ASCT and was associated with reduced toxicity. Although the findings are provocative, longer follow-up is required to definitively answer the question of ASCT omission. Furthermore, caveats remain about whether the omission of ASCT in the frontline setting truly results in longer disease control and survival over BTKi used in the second-line setting after ASCT. Until data matures, ASCT should remain the standard-of-care approach.

Second, the utility of a risk-adapted decision to pursue ASCT based on MRD-positivity will come from the ongoing North American EA4151 trial. This study will randomize patients who are MRD-negative by immunoglobulin NGS testing to either ASCT and 3 years of RM or to RM alone. This study will not only answer the question of the role of ASCT in MRD-positive patients at the end of induction, but may also provide an estimate of the benefit of ASCT in MRD-negative patients.

As studies exploring the role of ASCT are underway, the emergence of chemotherapy-free approaches aimed at reducing or eliminating chemotherapy may herald a further paradigm shift. However, Phase III trials are necessary to establish whether these approaches are superior to intensive induction strategies. Should chemotherapy-free approaches demonstrate superiority, treatment paradigms may converge

towards a similar approach regardless of age or fitness for intensive therapy.

Conclusions

The past decade has seen rapid advancements in therapeutic options for MCL, a disease with diverse clinical presentations and aggressiveness. The current preferred standard-of-care in transplant-eligible patients is cytarabine-based intensive induction chemoimmunotherapy followed by ASCT and RM, and for transplant-ineligible patients, chemoimmunotherapy with BR followed by RM. The emergence of novel targeted agents informing the design of recent pivotal prospective trials is challenging the traditional role of ASCT and chemotherapy alike and is anticipated to herald a paradigm shift in MCL frontline treatment. Whether integrating new agents into a chemoimmunotherapy regimen can eliminate the need for ASCT will soon be clarified with longer follow-up of the TRIANGLE trial. Moreover, once the findings from the MRD-guided ASCT omission study EA4151 are available, the decision regarding ASCT will become even more intricate as we analyze the implications considering the TRIANGLE results.

Although chemotherapy-free approaches are currently being explored in Phase II trials, prospective Phase III comparisons of these protocols against chemoimmunotherapy, as well as chemoimmunotherapy combined with novel agents are necessary to determine the most effective induction regimen.

Further investigation of MCL disease biology and prognostic biomarkers will likely be pivotal in developing personalized treatment strategies. Finally, the evolving landscape of frontline treatment will undoubtedly affect the sequencing of novel agents, including CAR T-cell therapy[64,65] and bispecific antibodies[66] in subsequent lines of therapy. Consequently, determining the optimal selection, sequence, and combination of these innovative treatments remains an ongoing endeavor.

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