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Relapsed or Refractory Mantle Cell Lymphoma: Available and Emerging Therapies

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Introduction

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for 5–7% of all NHL. In most cases, it is characterized by *t(11;14)* leading to cyclin D1 overexpression.¹ MCL displays a heterogeneous clinical behavior, ranging from a very indolent to a very aggressive clinical course. Biological features associated with aggressive disease include morphology (pleomorphic or blastoid), high proliferation index (Ki67 >30%)², adverse clinical scores (Mantle Cell Lymphoma International Prognostic Index [MIPIb])³, and *TP53* mutation status.^{4,5} Patients who relapse within 24 months of initial treatment (POD24) have a poor prognosis with median overall survival (OS) of approximately 12 months.^{6,7-9}

Most patients achieve long-term disease control with first-line treatment, which currently involves induction with rituximab-containing chemotherapy¹⁰⁻¹⁵ with or without autologous stem cell transplantation, followed by maintenance rituximab.^{16,17} Trials assessing Bruton tyrosine kinase inhibitors (BTKi) and other novel agents in the first-line setting have been recently published¹⁸⁻²⁰ or are ongoing.^{21,22} These options are currently not available in Canada outside of clinical trials but may become standard of care in the future.

Relapse after first-line therapy is inevitable, and curability outside the context of allogeneic stem cell transplant (alloSCT) remains unclear¹, with most patients eventually requiring second and subsequent lines of therapy.²³ In the last decade, new therapies have changed the treatment landscape of relapsed/refractory (R/R) MCL, and their optimal sequencing or combination remain unclear. Treatment options will be described herein, with a proposed treatment algorithm for R/R MCL (Figure 1).

Second-line Therapy: Chemoimmunotherapy Retreatment, Non-cytotoxic agents, or BTKi?

Prior to BTKi and chimeric antigen receptor T-cell therapy (CAR-T), treatment options for R/R MCL included agents such as bortezomib or lenalidomide, retreatment with rituximab-based therapy, and alloSCT. The response to these treatments was generally short-lived, especially in those with POD24 (Table 1).²⁴ AlloSCT remains a potentially curative option for fit and younger patients but is associated with significant toxicity, including non-relapse mortality of 10–20% as well as the morbidity associated with graft-versus-host disease.²⁵

The covalent, irreversible, first-generation BTKi ibrutinib demonstrated excellent overall responses in R/R MCL.²⁶ Frequent adverse effects (AEs) include rash, diarrhea, and arthralgia, often low-grade, which may lead to treatment discontinuation in 8–13% of patients.²⁶⁻²⁸ With time, serious AEs, such as bleeding, or cardiac events, including higher grade hypertension, atrial fibrillation, but also ventricular arrhythmias, and sudden death, have emerged.²⁹ Following the SHINE trial³⁰, which evaluated the addition of ibrutinib to first-line bendamustine and rituximab, the progression-free survival (PFS) benefit was offset by increased mortality from sudden death as well as infectious complications (including coronavirus disease 2019 [COVID-19] deaths). In addition to ~40% of patients crossing over to receive BTKi therapy in the placebo arm, there was also no overall survival (OS) benefit observed in the SHINE trial. Based on these results, the US Food and Drug Administration (FDA) approval for ibrutinib was withdrawn for MCL. Second-generation covalent BTKi, such as acalabrutinib³¹ and zanubrutinib³², have demonstrated similar outcomes with a better

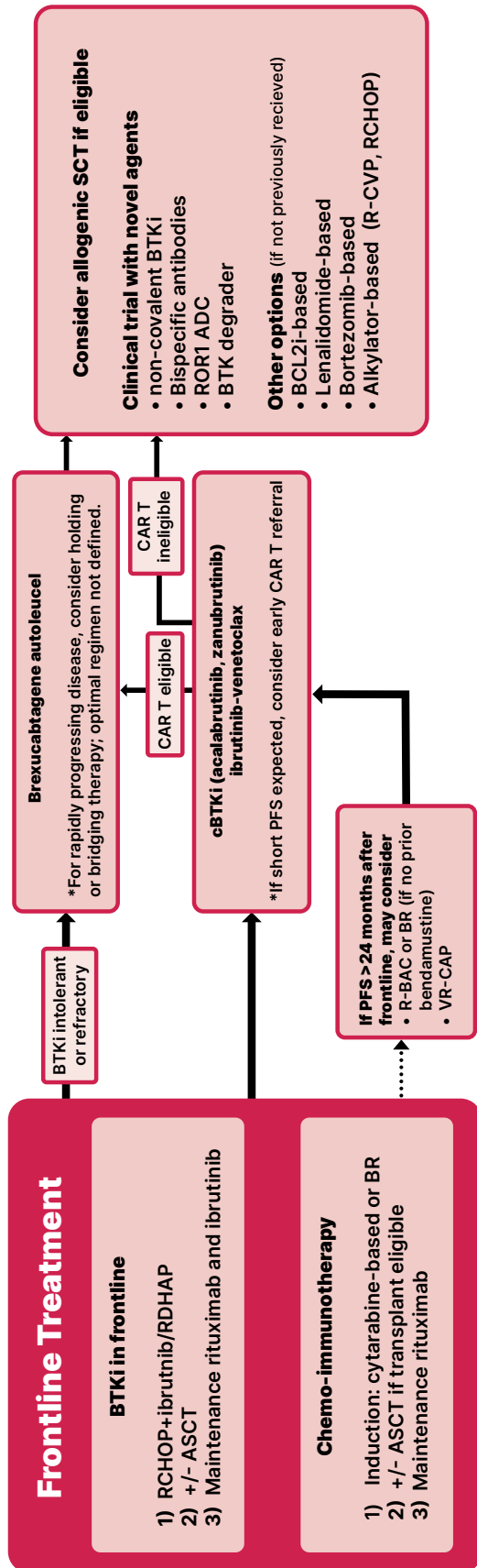


Figure 1. Treatment approach for Mantle Cell Lymphoma; courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.

Abbreviations: ADC: antibody-drug conjugate, ASCT: autologous stem cell transplant, BR: bendamustine and rituximab, BTKi: Bruton tyrosine kinase inhibitors, CAR-T: chimeric antigen receptor T cell, PFS: progression-free survival, R-BAC: rituximab, bendamustine, and cytarabine, RCHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-CVP: rituximab, cyclophosphamide, vincristine sulfate, and prednisone, RDHAP: rituximab, dexamethasone, cytarabine, and cisplatin, ROR-1: receptor-tyrosine-kinase-like orphan receptor 1, SCT: stem cell transplant, VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Class of Therapy	Regimen	Design (N)	ORR (CR)	Median PFS (mo)	Median OS (mo)	Reference
Bendamustine-based	BR	Phase 3 (n=47 MCL)	70.8% (37.5%)	17.6 (7.9–30.4)	35.3 (14.9–NR)	60
	R-BAC	Retrospective (n=36; prior BTKi)	83% (60%)	10.1 (6.9–13.3)	12.5 (11.0–14.0)	61
Lenalidomide-based	Lenalidomide, lenalidomide-rituximab, lenalidomide-others	Retrospective (n=58; prior BTKi)	29% (13.8%)	Not reported – DOR: 20 weeks (2.9–NR)	NR	MCL-004 ⁶²
Bortezomib-based	Monotherapy	Phase 2 (n=155; no prior BTKi)	33% (8%)	6.5 (4.0–7.2)	23.5 (20.3–27.9)	PINNACLE study ^{63, 64}
Lenalidomide and bendamustine-based	Rituximab, lenalidomide and bendamustine	Phase 2 (n=42)	79% (55%)	20	NR OS-24 mo 67% (95%CI 50–79)	65

Table 1. Therapies for R/R MCL prior to BTKi or CAR-T; courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.

Abbreviations: BR: bendamustine-rituximab, BTKi: Bruton tyrosine kinase inhibitor, CI: confidence interval, CR: complete response, DOR: duration of response, Mo: months, NR: not reached, ORR: overall response rate, OS: overall survival, PFS: progression-free survival, RBAC: rituximab, bendamustine, cytarabine.

tolerability profile in cross-trial comparisons, and are increasingly used as second-line therapy in MCL (**Table 2**).^{14,15}

No prospective trials have compared BTKi to standard chemoimmunotherapy in the R/R setting. Despite this, the practice pattern is evolving in recent years with increased utilization of BTKi as second-line therapy.³³ The retrospective MANTLE-FIRST study²⁴ suggests second-line BTKi monotherapy achieves better outcomes compared to traditional therapies for R/R MCL, including R-BAC (rituximab, bendamustine, and cytarabine), and a pooled analysis from three prospective ibrutinib trials showed superior outcomes from BTKi in second-line rather than in later lines (median PFS 24 months vs. 10 months).²⁶ Therefore, most patients today receive covalent BTKi monotherapy as second line therapy.^{14,15}

Venetoclax, an oral Bcl-2 inhibitor, demonstrated deep, yet often short-lived, responses in R/R MCL when used as a monotherapy.^{34–36} In preclinical models, it has synergistic effects with BTKi³⁷ and the combination with ibrutinib was safe in an early phase trial.³⁸ The phase 3 SYMPATICO trial³⁹ demonstrated that the addition of 24 months of venetoclax to continuous ibrutinib resulted in an absolute 10-month PFS improvement, with minimal incremental toxicity (**Table 2**). Despite no OS improvement, the clinical benefit from this combination therapy is considered clinically significant, and would likely replace BTKi monotherapy in the R/R setting if available in Canada.

Relapse after BTKi – Cellular Therapy

Relapse after a covalent BTKi has historically been associated with dismal outcomes. Even in those who receive subsequent treatment, historical response rates were ~30% and median overall survival was less than 1 year (8.4 months)⁴⁰ with therapies such as chemoimmunotherapy, bortezomib, or lenalidomide. CAR T-cell therapy has dramatically changed the treatment algorithm for R/R MCL. To date, the only Health Canada-approved product is brexucabtagene autoleucel, a CD19-directed CAR T-cell construct with a CD28 costimulatory domain, based on the pivotal phase 2 ZUMA-2 trial.⁴¹ In this study, two-thirds of patients achieved durable complete responses with a median PFS of over 24 months. High-grade toxicities included cytokine release syndrome (CRS) in 15%, immune effector cell-associated neurotoxicity syndrome (ICANS) in 31%, and infections in 32% of patients. CAR T-cell therapy appears effective in patients with adverse biology, including *TP53* mutations or high Ki67 (**Table 2**).⁴²

Real-world cohorts from the US (n=189)⁴² and Europe (n=74)⁴³ have shown similar outcomes, even when most patients did not meet the ZUMA-2 inclusion criteria. Although the treatment-related mortality is lower than with alloSCT, it is as high as 9% to 15% in the real-world setting, mainly from infections. More recently, lisocabtagene maraleucel, a CAR T-cell product with a 4-1BB costimulatory domain, has demonstrated high and durable response rates with a similar, and potentially reduced toxicity profile (**Table 2**).⁴⁴ The latest American Society for Transplantation and Cellular Therapy (ASTCT), Center for International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) guidelines favour CAR T-cell therapy over alloSCT²⁵, with the limitation that there are no head-to-head comparisons. Despite the durable responses with CAR T-cell therapy, there is currently no evidence that it is curative.

An important challenge to the optimal delivery of CAR T-cell therapy is the timelapse between progressive disease and product infusion. This period includes referral, funding application and approval, candidate evaluation and screening, leukapheresis, manufacturing procedures, and admission for lymphodepleting chemotherapy and

product infusion. In real-world studies, the median “vein-to-vein” time from collection to infusion varies between 33 to 41 days.^{42,43} During this interval, disease progression may occur, requiring “holding” or “bridging” therapy to stabilize disease in up to 68–82% of patients in real-world cohorts.^{42,43} Patients expected to have an early relapse on BTKi, particularly those with a short time to first relapse, Ki67 ≥30%, and MIPI score should be considered for early CAR T-cell therapy or alternate therapies.⁹

New Therapeutic Agents

Relapse after covalent BTKi and CAR T-cell therapy is a major clinical challenge. Emerging options in this setting include non-covalent BTKi, receptor-tyrosine-kinase-like orphan receptor 1 (ROR-1) antibody-drug conjugates (ADC), and bispecific antibodies (**Table 2**). There are multiple ongoing trials with these agents as monotherapy or in combinations (**Table 3**).

1) Non-covalent BTKi

The BTK mutation C481S has emerged as one of the resistance mechanisms to covalent BTKi⁴⁵, along with new-onset *TP53* or *NSD2* mutations.⁴⁶ Non-covalent BTKi reversibly bind to the ATP pocket in BTK, potentially overcoming the C481S point mutation. Pirtobrutinib, the first-in-class non-covalent BTKi, shows clinical activity in R/R MCL, including in patients with prior BTKi exposure, with an overall response rate (ORR) of 58%, but only 6 months of PFS in the entire study population.⁴⁷ However, those who respond may derive significant benefit with a median duration of response of 22 months.⁴⁷ The adverse effect profile is comparable to covalent BTKi, including cytopenias, musculoskeletal pain, diarrhea, bruising, and infections. Given the efficacy after BTKi exposure, the ongoing BRUIN-MCL-321 (NCT04662255) trial is currently testing pirtobrutinib against the investigator’s choice of covalent BTKi in BTKi-naïve R/R MCL. Nemtabrutinib is another non-covalent BTKi, also with a seemingly similar profile in an early phase trial⁴⁸, with ongoing trials testing it as monotherapy (NCT05458297⁴⁹) or in combination (NCT05458297⁵⁰).

Class of therapy	Regimen	Design (N)	ORR (CR)	Median PFS (mo)	Median OS (mo)	References
Covalent BTKi	Ibrutinib	Pooled data from 2 phase 2 and 1 phase 3 trials (N=370)	70% (27%)	if 1 prior line: 25.4 (17.5–51.8) if >1 line: 10.3 mo (8.1–12.5)	if 1 prior line: 61.6 (36.0–NR) if >1 line: 22.5 (16.2–26.7)	Pooled analysis from 3 trials ²⁶ - Phase 2 PCYC-1104 NCT01236391 ^{66, 67} - Phase 2 SPARK [NCT01599949] - Phase 3 RAY [NCT01646021] ⁶⁸
	Acalabrutinib	Phase 2 N=124	81% (40%)	22 (16.6–33.3)	59.2 (36.5–NR)	ACE-LY-004 ^{31, 69}
	Zanubrutinib	Phase 1/2 (n=32)	84.4% (25%)	21.1 (13.2–NR)	24mo OS 64.4%	Phase 1/2 ⁷⁰
		Phase 2 (n=86)	83.7% (77.9%)	33.0 (19.4–NR)	36mo OS 74.8% (63.7–83.0)	Phase 2 single arm ^{32, 71}
Covalent BTKi + Venetoclax	Ibrutinib + venetoclax	Phase 3 (vs. ibrutinib monotherapy) (N=267)	82% (54%)	31.9	44.9	SYMPATICO trial ³⁹
Treatment options in relapsed MCL after covalent BTKi						
CAR T-cell therapy	Brexucabtagene autoleucel	Phase 2 (n= 74) Prior treatment with anthracycline or bendamustine, anti-CD20 and BTKi	91% (68%)	25.8 (9.6–47.6)	46.6 (24.9–NR)	ZUMA-2 ^{41, 72}
	Lisocabtagene Maraleucel	Phase 1 (n=104 MCL, 88 infused) ≥2 prior lines, including BTKi, an alkylating agent, and anti-CD20	83.1% (72%) * infused patients	15.7 (6.2–24.0)	18.2 (12.9–36.3)	TRANSCEND-NHL 001 ⁴⁴
Non-covalent BTKi	Pirtobrutinib	Phase 1/2 (n= 90) *BTKi pretreated	57.8% (20.0%)	7.4 (5.3–12.5)	NR 18mo OS 59.3% (95% CI, 46.1 to 70.2)	BRUIN trial ⁴⁷

Class of therapy	Regimen	Design (N)	ORR (CR)	Median PFS (mo)	Median OS (mo)	References
Bispecific antibodies CD20 x CD3	Epcoritamab (subcutaneous, continuous treatment)	Phase 1/2 (n=4)	50% (25%)	Not reported	Not reported	55
	Glofitamab (intravenous, fixed duration – 12 3-week cycles)	Phase 1/2 (n=37)	83.8% (73.0%)	Not reported	Not reported	54
	Mosunetuzumab (intravenous, fixed duration 8 cycles if CR, up to 17 cycles if PR)	Phase 2 (n=15 MCL; 229 total)	Not reported for MCL, overall population 36.4% (21.7%)	Not reported	Not reported	56
	Mosunetuzumab and polatuzumab vedotin (fixed duration)	Phase1b/2 (n=20)	75% (70%)	Not reported	Not reported	73
ROR-1 ADC	Zilovetamab Vedotin	Phase 1 (n=17)	53% (12%)	11.4 (4.0–NR)	18.0 (7.1–NR)	waveLINE-001 ⁷⁴

Table 2. Selected prospective trials using novel agents in relapsed/refractory MCL; courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.

Abbreviations: **ADC:** antibody-drug conjugate, **BTkI:** bruton tyrosine kinase inhibitor, **CAR:** chimeric antigen receptor, **CR:** complete response, **MCL:** mantle cell lymphoma, **mo:** months, **NR:** not reached, **ORR:** overall response rate, **OS:** overall survival, **ROR-1:** receptor-tyrosine-kinase-like orphan receptor 1, **PFS:** progression-free survival.

Class of drug	Population	Planned accrual	Trial drug	Phase	Comparator	Primary outcome	Trial
Non-covalent BTKi	≥1 prior line BTKi naïve	500	Pirtobrutinib	Phase 3, open-label, randomized 1:1	Investigator's choice of BTKi	PFS	BRUIN MCL-321 NCT04662255 ⁷⁵
	≥1 prior line BTKi naïve	275	Nemtabrutinib (with ZV)	Phase 2	-	ORR	MK-2140-006, cohort C NCT05458297 ^{49,50}
Bispecific antibodies	≥1 prior line BTKi exposed	182	Glofitamab	Phase 3	Investigator's choice (BR or R-lenalidomide)	PFS	GLOBRYTE NCT06084936 ⁷⁶
	BTKi refractory excluded	50	Glofitamab + Pirtobrutinib	Phase 2	-	CR	NCT06252675 ⁷⁷
	≥1 prior line BTKi naïve	40	Acalabrutinib, Obinutuzumab, and Glofitamab	Phase 2	-	CR	NCT06054776 ⁷⁸
BCL2 inhibitor	≥1 prior line BTKi exposed	122	BGB-11417 (sonrotoclast)	Phase 1/2	-	ORR	NCT05471843 ⁷⁹
ROR-1 ADC	R/R MCL	275	Zilovertamab Vedotin, with various combination	Phase 2	-	ORR	waveLINE-006 NCT05458297 ⁵⁰
CD79b ADC	≥1 prior line BTKi exposed	16	Polatuzumab vedotin, with bendamustine-rituximab	Phase 2	-	ORR	NCT05868395 ⁸⁰
BTK degraders	Relapsed B-cell malignancies, including MCL	127 466	BGB-16673	Phase 1/2 Expansion	-	Safety ORR	NCT05294731 ⁸¹ NCT05006716 ⁸²
		160	NX-2127	Phase 1	-	Safety ORR	NCT04830137 ⁸³
		292	NX-5948	Phase 1	-	Safety ORR	NCT05131022 ⁸⁴
		128	ABBV-101	Phase 1	-	AE	NCT05753501 ⁸⁵
		60	AC676	Phase 1	-	AE	NCT05780034 ⁸⁶

Table 3 . Selected ongoing trials in relapsed/refractory (R/R) MCL; courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.

Abbreviations: **ADC:** antibody-drug conjugate, **AE:** adverse events, **BR:** bendamustine plus rituximab, **BTKi:** bruton tyrosine kinase inhibitor, **CR:** complete response, **MCL:** mantle cell lymphoma, **ORR:** overall response rate, **R-Len:** rituximab plus lenalidomide, **ROR-1:** receptor-tyrosine-kinase-like orphan receptor 1, **PFS:** progression-free survival.

2) ROR-1 ADC

ROR-1 is an oncoprotein expressed across most malignancies⁵¹, including R/R MCL.⁵² Zilovetamab vedotin is a ROR-1 targeting ADC with the microtubule inhibitor monomethyl auristatin E-containing (MMAE) as its payload, which is also part of brentuximab vedotin. As a single agent, it demonstrated response in ~50% of patients with R/R MCL.⁵³ Due to non-overlapping toxicity, combination therapy with nemtabrutinib is being explored in the Waveline-006 trial.⁵⁰ As expected with MMAE, toxicity includes neutropenia, infections, and peripheral neuropathy.

3) Bispecific Antibodies (CD20 x CD3)

Glofitamab⁵⁴, epcoritamab⁵⁵, and mosunetuzumab⁵⁶ are CD20-directed bispecific antibodies that simultaneously bind to CD3 to induce T cell-mediated killing of malignant B cells.⁵⁷ Despite some differences in the mode of administration (intravenous or subcutaneous) and the schedule (fixed duration or indefinite), they seem comparable in efficacy. In clinical trials including various R/R B-cell malignancies, including MCL, these molecules demonstrated a manageable toxicity profile with frequent, but low-grade CRS and rare ICANS, although the infectious risks remain a serious concern.⁵⁸ More experience is needed to better manage the CRS in an outpatient setting, as well as the infectious complications seen with these new treatments, but also to guide optimal treatment duration. In addition, compared to cellular therapy, these antibodies also provide the advantage of being an off-the-shelf treatment that can be deployed in a timely manner for patients presenting with rapidly progressing disease. The GLOBRYTE (NCT06084936) trial is testing glofitamab (CD3 x CD20 bispecific) against the investigator's choice of therapy in relapsed MCL with prior BTKi exposure.

4) Other Emerging Agents

Emerging agents include BTK degraders and other small molecule inhibitors targeting other pathways such as PI3K or NFKB. In addition, combination strategies of the previously described treatments are ongoing, such as mosunetuzumab and polutuzumab vedotin⁵⁹, or nemtabrutinib and zilovetamab vedotin⁵⁰ (Table 3).

Conclusion

Treatment options for R/R MCL have expanded in the last decade with the emergence of several agents with novel mechanisms of action. Clinicians are currently challenged by choosing the optimal sequence, but also ensuring that all treatments are provided to patients in the context of what remains an incurable disease. A proposed treatment algorithm for the management of R/R MCL in the current era is suggested in Figure 1. Clinicians will be increasingly challenged by identifying the most effective combinations for specific patients given the biological heterogeneity of MCL. In the Canadian setting, access and funding will remain an additional challenge.

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Financial Disclosures

JNC: Honoraria: BeiGene.

DV: Advisory Boards and Honoraria: Janssen, BeiGene, AstraZeneca, Roche, AbbVie, Kite/Gilead, BMS/Celgene, Merck, and Zetagen;

Research Funding: Roche and AstraZeneca.

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