About the Authors

Jean-Nicolas Champagne, MD, FRCPC

Dr. Champagne obtained his medical degree from Université Laval in 2017. He achieved dual certification in Hematology and Medical Oncology after completing his residency a Université de Montréal. With a strong interest in lymphoproliferative disease, he is currently pursuing a clinical fellowship in lymphoma at BC Cancer, Vancouver.

Affiliations: BC Cancer – Vancouver Cancer Centre and University of British Columbia, Vancouver, BC, Canada

Diego Villa, MD, MPH, FRCPC

Dr. Diego Villa is a medical oncologist at the BC Cancer – Vancouver Cancer Centre and Clinical Associate Professor at the University of British Columbia. In addition to attending to patients with lymphomas and breast cancer, he also teaches trainees and conducts research in B-cell non-Hodgkin lymphomas. His main research interests include mantle cell lymphoma, primary and secondary CNS lymphomas, and the role of PET/CT in lymphoid malignancies. He presently leads national prospective trials of novel therapies in aggressive lymphomas. Over the years he has collaborated with several international groups on NHL studies, with over 100 publications in the peer-reviewed literature. Dr. Villa is also lymphoma co-chair with the Canadian Cancer Trials Group.

Affiliations: BC Cancer – Vancouver Cancer Centre and University of British Columbia, Vancouver, BC, Canada

doi.org/10.58931/cht.2024.3356

Relapsed or Refractory Mantle Cell Lymphoma: Available and Emerging Therapies

Jean-Nicolas Champagne, MD, FRCPC
Diego Villa, MD, MPH, FRCPC

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 chemotherapy[10-15] 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 published[18-20] 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 unclear[1], 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 BKTi 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 trial[30], 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 acalabrutinib[31] and zanubrutinib[32], have demonstrated similar outcomes with a better

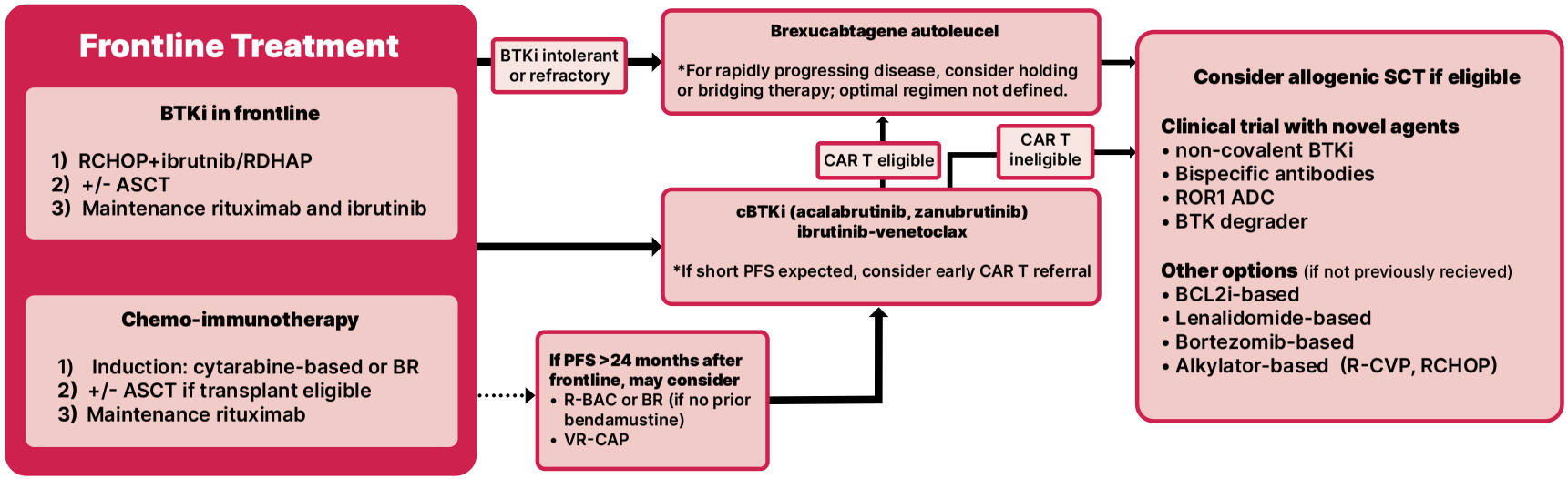

Figure 1. Treatment approach for Mantle Cell Lymphoma; *courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

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 study[24] 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 BTKi[37] and the combination with ibrutinib was safe in an early phase trial.[38] The phase 3 SYMPATICO trial[39] 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 alloSCT[25], 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 BTKi[45], 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. Nembrabrutinib is another non-covalent BTKi, also with a seemingly similar profile in an early phase trial[48], with ongoing trials testing it as monotherapy (NCT05458297[49]) or in combination (NCT05458297[50]).

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
	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
Bispecific antibodies CD20 x CD3	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	Zilovertamab 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 naive	40	Acalabrutinib, Obinutuzumab, and Glofitamab	Phase 2	-	CR	NCT06054776[78]
BCL2 inhibitor	≥1 prior line BTKi exposed	122	BGB-11417 (sonrotoclax)	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 malignancies[51], including R/R MCL.[52] Zilovertamab 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)

Glofitamab[54], epcoritamab[55], and mosunetuzumab[56] 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 vedotin[59], or nemtabrutinib and zilovertamab vedotin[50] (**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.

Correspondence

Diego Villa, MD, MPH, FRCPC
Email: dvilla@bccancer.bc.ca

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.

References

1. Armitage JO, Longo DL. Mantle-Cell Lymphoma. NEJM. 2022;386(26):2495-506.
2. Determann O, Hoster E, Ott G, Wolfram Bernd H, Loddenkemper C, Leo Hansmann M, et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood. 2008;111(4):2385-7.
3. Hoster E, Dreyling M, Klapper W, Gisselbrecht C, van Hoof A, Kluin-Nelemans HC, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-65.
4. Eskelund CW, Dahl C, Hansen JW, Westman M, Kolstad A, Pedersen LB, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130(17):1903-10.
5. Simone F, Davide R, Andrea R, Alessio B, Valeria S, Christian WE, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. Haematologica. 2020;105(6):1604-12.

6. Visco C, Tisi MC, Evangelista A, Di Rocco A, Zoellner A-K, Zilioli VR, et al. Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death. Br J Haematol. 2019;185(5):940-4.
7. Bond DA, Switchenko JM, Maddocks KJ, Churnetski MC, Goyal S, Shanmugasundaram K, et al. Outcomes Following Early Relapse in Patients with Mantle Cell Lymphoma. Blood. 2019;134:753.
8. Bond DA, Switchenko JM, Villa D, Maddocks K, Churnetski M, Gerrie AS, et al. Early relapse identifies MCL patients with inferior survival after intensive or less intensive frontline therapy. Blood Adv. 2021;5(23):5179-89.
9. Villa D, Jiang A, Visco C, Crosbie N, McCulloch R, Buege MJ, et al. Time to progression of disease and outcomes with second-line BTK inhibitors in relapsed/refractory mantle cell lymphoma. Blood Adv. 2023;7(16):4576-85.
10. Villa D, Sehn LH, Savage KJ, Toze CL, Song K, den Brok WD, et al. Bendamustine and rituximab as induction therapy in both transplant-eligible and -ineligible patients with mantle cell lymphoma. Blood Adv. 2020;4(15):3486-94.
11. Tessoulin B, Chiron D, Thieblemont C, Oberic L, Bouadballah K, Gyan E, et al. Oxaliplatin before autologous transplantation in combination with high-dose cytarabine and rituximab provides longer disease control than cisplatin or carboplatin in patients with mantle-cell lymphoma: results from the LyMA prospective trial. Bone Marrow Transplant. 2021;56(7):1700-9.
12. Hermine O, Hoster E, Walewski J, Bosly A, Stilgenbauer S, Thieblemont C, et al. Addition of high-dose cytarabine to immunochemotherapy before autologous stem-cell transplantation in patients aged 65 years or younger with mantle cell lymphoma (MCL Younger): a randomised, open-label, phase 3 trial of the European Mantle Cell Lymphoma Network. The Lancet. 2016;388(10044):565-75.
13. Eskelund CW, Kolstad A, Jerkeman M, Raty R, Laurell A, Eloranta S, et al. 15-year follow-up of the Second Nordic Mantle Cell Lymphoma trial (MCL2): prolonged remissions without survival plateau. Br J Haematol. 2016;175(3):410-8.
14. Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Andreadis B, Bartlett NL, et al. NCCN Guidelines® Insights: B-Cell Lymphomas, Version 6.2023: Featured Updates to the NCCN Guidelines. Journal of the National Comprehensive Cancer Network. 2023;21(11):1118-31.
15. Eyre TA, Bishton MJ, McCulloch R, O'Reilly M, Sanderson R, Menon G, et al. Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline. Br J Haematol. 2024;204(1):108-26.
16. Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, et al. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. NEJM. 2017;377(13):1250-60.
17. Di M, Long JB, Kothari SK, Sethi T, Zeidan AM, Podoltsev NA, et al. Treatment patterns and real-world effectiveness of rituximab maintenance in older patients with mantle cell lymphoma: a population-based analysis. Haematologica. 2023;108(8):2218-23.
18. Dreyling M, Doorduijn J, Giné E, Jerkeman M, Walewski J, Hutchings M, 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. 2024.
19. Villa D, Larouche JF, Cheung M, Keating MM, Zukotynski K, Tonseth P, et al. Rituximab combined with chemotherapy and acalabrutinib prior to autologous stem cell transplantation in mantle cell lymphoma: The Rectangle Trial. Hematol Oncol. 2023;41(S2):483-4.
20. Michael Wang JM, David Belada, Yuqin Song, Wojciech Jurczak, Jonas Paludo, Michael P. Chu, Irina Kryachok, Laura Fogliatto, Chan Cheah, Marta Morawska, Juan Manuel Sancho, Yufu Li, Caterina Patti, Cecily Forsyth, Jingyang Zhang, Robin Lesley, Safaa Ramadan, Simon Rule, Martin Dreyling. Acalabrutinib plus bendamustine and rituximab in untreated mantle cell lymphoma: Results from the phase 3, double-blind, placebo-controlled ECHO trial. EHA 2024 Late Breaking Abstract. 2024.
21. Dreyling M, Tam CS, Wang M, Smith SD, Ladetto M, Huang H, et al. A Phase III study of zanubrutinib plus rituximab versus bendamustine plus rituximab in transplant-ineligible, untreated mantle cell lymphoma. Future Oncol. 2021;17(3):255-62.
22. AstraZeneca. A Study of Acalabrutinib Plus Venetoclax and Rituximab in Participants With Treatment Naïve Mantle Cell Lymphoma (TrAVeRse). 2023.
23. Minson A, Hamad N, Di Ciaccio P, Talaulikar D, Ku M, Ratnasingam S, 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. 2024;204(2):548-54.
24. Visco C, Di Rocco A, Evangelista A, Quaglia FM, Tisi MC, Morello L, et al. Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: results from the MANTLE-FIRST study. Leukemia. 2021;35(3):787-95.
25. Munshi PN, Hamadani M, Kumar A, Dreger P, Friedberg JW, Dreyling M, et al. ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma. Bone Marrow Transplant. 2021;56(12):2911-21.
26. Dreyling M, Goy A, Hess G, Kahl BS, Hernández-Rivas J, Schuier N, et al. Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up. Hemasphere. 2022;6(5):e712.
27. Tivey A, Shotton R, Eyre TA, Lewis D, Stanton L, Allchin R, et al. Ibrutinib as first-line therapy for mantle cell lymphoma: a multicenter, real-world UK study. Blood Adv. 2024;8(5):1209-19.

28. Dartigeas C, Slama B, Doyle M, Tapprich C, Albrecht C, Dupuis S, et al. FIRE Study: Real-World Effectiveness and Safety of Ibrutinib in Clinical Practice in Patients with CLL and MCL. Clin Hematol Int. 2022;4(3):65-74.
29. Lampson BL, Yu L, Glynn RJ, Barrientos JC, Jacobsen ED, Banerji V, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood. 2017;129(18):2581-4.
30. Wang ML, Jurczak W, Jerkeman M, Trotman J, Zinzani PL, Belada D, et al. Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma. NEJM. 2022;386(26):2482-94.
31. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-67.
32. Song Y, Zhou K, Zou D, Zhou J, Hu J, Yang H, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. Clin Cancer Res. 2020;26(16):4216-24.
33. Bock AM, Gile JJ, Larson MC, Poonsombudlert K, Tawfiq RK, Maliske S, et al. Evolving treatment patterns and improved outcomes in relapsed/refractory mantle cell lymphoma: a prospective cohort study. Blood Cancer J. 2023;13(1):169.
34. Davids MS, Roberts AW, Seymour JF, Pagel JM, Kahl BS, Wierda WG, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol. 2017;35(8):826-33.
35. Eyre TA, Walter HS, Iyengar S, Follows G, Cross M, Fox CP, et al. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica. 2019;104(2):e68-e71.
36. Sawalha Y, Goyal S, Switchenko JM, Romancik JT, Kamdar M, Greenwell IB, et al. A multicenter analysis of the outcomes with venetoclax in patients with relapsed mantle cell lymphoma. Blood Adv. 2023;7(13):2983-93.
37. Li Y, Bouchlaka MN, Wolff J, Grindle KM, Lu L, Qian S, et al. FBXO10 deficiency and BTK activation upregulate BCL2 expression in mantle cell lymphoma. Oncogene. 2016;35(48):6223-34.
38. Tam CS, Anderson MA, Pott C, Agarwal R, Handunnetti S, Hicks RJ, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. NEJM. 2018;378(13):1211-23.
39. Wang M, Jurczak W, Trněný M, Belada D, Wrobel T, Ghosh N, 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. 2023;142(Supplement 2):LBA-2-LBA-.
40. Cheah CY, Chihara D, Romaguera JE, Fowler NH, Seymour JF, Hagemeister FB, et al. Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol. 2015;26(6):1175-9.
41. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. NEJM. 2020;382(14):1331-42.
42. Wang Y, Jain P, Locke FL, Maurer MJ, Frank MJ, Munoz JL, et al. Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma in Standard-of-Care Practice: Results From the US Lymphoma CAR T Consortium. J Clin Oncol. 2023;41(14):2594-606.
43. Iacoboni G, Rejeski K, Villacampa G, van Doesum JA, Chiappella A, Bonifazi F, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv. 2022;6(12):3606-10.
44. Wang M, Siddiqi T, Gordon LI, Kamdar M, Lunning M, Hirayama AV, et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study. J Clin Oncol. 2024;42(10):1146-57.
45. Woyach JA, Ruppert AS, Guinn D, Lehman A, Blachly JS, Lozanski A, et al. BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. J Clin Oncol. 2017;35(13):1437-43.
46. Jain N, Mamgain M, Chowdhury SM, Jindal U, Sharma I, Sehgal L, et al. Beyond Bruton's tyrosine kinase inhibitors in mantle cell lymphoma: bispecific antibodies, antibody–drug conjugates, CAR T-cells, and novel agents. J Hematol Oncol. 2023;16(1):99.
47. Wang ML, Jurczak W, Zinzani PL, Eyre TA, Cheah CY, Ujjani CS, et al. Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma. J Clin Oncol. 2023;41(24):3988-97.
48. Simmons ME, McIntosh J, Zhang T, Li Y, Yan F, Yao Y, et al. The Reversible BTK Inhibitor Nemtabrutinib Demonstrates Favorable Antitumor Efficacy and Enhances the Function of CAR T Cells in Mantle Cell Lymphoma. Blood. 2023;142:5789.
49. LLC MSD. A Study of Zilovertamab Vedotin (MK-2140) as Monotherapy and in Combination in Participants With Aggressive and Indolent B-cell Malignancies (MK-2140-006). 2024.
50. Zinzani PL, Mayer J, Benjamini O, Berkovits A, Glimelius I, Stevens DA, et al. waveLINE-006: A phase 2 study of the safety and efficacy of zilovertamab vedotin as monotherapy or in combination in patients (pts) with aggressive and indolent B-cell malignancies. J ClinOncol. 2023;41(16_suppl):TPS7595-TPS.
51. Kipps TJ. ROR1: an orphan becomes apparent. Blood. 2022;140(14):1583-91.
52. Jiang VC, Liu Y, Jordan A, McIntosh J, Li Y, Che Y, et al. The antibody drug conjugate VLS-101 targeting ROR1 is effective in CAR T-resistant mantle cell lymphoma. J Hematol Oncol. 2021;14(1):132.
53. Wang ML, Barrientos JC, Furman RR, Mei M, Barr PM, Choi MY, et al. Zilovertamab Vedotin Targeting of ROR1 as Therapy for Lymphoid Cancers. NEJM Evidence. 2022;1(1):EVIDoa2100001.
54. Phillips TJ, Dickinson M, Morschhauser F, Bachy E, Crump M, Trněný M, et al. Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma. Blood. 2022;140(Supplement 1):178-80.
55. Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, et al. Subcutaneous Epcoritamab Induces Complete Responses with an Encouraging Safety Profile across Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma Subtypes, Including Patients with Prior CAR-T Therapy: Updated Dose Escalation Data. Blood. 2020;136(Supplement 1):45-6.

56. Budde LE, Assouline S, Sehn LH, Schuster SJ, Yoon S-S, Yoon DH, et al. Durable Responses With Mosunetuzumab in Relapsed/Refractory Indolent and Aggressive B-Cell Non-Hodgkin Lymphomas: Extended Follow-Up of a Phase I/II Study. J Clin Oncol. 2024;0(0):JCO.23.02329.
57. Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. Blood. 2023;141(5):467-80.
58. Crombie JL, Graff T, Falchi L, Karimi YH, Bannerji R, Nastoupil L, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. Blood. 2024;143(16):1565-75.
59. Budde LE, Olszewski AJ, Assouline S, Lossos IS, Diefenbach C, Kamdar M, et al. Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: a phase 1b/2 trial. Nat Med. 2024;30(1):229-39.
60. Rummel M, Kaiser U, Balser C, Stauch M, Brugger W, Welslau M, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol. 2016;17(1):57-66.
61. McCulloch R, Visco C, Eyre TA, Frewin R, Phillips N, Tucker DL, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. British journal of haematology. 2020;189(4):684-8.
62. Wang M, Schuster SJ, Phillips T, Lossos IS, Goy A, Rule S, 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. 2017;10(1):171.
63. Goy A, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, Boral A, et al. Bortezomib in relapsed or refractory mantle cell lymphoma (MCL): Results of the PINNACLE study. Journal of Clinical Oncology. 2006;24(18_suppl):7512-.
64. Goy A, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Annals of Oncology. 2009;20(3):520-5.
65. Zaja F, Ferrero S, Stelitano C, Ferrari A, Salvi F, Arcari A, et al. Second-line rituximab, lenalidomide, and bendamustine in mantle cell lymphoma: a phase II clinical trial of the Fondazione Italiana Linfomi. Haematologica. 2017;102(5):e203-e6.
66. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126(6):739-45.
67. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-16.
68. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. The Lancet. 2016;387(10020):770-8.
69. Le Gouill S, Długosz-Danecka M, Rule S, Zinzani PL, Goy A, Smith SD, et al. Final results and overall survival data from a phase II study of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma, including those with poor prognostic factors. Haematologica. 2024;109(1):343-50.
70. Tam CS, Opat S, Simpson D, Cull G, Munoz J, Phillips TJ, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv. 2021;5(12):2577-85.
71. Song Y, Zhou K, Zou D, Zhou J, Hu J, Yang H, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study. Blood. 2022;139(21):3148-58.
72. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, 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. 2023;41(3):555-67.
73. Wang ML, Assouline S, Kamdar M, Ghosh N, Naik S, Nakhoda SK, et al. Fixed Duration Mosunetuzumab Plus Polatuzumab Vedotin Has Promising Efficacy and a Manageable Safety Profile in Patients with BTKi Relapsed/Refractory Mantle Cell Lymphoma: Initial Results from a Phase Ib/II Study. Blood. 2023;142(Supplement 1):734-.
74. Wang ML, Mei M, Barr PM, Barrientos JC, de Vos S, Furman RR, et al. Zilovertamab vedotin (MK-2140) in relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL): 14-month follow-up of the phase 1 waveLINE-001 study. Hematological Oncology. 2023;41(S2):571-2.
75. Wang M, Eyre TA, Shah NN, Gouill SL, Dreyling MH, Vandenberghe E, et al. BRUIN MCL-321: A phase 3, open-label, randomized study of pirtobrutinib versus investigator choice of BTK inhibitor in patients with previously treated, BTK inhibitor naïve mantle cell lymphoma. Journal of Clinical Oncology. 2023;41(16_suppl):TPS7587-TPS.
76. Phillips TJ, Matasar M, Eyre TA, Gine E, Filézac De L'Étang A, Byrne B, et al. GLOBRYTE: A Phase III, Open-Label, Multicenter, Randomized Trial Evaluating Glofitamab Monotherapy in Patients with Relapsed or Refractory Mantle Cell Lymphoma. Blood. 2023;142(Supplement 1):3052-.
77. Andreadis B. Glofitamab With Pirtobrutinib for Relapsed or Refractory Mantle Cell Lymphoma. 2024.
78. Center CoHM. Acalabrutinib, Obinutuzumab, and Glofitamab for the Treatment of Relapsed or Refractory Mantle Cell Lymphoma. 2024.
79. Beigene. Study of BGB-11417 Monotherapy in Participants With Relapsed or Refractory Mantle Cell Lymphoma. 2022.
80. Vienna MUo. Efficacy of Polatuzumab, Bendamustine and Rituximab in Patients With Relapsed/ Refractory Mantle Cell Lymphoma. 2024.
81. Beigene. Treatment of Chinese Participants With B-Cell Malignancies With BGB-16673, a Bruton Tyrosine Kinase-Targeted Protein-Degrader. 2022.
82. Beigene. A Dose-Escalation and Expansion Study of BGB-16673 in Participants With B-Cell Malignancies. 2021.
83. Therapeutics N. A Study of NX-2127 in Adults With Relapsed/Refractory B-cell Malignancies. 2021.
84. Therapeutics N. A Study of NX-5948 in Adults With Relapsed/Refractory B-cell Malignancies. 2022.
85. Abbvie. Study to Evaluate Adverse Events, Change in Disease Activity, and How Oral ABBV-101 Moves Through the Body in Adult Participants With B-Cell Malignancies. 2023.
86. Inc AB. A Study of AC676 for the Treatment of Relapsed/Refractory B-Cell Malignancies. 2023.