VOL. 3
ISSUE 2
Summer 2024

ISSN 2816-5152 (PRINT)
ISSN 2816-5160 (ONLINE)

Canadian Hematology Today

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Table of contents

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RRMM, relapsed refractory multiple myeloma.

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†Clinical significance is unknown.

References:
1. FORUS Therapeutics Inc. XPOVIO® (selinexor tablets) Product Monograph. May 31, 2022.
2. CADTH. Provisional Funding Algorithm for Multiple Myeloma. November 14, 2022.

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Mantle cell lymphoma: Evolving frontline treatment strategies

Inna Y. Gong, MD
John Kuruvilla, MD
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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.

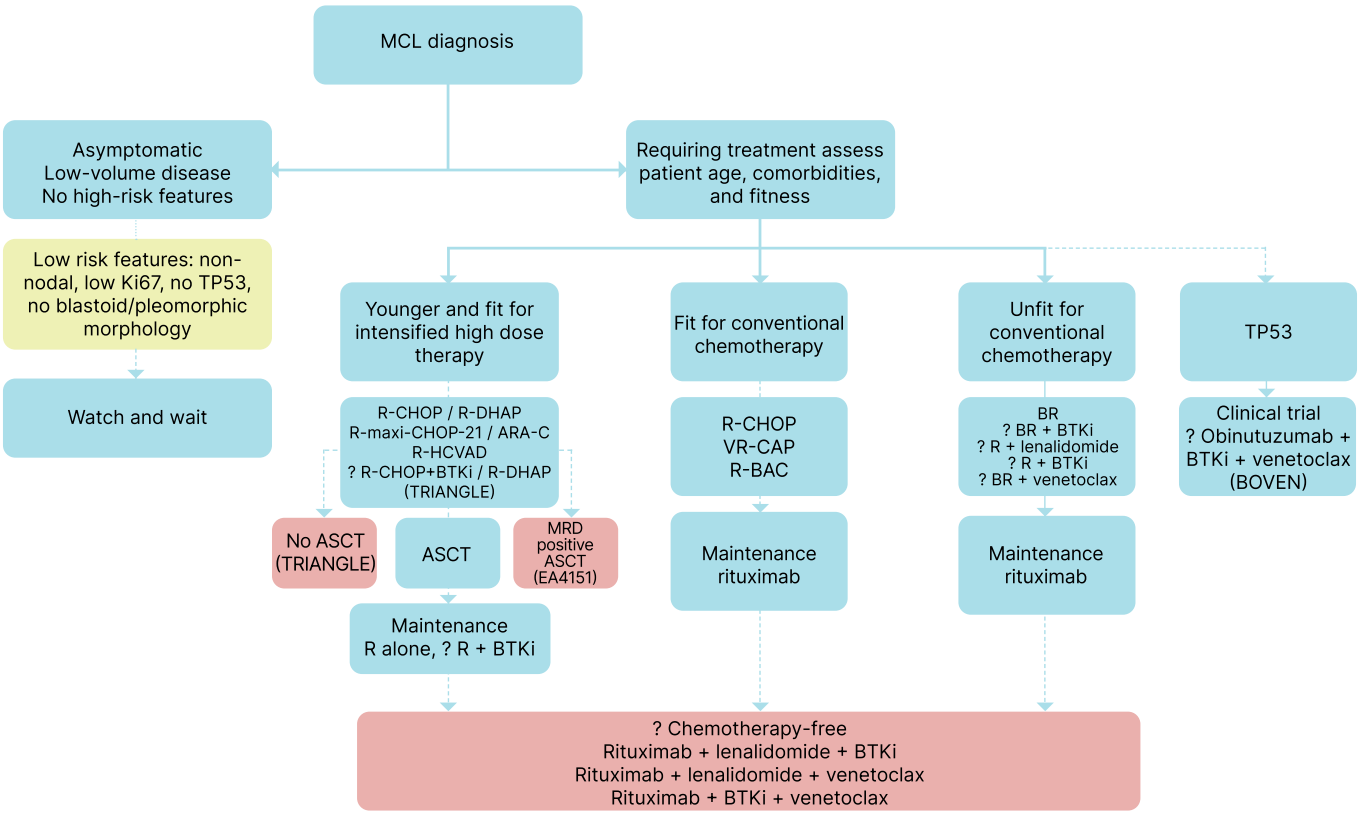


Figure 1. Flow chart reflecting the current treatment algorithm for frontline management of mantle cell lymphoma, with integration of the evolving treatment landscape with recent pivotal trials integrating novel targeted agents in the frontline setting. Dashed lines represent areas of uncertainty and 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.

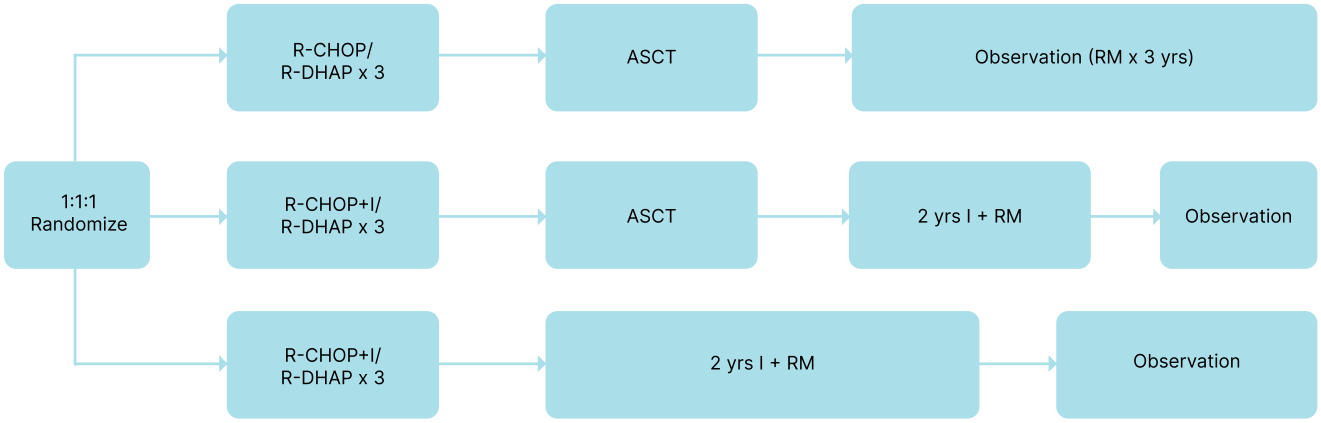
RM following chemoimmunotherapy is supported by the MCL ELDERLY trial, which compared RM with IFN-α maintenance. In patients who responded to R-CHOP, RM led to a longer median PFS (51 vs. 24 months) and OS (9.8 vs. 7.1 years).[35] Improved outcomes with RM have also been corroborated in retrospective 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

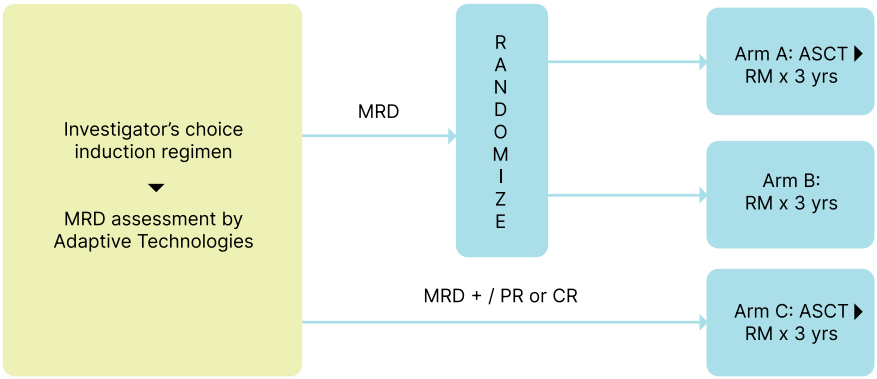


Figure 2. Simplified schema of the TRIANGLE trial integrating a Bruton tyrosine kinase inhibitor in the frontline setting and the EA4151 response-adapted trial evaluating the role of ASCT in patients achieving MRD-negativity post-induction. *Courtesy of Inna Y. Gong, MD. John Kuruvilla, MD and Michael 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

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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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Financial Disclosures :

I.Y.G.: None declared.

J.K.: Research funding: Astra Zeneca, Kite, Merck, Novartis, Roche; Consulting/Honoraria: Abbvie, Amgen, Astra Zeneca, BMS, Gilead, Incyte, Janssen, Karyopharm, Merck, Novartis, Pfizer, Roche, Seattle Genetics; DSMB: Karyopharm
M.C.: Consultancy fees: Kite-Gilead, Novartis, Epizyme/Epson; **Institutional research funding:** Roche, Epizyme/Epson

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R/R: relapsed or refractory; HL: Hodgkin lymphoma; sALCL: systemic anaplastic large cell lymphoma; ASCT: autologous stem cell transplant; pcALCL: primary cutaneous anaplastic large cell lymphoma; MF: mycosis fungoides; AVD: doxorubicin, vinblastine, and dacarbazine; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; CHP: cyclophosphamide, doxorubicin, and prednisone

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‡Clinical effectiveness in R/R sALCL was based on promising response rates demonstrated in single-arm trials. No survival benefits have been established.

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Rena Buckstein is a clinician investigator at the Odette Cancer Centre, Sunnybrook Health Sciences who specializes in malignant hematology. She is an associate professor in the department of medicine at University of Toronto. She completed her medical school training at Boston University and Internal Medicine/Hematology specialty and subspecialty training in Toronto, followed by a fellowship in lymphoma and high dose therapy at Sunnybrook Hospital. She also completed a diploma in clinical epidemiology. She chaired the hematology site group for 15 years and currently leads the hematology clinical trials program at the Odette Cancer Center. Dr. Buckstein founded and chairs a national registry for myelodysplastic syndromes (MDS-CAN) of more than 1400 patients and is an affiliate scientist of Sunnybrook Research Institute. She is a member of the International MDS Foundation scientific advisory board, the Canadian Cancer Society hematology clinical trials sub-committee, a co-chair of an international MDS Guidelines panel for MDS-RIGHT and has chaired national clinical trials in lymphoma and MDS. She has authored and co-authored 144 publications and holds peer reviewed grants from Canadian Cancer Society Research Institute (CCSRI), Canadian Institute of Health Research (CIHR), Ontario Institute for Cancer Research (OICR), and the Leukemia Lymphoma Society of Canada (LLSC) that fund investigator-initiated research in MDS and lymphoma. She is a recipient of the LLSC/UFCW award for leukemia research in Canada. She enjoys teaching and mentoring undergraduate and graduate students. Her interventional research focuses on novel targeted biologic and immunologic therapies for hematologic malignancies focusing on myelodysplastic syndromes and acute myelogenous leukemia and improving the transfusion experience for MDS patients. Her non-interventional research focuses on documenting QOL longitudinally and its predictors and the impact of patient-related factors like frailty and disability on quality of life, and clinical outcomes independent of disease-related prognostic factors. She collaborates on health services research pertaining to ‘real-life’ experience of approved therapies in MDS and the cost/predictors of health care resource utilization. Currently, she is evaluating the impact of age-related clonal hematopoiesis (ARCH) on chemotherapy outcomes in older adults with lymphoid cancers, the association of specific mutations with occult coronary artery disease in MDS patients.

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Therapy for myelodysplastic syndromes beyond the front line in 2024 in Canada

Rena Buckstein, MD, FRCPC

Introduction

Management of anemia and/or transfusion dependence (TD) after failure of erythropoietic-stimulating agents (ESA) and therapeutic options after hypomethylating agent (HMA) failures remain the biggest challenges for physicians treating lower and higher-risk myelodysplastic syndromes (MDS), respectively. Fortunately, new therapies are available (or soon to be approved), and innovations in prognostic refinement using next-generation sequencing may also facilitate more precision medicine. This review highlights commercially available (or soon to be) options for the amelioration of anemia and transfusion dependence when ESA's fail and the management of higher-risk MDS when hypomethylating agents fail or cease working. While not all of these agents are currently funded or approved in Canada, some are available for off-label access or purchase.

ESA background

The use of ESAs is the front-line treatment recommended by most guidelines for patients with low transfusion burden and lower endogenous serum erythropoietin (EPO) levels. Response rates vary between 20 to 60%, with median response durations ranging from 12 to 24 months.[1] In a large multinational series comprised of 1,698 patients, primary failure was observed in 34% of patients and 29% of patients experienced secondary failure (after an initial response) of therapy. Primary failure was associated with a higher risk of acute myeloid leukemia (AML) progression at 5 years than secondary failure (13.4% vs. 8.1%; p=0.001), but median survival did not differ between these groups (52.2 vs. 60 months; p=0.12). Prognostic factors after ESA failure were age >75 years, and intermediate revised international prognostic scoring system (IPSS-R) risk score.[2] Recently, evidence has emerged showing that a higher genetic complexity (>3 mutated genes) is a negative prognostic factor for ESA response.[3]

Second-line options after ESA failure

Lenalidomide for del5q MDS

Lenalidomide is an effective therapy for patients with del5q TD lower-risk MDS who lose response to or are refractory to ESAs **(Table 1)**. In a randomized phase 3 trial comparing placebo with two lenalidomide doses, lenalidomide at a dose of 10 mg daily for 21 out of 28 days was associated with the achievement of red blood cell transfusion independence (RBC-TI) in 56% of patients and had a cytogenetic response rate of 50%. For the lenalidomide groups combined, the 3-year overall survival (OS) and AML risk were 56.5% and 25.1%, respectively. RBC-TI for ≥8 weeks was associated with 47% and 42% reductions in the relative risks of death and AML progression or death, respectively (P = .021 and .048).[4] The median response duration in this study was two years. In a pooled analysis of all lenalidomide trials in patients with del5q and non-del5q MDS, the achievement of RBC-TI was associated with improved OS. In addition to advanced age and lower platelet count, elevated ferritin (>1,600 µg/L) and the transfusion of >6 units/8 weeks were associated with inferior OS.[5] The OS was 23 months following lenalidomide failure with longer survival for patients with relapsed disease or secondary loss of hematologic improvement (HI) (39 months) and in those that subsequently received HMAs (median OS 39 months).[6] The Spanish randomized controlled trial (RCT) SINTRA-REV demonstrated that the initiation of lenalidomide at 5 mg po daily for 24 months before TD significantly delayed time to TD compared with placebo (66 vs. 11.6 months) and achieved high rates of cytogenetic remissions (87.5%).[7] Up to 20% of patients will harbour *TP53* mutations. These patients are less likely

to achieve cytogenetic remissions and have a 5-year cumulative risk for leukemia development of 77% (compared with 24% for those without these mutations). These patients also have lower rates of RBC-TI (50% vs. 75%).[8] If detected, these patients need close surveillance and consideration for HMAs or allogeneic stem cell transplant (ASCT) when responses are lost or not achieved.

Lenalidomide for non del5q MDS

For the 90-95% of patients with lower-risk MDS without del5q, lenalidomide has activity at reversing TI, albeit at greatly reduced rates and duration **(Table 1)**. In addition, there is no anti-clonal activity, as observed in those with del5q. In the MDS-005 study, RBC-TI lasting ≥8 weeks was observed in 27% of the patients treated with lenalidomide. As 90% of patients responded within 16 weeks, drug exposure should not exceed this in non-responders. The median duration of RBC-TI with lenalidomide was 30.9 weeks, and the median OS was 617 days. Higher response rates were observed in patients with lower baseline endogenous erythropoietin ≤500 mU/mL (34.0% vs. 15.5% for >500 mU/mL). The most common treatment-emergent adverse events were neutropenia and thrombocytopenia.[9] Lenalidomide did not adversely affect health-related quality of life (HrQOL), which improved in responding patients.[10] Baseline somatic mutations may predict response since the proportion of patients achieving RBC-TI ≥8 weeks was significantly lower in those with *ASXL1* mutations than in those without (10.3% vs. 31.7%; p=0.031). Furthermore, the proportion of patients achieving RBC-TI ≥8 weeks was nominally higher in those with *DNMT3A* mutations (43.8%), *SF3B1* mutations (42.9%) and *EZH2* mutations (44%).[11]

Luspatercept for MDS with ring sideroblasts (RS) or SF3B1 mutations

Patients with MDS and RS have shorter response durations to ESAs.[12] Luspatercept is a recombinant fusion protein that binds select transforming growth factor β (TGF-β) superfamily ligands to decrease SMAD2 and SMAD3 signalling, thereby enabling erythroid maturation by means of late-stage erythroblast differentiation.[13] Based on promising results from the phase 2 PACE study[14], in particular, in the patients with RS, luspatercept was evaluated in a randomized, double-blind placebo-controlled trial (MEDALIST) in patients who had relapsed or refractory disease or were unsuitable for ESA **(Table 1)**. RBC-TI for ≥ 8 weeks was observed in 38% of patients in the luspatercept group compared with 13% of patients receiving a placebo, and over the course of 48 weeks, 33% (vs. 12% in the placebo group) achieved and maintained RBC-TI for ≥12 weeks. Patients who were more likely to achieve TI were those with a lower transfusion burden (TI 80% vs. 37% with low [<4 units/8weeks] vs. intermediate [4-<6 units/8 weeks]. Luspatercept had a very low (9%) likelihood of response in patients with high transfusion burden (6+ units/8 weeks). Contrary to low response rates to ESA observed when the endogenous EPO level exceeds 200 U/L, luspatercept achieved RBC-TI rates of 40%. Unfortunately, some patients treated with luspatercept still required intermittent RBC transfusions and the median duration of the longest single period of TI was 30.6 weeks (vs. 13.6 weeks in the placebo group). Another lesson from this study was that most patients ultimately required the highest dose of luspatercept (1.75 mg/kg) to achieve or maintain response. In patients with moderate transfusion burden or with EPO levels >200 U/L, it is reasonable to commence luspatercept at 1.33 mg/kg and dose escalate quickly, given the lower expected response rates in these patients.[15] A front-line open-label phase 3b trial of luspatercept at this maximum dose of 1.75 mg/kg is underway (MAXILLUS NCT06045689). In some instances, luspatercept achieved RBC-TI or a meaningful reduction in transfusion burden from baseline that was subsequently lost. In a study from the Moffitt Cancer Center in the US, 5/7 (71%) patients who lost response to luspatercept responded to the addition of ESA (2nd failure), but the response rate was only 17% (3/18) in those with primary failures to luspatercept.[16] Luspatercept in combination with roxadustat (NCT06006949) and lenalidomide (NCT04539236) is being evaluated in prospective clinical trials for patients in whom therapy with ESAs failed.

Imetelstat

Imetelstat, which is not currently available in Canada, is an oligonucleotide that binds the RNA template of human telomerase and acts as a potent competitive inhibitor of enzymatic telomerase activity. By targeting cells with increased telomerase activity, imetelstat selectively induces apoptosis of malignant haematopoietic progenitor cells, facilitating bone marrow recovery and improved erythropoiesis.[17,18] The IMerge study evaluated imetelstat

Agent	Study	Design	TI	Details
Lenalidomide del5q	Phase 3 MDS-003 MDS-004	Lenalidomide vs. placebo	56%	• Achieving RBC-TI is associated with improved OS • Median TI duration: 2 years • HMA may be effective after lenalidomide • 10-20% harbor *TP53* mutations: lower responses and duration; worse LFS • Starting before TD associated with improved TFS
Lenalidomide non-del5q	Phase 3 MDS-005	Lenalidomide vs. placebo	27%	• Not very durable • Myelosuppressive • QoL improved in responding patients • Higher responses with lower baseline EPO levels and non-*ASXL1* mutations
Luspatercept	Phase 3 Medalist	Luspatercept vs. placebo	38%	• Only for MDS-RS who are TD • Response associated with lower transfusion burden, lower EPO levels • Longest period of TI: 31 weeks • Response agnostic to somatic mutations • Highest doses often needed (1.75 mg/kg)
Imetelstat	Phase 3 IMerge	Imetelstat vs. placebo	40%	• Patients enrolled had higher transfusion burden than Medalist • Median duration of TI: 52 weeks • Active with non-RS subtypes and high transfusion burden • Anti-clonal activity appreciated
Decitabine-cedazuridine	Phase 3 Ascertain	Oral vs. IV decitabine	48%	• Comprised 69/133 patients of larger trial including higher risk • Myelosuppressive: neutropenia (59%) and thrombocytopenia (58%) • Median OS and LFS not reached

Table 1. Clinical trials for treatment after ESA failure in lower risk disease. *Courtesy of Rena Buckstein, MD, FRCPC*
Abbreviations: EPO: erythropoietin; **ESA:** erythropoietic-stimulating agents; **HMA:** hypomethylating agent; **LFS:** leukemia-free survival; **MDS-RS:** myelodysplastic syndromes ring sideroblasts; **OS:** overall survival; **QoL:** quality of life; **RBC-TI:** red blood cell transfusion independence; **TD:** transfusion dependence; **TFS:** transformation free survival; **TI:** transfusion independence

Agent	Study	Design	Response or OS	Details
Induction CHEMO	Many		9-11 months	• As a bridge to transplant
Venetoclax	Phase 1-2	Open-Label	36% TI; CR 7%; OS: 12.6 months	• As a bridge to transplant • ++ myelosuppressive
Ivosidenib	Phase 1	Open-Label	83% ORR 39% CR OS: 36 months 67% TI	• For the 3.6% with *IDH1* mutations • Not funded • Differentiation syndrome and QTc prolongation
Enasidenib	Phase 1	Open-Label	43% ORR 35% CR OS: 20 months 30% TI	• For the 5% with IDH2 mutations • Not Funded

Table 2. Clinical trials for therapy after HMA failure. *Courtesy of Rena Buckstein, MD, FRCPC*
Abbreviations: CR: complete remission; **HMA:** hypomethylating agents; **ORR:** objective response rate; **OS:** overall survival; **TI:** transfusion independence

versus placebo in a double-blind study (2:1 randomization) including a lower risk TD patient population similar to that of MEDALIST albeit in all World Health Organization (WHO) subtypes of MDS, all EPO levels and in a population that was more heavily TD (median of 6 units/8 weeks) **(Table 1)**. The drug was intravenously (IV) administered as a fixed dose of 7.5 mg/kg every 3 weeks. RS was observed in 62% of patients. An RBC-TI of ≥8 weeks was reached in 40% of patients in the imetelstat group versus 15% of patients in the placebo group. The objective response rate (ORR) was higher in patients with RS (45%) but still quite respectable in MDS patients who were non-RS (32%). In addition, the ORR was quite impressive for patients who were heavily TD, defined as >6 units/8 weeks at 34% and higher in those with 4-6 units/8 weeks (ORR: 45%). The median duration of RBC-TI in the imetelstat group was 51.6 weeks vs. 13 weeks for those receiving placebo. The median increase in blood hemoglobin was 35.5 g/L. Anti-clonal activity was also observed, as supported by the achievement of cytogenetic responses in 35% of patients in the imetelstat arm. In addition, the reduction in variant allele frequency (VAF) of *SF3B1*, *TET2*, *DNMT3A*, and *ASXL1* was numerically greater with imetelstat than placebo and correlated with RBC-TI. Improvements in fatigue were observed faster with imetelstat, and a higher proportion of imetelstat responders showed a sustained, meaningful improvement in fatigue scores compared to non-responders. However, imetelstat was complicated by reversible grade 3-4 thrombocytopenia (62%) and neutropenia (68%). This agent was just granted approval by the US Food and Drug Administration (FDA) and will hopefully undergo Health Canada approval following that.[19]

Hypomethylating agents

Despite the survival benefit observed with HMAs for higher-risk disease, the HMAs azacitidine and decitabine have single-agent activity in lower-risk MDS. In the ASCERTAIN study, 69 of 133 enrolled patients had lower-risk disease (93% Int-1, 7% low). The ORR to oral decitabine-cedazuridine (complete remission [CR], partial remission [PR], or marrow CR+ HI) was 57%, and 48% of patients achieved RBC-TI. This agent was associated with neutropenia (59%) and thrombocytopenia (58%). With approximately 32 months of median follow-up, the median leukemia-free survival (LFS) or OS had not been reached.[20] Subcutaneous azacitidine and IV decitabine for 3 days also have single-agent activity in lower-risk MDS[21], but are less convenient to administer than oral decitabine-cedazuridine, which is pharmacokinetically identical to IV decitabine. In a recent retrospective study from the MD Anderson Cancer Center and the Moffitt Cancer Center, the ORR to HMAs in lower-risk MDS was 36%. The median number of cycles administered was 6 (range 1-64 cycles), and the median response duration was 7 months (range 1-73 months). At the time of HMA failure, the majority (54-77%) of patients continued to have lower-risk disease, as assessed by the IPSS-R and IPSS. The median transformation-free survival and OS were 15 and 17 months, respectively, with no differences observed between the two types of HMAs administered. Patients who remained lower risk at the time of HMA failure had longer OS (3 years). Those who received salvage therapy (compared with best supportive care) also lived longer.[22]

Second-line therapy in higher-risk disease

The median OS of patients with higher-risk MDS treated with HMAs is 17.5 months[23], and median response durations are 9-15 months. Patients who relapse or are refractory to HMAs as front-line therapy have a short survival of 4-6 months[24], and less than a third survive for one year.[25] A post-HMA prognostic model comprised of age, performance status, complex karyotype, marrow blast >20%, platelet count, and RBC-TD, separates MDS patients evaluated after HMA failure into two risk categories: lower-risk with a median OS of 11 months, and higher-risk with a median OS of 4.5 months.[26] HMA resistance can be defined as primary resistance comprised of any of the following: stable disease without any of the following: HI, CR or PR, hypoplastic marrow and pancytopenia or progression to higher-risk MDS or AML after 4-6 cycles. Secondary resistance occurs when, after initial response (CR, PR, or HI), the patient experiences any of the primary resistance scenarios.[27] Revised consensus International Working Group (IWG) response and progression criteria for higher-risk disease should be applied.[28] What are the current treatment options for these patients? Unfortunately, in the absence of ASCT or a clinical trial, treatment options are currently limited.

Intensive chemotherapy

Induction AML-type chemotherapy may be considered in selected patients with good performance status MDS as a bridge to transplant,

which has been shown to result in a median OS of 8.9[24]-10.8 months[29] and an ORR of 41% **(Table 2)**. In patients who progress to AML, CPX-351 may be another treatment option in patients being considered for ASCT[30] and this strategy is being evaluated in the context of clinical trials for patients with higher-risk MDS.

Venetoclax

Following HMA treatment, an increase in BCL-2 and a decrease in MCL-1 levels have been described. Venetoclax may restore responsiveness to HMA-resistant cells **(Table 2)**.[31] In an open-label multicenter study in 44 patients with R/R MDS, venetoclax in escalating doses (100-400 mg x 14 days) was tested in combination with azacitidine at usual doses. The recommended phase 2 dose was determined to be 400 mg po daily x 14 days. In the 37 patients evaluable for response, the CR rate was 7%, and the marrow CR rate was 32%, with a median time to response of 1.2 months and a median duration of response of 8.6 months. Out of those who achieved marrow CR, 43% also achieved HI, with 36% of patients achieving post-baseline TI for RBC and platelets lasting 4.3 months. The median OS was 12.6 months, the median PFS 8.6 months, and 21% of patients were able to proceed to ASCT. Therefore, this is a treatment option for blast count reduction in patients who are candidates for ASCT. This regimen is highly myelosuppressive, with febrile neutropenia observed in 34% and pneumonia in 23% of patients. Furthermore, in 9% of cases, possibly-related deaths occur within 30 days of the last study treatment. In the six patients with *IDH2* mutations in this study, the ORR was 83%.[32] Other studies of this combination are ongoing (NCT04160052).

IDH1 and IDH2 inhibitors

While *IDH* mutations are uncommon in MDS (3.6% *IDH1*, 5% *IDH2*), the FDA has approved the IDH1 inhibitor ivosidenib based on a phase 1 study in 18 adults aged 61-82 with *IDH1*-mutated R/R MDS **(Table 2)**. At a dose of 500 mg po daily, 83% had an objective response, and 39% had a CR after a median of two months of treatment. The median treatment duration was 9.3 months and the OS was 36 months. Among the nine patients who had RBC or platelet TD at baseline, 67% achieved TI. Toxicities may include differentiation syndrome and QTc prolongation.[33] The ongoing GFM IDIOME study confirms the high response rates (50%) in R/R *IDH1*-mutated MDS treated with ivosidenib (n=7/13) and even in EPO-refractory lower-risk disease.[34] Similarly, the IDH2 inhibitor enasidenib is active as a monotherapy in 48% of patients with HMA-refractory MDS with *IDH2* mutations (CR 35%, mCR + HI 13%, RBC-TI 30%) **(Table 2)**.[35] The median OS was 20 months in this study, but was not yet reached in the 8 patients achieving CR or mCR. Ivosedinib, enasidenib, and newer IDH inhibitors are being evaluated in combination with HMAs in the front-line and relapsed setting in numerous clinical trials. There are a plethora of ongoing clinical trials of experimental agents and combinations in R/R MDS combined with AML. Furthermore, chimeric antigen receptor CAR T-cell therapy against myeloid antigens including CD33, CD123, CLL-1, CD70, and TIM-3[36] is under investigation in the R/R scenario.[37]

Conclusion

Despite almost a decade of stagnation, newer agents for second-line use in both lower and higher-risk MDS are emerging. Clinical trials remain critical for progress to be made and serial next-generation sequencing is of paramount importance to help guide precision therapies, such as luspatercept for *SF3B1*-mutated, lenalidomide in del5q, and ivosidenib and enasidenib in *IDH1* and *IDH2*-mutated disease. Newer erythroid maturation agents are on the horizon, and we await the results of the VERONA study for higher-risk disease that may establish a new standard of care for higher-risk disease.

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Financial Disclosures :

R.B.: Research Funding: BMS, TAIHO; **Honoraria:** BMS, TAIHO, AbbVie

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References: 1. BRUKINSA (zanubrutinib) Product Monograph. BeiGene Canada. January 31, 2024.

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Management of chronic myeloid leukemia that is intolerant or resistant to front-line treatment.

Lisa Bilston, MD, FRCPC
Kareem Jamani, MD, FRCPC

Introduction

With advances in treatment for chronic myeloid leukemia (CML), the natural history of chronic phase (CP) CML has changed, with most individuals expected to live a normal life expectancy.[1] The goal of therapy for most is to achieve a long-term deep molecular response (DMR) with the potential for medication discontinuation and treatment-free remission (TFR).[1] Currently, six oral therapies have been approved for CP-CML in Canada: (1) imatinib, a first-generation tyrosine kinase inhibitor (TKI); (2) dasatinib, (3) nilotinib, and (4) bosutinib, the second-generation TKIs (2G-TKIs); (5) ponantinib, a third-generation TKI; and (6) asciminib, specifically targeting the ABL Myristoyl pocket (STAMP) inhibitor. Classically, treatment for CP-CML has consisted of front-line imatinib and switching to a 2G-TKI upon treatment resistance or intolerance. Increasingly, patients are being prescribed an upfront 2G-TKI with the goal of achieving quicker and deeper molecular remissions and a TFR.[2] Challenges arise in CML when treatment with either two TKIs (imatinib + 2G-TKI) or one 2G-TKI fails, given the lack of evidence to inform clinical decision-making at this juncture. This paper aims to define TKI failure and help guide the selection of second-line treatment after failure of front-line therapy.

Defining treatment failure in CP-CML

TKI failure can be defined as either (1) resistance: a lack of hematologic response or failure to achieve molecular milestones or (2) intolerance: any adverse events or hematological toxicities mandating a switch in therapy.

The European LeukemiaNet 2020 guideline outlines milestones for molecular response in CP-CML at 3, 6, and 12 months during front- and second-line treatment with a TKI.[1] Molecular response is assessed as the ratio of BCR-ABL1 transcripts to ABL1 transcripts on the International Scale (IS) and reported as BCR-ABL1% on a log scale. Responses are divided into three zones: (1) optimal: treatment can be continued without modification; (2) warning: concerns for treatment resistance, with careful consideration as to continuing versus switching therapy; and (3) failure: defined treatment resistance mandating a switch in therapy **(Table 1)**.[1] The NCCN 2021 guideline offers similar milestones.[3]

Long-term outcomes of the pivotal trials that led to the approval of the first and second-generation TKIs in front-line treatment of CP-CML highlight the rates and reasons for treatment discontinuation **(Table 2)**.[4-7] Ten-year follow-up from the IRIS trial examining imatinib in front-line CP-CML demonstrated a discontinuation rate of 49.2%, 16% due to resistance, and 7% due to intolerance.[4] In contrast, five-to-ten-year follow-up of the 2G-TKIs in front-line CP-CML demonstrated lower discontinuation rates for resistance (5-6%), but higher discontinuation due to intolerance (19-34%).[5-7]

Selection of second-line therapy at the time of treatment failure is determined by: (1) the initial TKI used, (2) patient co-morbidities, and (3) the reason for drug discontinuation – resistance vs. intolerance. While several studies support the switch from front-line imatinib to a 2G-TKI, there is limited data to inform on the next best treatment post-front-line 2G-TKI. A summary of our approach to treatment failure can be found in **Figure 1**.

Second-line therapy post-imatinib

Switching to a 2G-TKI post-imatinib failure can provide long-term responses with complete cytogenetic remissions (CCyRs) of 40-50% and major molecular responses (MMRs) of 30-50%.[8-10]

	Optimal	Warning	Failure
3 months	≤10%	>10%	>10% if confirmed within 1-3 months
6 months	≤1%/CCyR	>1-10%	>10%
12 months	≤0.1%/MMR	>0.1-1%	>1%
Any time	≤0.1%/MMR	>0.1-1%, Loss of ≤0.1%	>1%, resistance mutations, high-risk cytogenetics

Table 1. Milestones for treating BCR-ABL1 on the international scale (IS). *Courtesy of Lisa Bilston, MD, FRCPC and Kareem Jamani, MD, FRCPC*
Abbreviations: CCyR: complete cytogenetic response; **MMR:** major molecular response

	Imatinib	Dasatinib	Nilotinib		Bosutinib
Trial	IRIS[4] (10-year, n=553)	DASISION[5] (5-year, n=258)	ENESTnd[6] (10-year)		BFORE[7] (5-year, n=268)
			300 BID (n=282)	400 BID (n=281)	
Rate of discontinuation	49.2% (n=272)	39% (n=100)	62% (n=175)	65% (n=182)	40% (n=108)
Treatment failure/ resistance	16% (n=88)	11% (n=28)	5% (n=13)	6% (n=17)	5% (n=15)
Intolerance	7% (n=38)	16% (n=42)	21% (n=62)	34% (n=98)	19% (n=53)

Table 2. Rates and reasons for discontinuation of front-line treatment with imatinib or a 2G-TKI. *Courtesy of Lisa Bilston, MD, FRCPC and Kareem Jamani, MD, FRCPC*
Abbreviations: 2g-TKI: second-generation tyrosine kinase inhibitor; **BID:** twice daily

Second-line dasatinib has demonstrated a seven-year progression-free survival (PFS) and overall survival (OS) of 30-50% and 60-70%, respectively, with higher rates in patients intolerant as opposed to resistant to imatinib.[8] Similar data favouring a switch to either nilotinib or bosutinib is outlined in **Table 3**.[9,10] Rates of discontinuation of 2G-TKI post-imatinib therapy due to treatment resistance range from 20-30%.[8-10]

While these data support a switch from imatinib to a 2G-TKI, selecting a 2G-TKI is based on the patient's co-morbidities to minimize intolerance.[2] Dasatinib is associated with an increased risk of pleural effusions, pulmonary arterial hypertension (PAH) and bleeding; avoiding use in patients with existing cardiopulmonary disease, uncontrolled hypertension, PAH, or at increased bleeding risk is recommended.[2,5]

Nilotinib can cause hyperglycemia, pancreatitis, QTc prolongation, and arterial occlusive events (AOE), with a ten-year follow-up from the ENESTnd trial demonstrating AOE rates of 24.8%.[2,6] Nilotinib should be avoided in patients with cardiovascular risk factors, a history of AOE's, or uncontrolled diabetes. Bosutinib's main side effect is diarrhea, and it should not be used in patients with inflammatory bowel disease or other conditions associated with chronic diarrhea.[2,7]

Treatment post-2G-TKI

Limited data exists to guide therapy after the use of a 2G-TKI in the front- or second-line setting. If treatment failure is due to resistance (as opposed to intolerance) mutational analysis should be done via Sanger Sequencing or next-

generation sequencing to help guide the selection of second-line therapy, with treatment tailored to the mutation found.[1] In the absence of a mutation to guide treatment, two options exist:

1. Switch to a different 2G-TKI:

The cohort studies SIMPLICITY and AIFA examined rates of switching from upfront 2G-TKI in a real-world setting.[11,12] SIMPLICITY demonstrated that at two years, rates of switching from dasatinib and nilotinib were 23.8% and 21.1%, respectively,[11] whereas AIFA had a rate of switching from front-line 2G-TKI of 13.2% at six years.[12] Neither study reported on clinical outcomes after switching.

Several studies have attempted to examine outcomes after treatment with a 2G-TKI in the front- or second-line setting. In an Albertan retrospective review, 232 patients were initiated on nilotinib (n=45) or dasatinib (n=187) in front-line treatment of CP-CML.[13] A total of 76 patients switched therapy, with rates of CCyR, MMR (without MR4.5 – 4.5 log reduction), and MR4.5 being 17%, 28%, and 13%, respectively. Of the 76 patients who switched therapy, only 6% (n=16) switched due to resistance. Rates of MMR (without MR4.5) and MR4.5 were 35% and 53% in the intolerant group vs. 44% and 6% in the resistant group, respectively. A similar study examining the long-term outcomes after front-line treatment with a 2G-TKI in CP-CML demonstrated comparable results, with 42.4% of patients requiring a switch in therapy, 26.4% due to intolerance and 16% due to resistance.[14] While intolerant patients could obtain a DMR, outcomes were inferior in resistant patients; resistant patients not responding to second-line 2G-TKI had a 7-year-OS of 66.1% compared to an OS of 100% in intolerant patients. Several other studies, which included small

	Dasatinib (100 mg OD)		**Nilotinib (400 mg BID)**		**Bosutinib (500 mg OD)**	
Trial	CA180-034[8] (n= 167)		Giles *et al.* (2013)[9] (n=321)		Brummendorf *et al.* (2020)[10] (n=284)	
Reason for imatinib discontinuation	Intolerant (n= 43)	Resistant (n=124)	Intolerant (n=90)	Resistant (n=226)	Intolerant (n=89)	Resistant (n=195)
Follow-up	7 years		48+ months		8+ years	
CCyR	44%		45%		42 (53%)	88 (48%)
MMR	22 (55%)	51 (43%)	NA		25 (36%)	58 (46%)
PFS	51%	39%	4 year - 57%		NA	NA
OS	70%	63%	4 year- 78%		9 year - 74%	
Rate of discontinuation	166 (includes study closure)		224		NA	
Resistance/progression	35 (21%)		96 (30%)		27%	
Intolerance/AEs	39 (24%)		66 (21%)		NA	
Adverse events	• Pleural effusions • Pulmonary arterial HTN • Bleeding		• Arterio-occlusive events (AOEs) • Elevated blood glucose • Pancreatitis • QTc prolongation		• Diarrhea • Nausea • Elevated liver enzymes	

Table 3. Second-line treatment with a 2G-TKI after imatinib failure. *Courtesy of Lisa Bilston, MD, FRCPC and Kareem Jamani, MD, FRCPC*

Abbreviations: AE: adverse event; **BID:** twice daily; **CCyR:** complete cytogenetic response; **HTN:** hypertension; **MMR:** major molecular response; **PFS:** progression-free survival; **OD:** once daily; **OS:** overall survival

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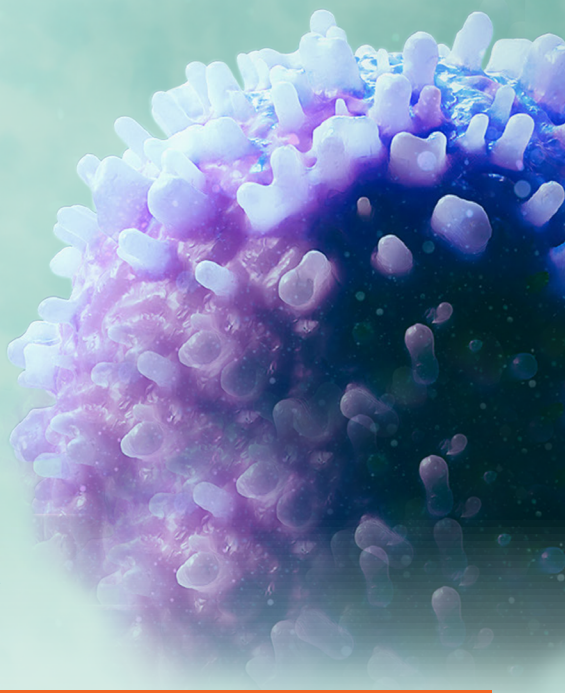

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R/R: relapsed or refractory; DLBCL: diffuse large B-cell lymphoma; ASCT: autologous stem cell transplant.

References: 1. MINJUVI™ Product Monograph. Incyte Corporation. August 19, 2021. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). B-Cell Lymphomas. Version 4.2021. May 5, 2021.

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numbers of patients, have examined 2G-TKI's in the third-line setting.[15] Results of the Phase 4 BYOND study examining bosutinib in the second, third, and fourth line of treatment demonstrated a progressive reduction in rates of MMR at two years with each successive line of therapy (second-line: 82.6%, third-line: 74.5%, and fourth-line: 56.3%), with rates of response at 2 years being higher in patients intolerant (MMR of 80.8%) vs. resistant (MMR of 61.8%) to treatment.[16] These studies highlight that patients who have demonstrated resistance to a 2G-TKI are a particularly high-risk group of individuals; if the choice is made to pursue a 2G-TKI in this setting, it should only be done with close monitoring and response assessments at 3-6 months, with a prompt switch to third-line therapy (asciminib or ponatinib) if molecular targets are not being met.

2. Switch to Asciminib vs. Ponatinib:

CP-CML that is resistant to two or more TKIs is eligible for therapy with either ponatinib or asciminib.

Ponatinib is a potent third-generation TKI, with activity against several clinically relevant BCR-ABL1 kinase domain mutations, including the T315I mutation.[1] Ponatinib was studied in the Phase 2 PACE trial, which demonstrated the efficacy of ponatinib in the treatment of CP-CML that was resistant or intolerant to dasatinib, nilotinib, or in the presence of the BCR-ABL1 T315I mutation.[17] The major limitation of ponatinib was the high rates of AOEs at 31%. The OPTIC trial subsequently examined the efficacy of ponatinib at starting doses of 45 mg/day, 30 mg/day or 15 mg/day, with a dose reduction to 15 mg/day at MR2 (2-log reduction) (BCR-ABL1 <1%).[18] The OPTIC trial demonstrated that upfront high-dose ponatinib followed by dose de-escalation was both highly efficacious and superior to the lower dose arms (MR2 at 12 months of 52% vs. 36% vs. 25% in the 45 mg, 30 mg, and 15 mg cohort, respectively). Dose de-escalation reduced AOEs compared to the PACE data, with AOEs of 9.6%, 5.3%, and 3.2% in the 45 mg, 30 mg, and 15 mg cohorts, respectively. In the T315I group, upfront treatment with 45 mg/day was superior to 30 mg/day with MR2 rates of 60% and 25% at 12 months, respectively. Without resistance or a documented KD mutation, the advantage of higher dose ponatinib was less apparent.

Asciminib is a novel, first-in-class STAMP inhibitor that inhibits the kinase activity of BCR-ABL1 via allosteric binding. Asciminib was studied in the Phase 3 ASCEMBL trial, which compared asciminib 40 mg twice daily (BID) to bosutinib 500 mg once daily (OD) in CP-CML previously treated with two or more TKIs.[19] Asciminib was found to have superior

	Ponatinib 45 mg OD	Asciminib 40 mg BID
Trial	OPTIC (n= 92)	ASCEMBL (n=157)
Follow-up	32 months	19 months
≥3 prior TKI lines	53%	48%
Resistant to the last TKI	98%	61%
Intolerant to prior TKI	2%	38%
MR2 at 12 months	44%	42%
Discontinuation due to resistance/progression	19%	24%
Discontinuation due to intolerance/AE's	17%	6%
AOEs per 100 patient years	9.6	3.4

Table 4. Choice of TKI after use of prior 2G-TKI. *Courtesy of Lisa Bilston, MD, FRCPC and Kareem Jamani, MD, FRCPC*
Abbreviations: 2G-TKI: second-generation tyrosine kinase inhibitor; **AOE:** arterial occlusive events; **BID:** twice daily; **MR2:** 2-log molecular response; **OD:** once daily; **TKI:** tyrosine kinase inhibitor

MR2 rates at 12 months compared to bosutinib at 42% vs. 19%, respectively.

Randomized controlled trials comparing the efficacy of asciminib to ponatinib in the third-line setting are lacking, but a comparison of the trials leading to their approval can inform decision-making **(Table 4)**.[20] The OPTIC trial included more patients with TKI resistance or documented kinase domain mutations than the ASCEMBL trial, which included more patients intolerant to prior therapies.[18,19] Molecular response rates at 12 months were similar for ponatinib vs. asciminib, with MR2 rates of 44% vs. 42%, respectively. Both drugs have demonstrated activity against the T315I mutation at higher doses. In a Phase 1 trial, asciminib at 200 mg BID demonstrated efficacy against the T315I mutation, with MMR rates at six months of 57% in ponatinib-naïve patients and 29% in ponatinib resistant/intolerant patients.[21] Toxicity appeared comparable to standard dose therapy. The OPTIC trial demonstrated the efficacy of ponatinib at 45 mg OD against the T315I mutation, but with dose de-escalation to prevent AOEs, loss of response exceeded 30%.[18] Despite both asciminib and ponatinib having efficacy against the T315I mutation and in CP-CML resistant to prior 2G-TKIs, current recommendations favour the use of ponatinib in CP-CML resistant to a 2G-TKI, especially in the setting of low cardiovascular disease risk. In contrast, asciminib is preferred when there has been intolerance to prior TKIs or when cardiovascular risk is high.[2,20,22] In addition, the higher dose of asciminib that has demonstrated efficacy against the T315I mutation (200 mg) is not routinely available/funded in Canada, limiting its utility in this setting.

Role of allogeneic-hematopoietic stem cell transplant (allo-HSCT)

Allo-HSCT remains the only true curative treatment for CML. However, with second- and third-generation TKIs, it is far less commonly utilized in CP-CML. The ELN-2020 guides indications for allo-HSCT in CP-CML.[1] Allo-HSCT should be considered in CP-CML that has demonstrated:

1. Resistance or intolerance to 2+ TKI's
2. Inadequate recovery of hematopoiesis
3. Resistance to a 2G-TKI used either in the front- or second-line setting
4. Resistance to ponatinib or failure to respond to ponatinib after three months of treatment
5. Emergence of high-risk cytogenetics

The timing of allo-HSCT is critical. Outcomes are best in early CP-CML compared to late CP-CML, with the latter at an increased risk of progression to accelerated phase CML. The goal of therapy prior to transplant is to return to chronic phase CML if the patient had transformed prior to transplant.[1,20]

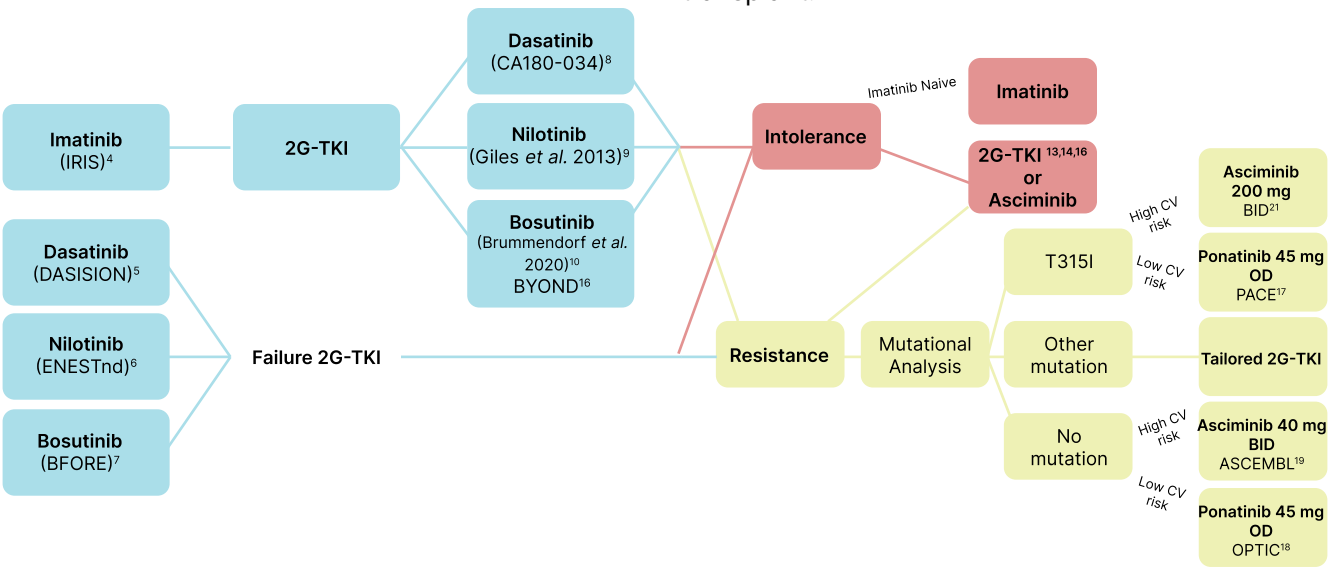

Figure 1. Choice of tyrosine kinase inhibitor after resistance or intolerance to upfront treatment with imatinib or a 2G-TKI. *Courtesy of Lisa Bilston, MD, FRCPC and Kareem Jamani, MD, FRCPC*

Abbreviations: 2G-TKI: second-generation tyrosine kinase inhibitor; **allo-HSCT:** allogeneic hematopoietic stem cell transplant; **BID:** twice daily; **OD:** once daily

Conclusion:

TKIs have markedly changed the landscape of CP-CML treatment, with ten-year OS rates approaching 80%.[22] Most patients require a change in TKI at some point in the treatment of CP-CML, with rates of switching from imatinib or a 2G-TKI approaching 50% and 60%, respectively.[4-7] Clinical outcomes diverge based on the reason for treatment discontinuation, with intolerance in the form of adverse events or hematological toxicities having better long-term outcomes with switching to a 2G-TKI compared to treatment resistance.[13,14,16] In the event of treatment resistance to imatinib, switching to a 2G-TKI confers good outcomes.[8-10] In the event of resistance to a 2G-TKI, kinase domain mutations should be assessed to help guide further therapies.[1] Inferior outcomes are found in patients resistant to a 2G-TKI; an early switch in therapy to either ponatinib or asciminib should be considered and guided by cardiovascular risk.[2,20,22] Allo-HSCT remains a treatment consideration for all patients refractory to at least one 2G-TKI.[20]

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Financial Disclosures :

Lisa Bilston: None declared.
Kareem Jamani: Advisory board: Jazz, Vertex, Avir, Takeda, Paladin; **Speaker:** Novo-Nordisk, Pfizer, Jazz; **Research Funding:** Jazz

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AE = adverse event; CLL = chronic lymphocytic leukemia; SAE = serious adverse event
† Comparative clinical significance unknown.

References: 1. IMBRUVICA® Product Monograph, Janssen Inc., August 1, 2023. **2.** Data on file. Janssen Inc., 2023.

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High-risk myeloma: Definitions and treatments

Rintu Sharma, MD
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Introduction

Multiple myeloma is characterized by clonal proliferation of biologically heterogeneous plasma cells, leading to diverse clinical presentations and outcomes. Although outcomes have improved dramatically over the past decade with the rapid change in the treatment paradigm in standard-risk myeloma, a subset of patients remains who respond poorly to treatment and experience early relapses.[1,2] These patients are considered high-risk and can be identified at the time of diagnosis based on several factors and their response to treatment **(Table 1)**. Therefore, it is important to consider high-risk status as a dynamic assessment.

High-risk myeloma - definition

A) At diagnosis:

1. Disease and patient-related factors:
i) Cytogenetics and staging: Traditionally, patients were defined as high-risk based on advanced international staging system (ISS) stage and later, the revised ISS (R-ISS), which incorporates the presence of elevated lactate dehydrogenase (LDH) and/or certain cytogenetic fluorescence *in situ* hybridization (FISH) abnormalities, including t(4;14), t(14;16), and deletion of 17p, to better demarcate the survival outcomes in this group. The estimated 5-year overall survival (OS) of R-ISS I is 82%, compared to 40% for R-ISS III.[3,4] Although other abnormalities like t(14;20) and monosomy 13 have also been identified as high-risk, these were not included in R-ISS because of their lower prevalence.[5] With the identification of copy number alterations in chromosome 1q as a poor prognostic marker, R-ISS 2 and mSMART classifications incorporate 1q gain/amplification in the staging, allowing a better stratification of patients into four groups.[6,7] Deletion of 1p is another adverse feature but is yet to be incorporated into the current R2 ISS system.[8] Patients with the co-existence of more than one high-risk chromosomal abnormality are categorised as ultra-high risk and have even worse survival outcomes compared to their counterparts with no or one high-risk cytogenetic abnormalities.[9,10]

ii) Gene expression profiling assays like SKY92 and GEP 70 utilise the expression of messenger RNA to identify mutational signatures that are independent prognostic markers to predict early relapses.[11,12] Several genes involved in DNA damage repair pathways, glycolysis, oxidative stress, epithelial-mesenchymal transition, and numerous factors in the tumour microenvironment have been recognised as risk factors for early relapse; however, a detailed discussion of these is beyond the scope of this review.[13]

iii) Patients presenting with renal failure have worse outcomes compared to patients who present with normal renal function, even if the kidney function is recovered.[14] Additionally, extramedullary plasmacytomas, central nervous system involvement, and primary plasma cell leukemia (PCL) also represent aggressive disease biology, respond poorly to treatment, and have a shorter progression-free survival (PFS) and OS, and as such are a high-risk population requiring aggressive treatment.[15,16]

iv) Patient-related factors: the international myeloma working group (IMWG) identified a significant impact of geriatric assessment on the survival and toxicity prediction in elderly patients with myeloma enrolled in several clinical trials with frail patients having a shorter OS (57% at 3 years) than fit patients (84% at 3 years), which may guide myeloma physicians for better decision-making.[17]

B) Based on the response to treatment:

Functional high-risk (FHR): Patients who are not labelled as high-risk at diagnosis but progress within 12-18 months of therapy or are refractory to treatment despite an optimal initial therapy are considered functional high-risk and have significantly inferior PFS and OS.[18,19] These patients can only be assessed by dynamic response assessments. Failure to achieve very good partial response (VGPR) or better has been reported as an independent factor predicting an early relapse within 12 months of high-dose chemotherapy treatment, translating to a significantly worse OS.[20,21] A common observation in these studies was the mislabelling of almost a quarter to half of the functional high-risk patients as standard risk because they fell into the ISS-I or II subgroups with standard-risk cytogenetics. Several scoring systems have been devised to identify early relapses and functional high-risk, which incorporate different combinations of age, performance status, markers of high tumour burden (high LDH, albumin, bone marrow plasma cells), ISS stage, and disease status at autologous stem cell transplantation (ASCT), which could be integrated into daily clinical practice.[22-24]

Sustained minimal residual disease (MRD) negativity is a better prognostic marker than VGPR; however, its routine use in clinical practice is yet to be established.[25]

Thus, defining high-risk patients requires a comprehensive baseline assessment with longitudinal response monitoring and, thus, is a dynamic process and should not be limited to baseline R-ISS and cytogenetic abnormalities.

At Diagnosis:	
Disease-related factors o High tumour burden/ aggressive clinical presentation	High LDH, extramedullary disease, central nervous system involvement, primary plasma cell leukemia, renal failure
o Cytogenetic abnormalities	Primary cytogenetic abnormalities: t(4;14), t(14,16), t(14;20); secondary cytogenetic abnormalities: 17p deletion, 1q gain/ amplification, 1p deletion
o Staging systems: R-ISS, R2- ISS	**R- ISS III**: beta 2 microglobulin >5.5 mg/L with either raised serum LDH and/or positive del 17p, t(4;14), or t(14;16) by FISH. **R2- ISS**: Scoring system incorporating ISS II or III, del17p, high LDH, t(4;14), or presence of 1q gain/amplification with an additive score of 3-5 **mSMART** classification: high-risk abnormalities include t(4;14), t(14;16), t(14;20), del 17p, or p53 mutation, chromosome 1q abnormalities (1q gain or 1p deletion), gene expression profiling high-risk signature.[7] Sky 92, UAMS/ GEP 70
o Gene Expression Profiling	IMWG frailty score R-MCI
Patient-related factors o Frailty	
After treatment	
Functional high-risk	• Primary refractory patients • Patients who progress within 12-18 months of initiating optimal therapy.

Table 1. Definition of High-Risk Myeloma. *Courtesy of Guido Lancman, MD, MSc, Rintu Sharma, MD and Karla Alexandra Sánchez Hernández, MD*

Abbreviations: FISH: fluorescence in situ hybridization; **IMWG:** international myeloma working group; **LDH:** lactate dehydrogenase; **mSMART:** Mayo stratification for myeloma and risk-adapted therapy; **R-ISS:** revised international staging system; **R-MCI:** revised myeloma comorbidity index

What are we doing today to treat high-risk multiple myeloma?

In Canada, the current standard of care (SOC) treatment for newly diagnosed patients with multiple myeloma (MM) who are eligible for transplant, regardless of the presence of high-risk features at diagnosis, is the VRd regimen (bortezomib, lenalidomide, and dexamethasone). The DETERMINATION trial showed that VRd induction, followed by ASCT, VRd consolidation, and lenalidomide maintenance, resulted in a median PFS of 67.5 months. However, in the subgroup of patients with at least one high-risk cytogenetic abnormality (HRCA), the PFS dropped to 55.5 months and 35.9 months for patients with ISS III at diagnosis, respectively.[26] In other countries, quadruplet therapies are now being used as the first line of treatment for newly diagnosed MM, with the addition of anti-CD38 monoclonal antibodies to the VRd therapy. The Phase 3 PERSEUS trial added subcutaneous daratumumab to the VRd regimen (D-VRd) during induction, consolidation, and maintenance in transplant-eligible patients. After a median follow-up of 47.5 months, the PFS was significantly improved with D-VRd to 84.3% compared to 67.7% for VRd.[27]

Although the quadruplet treatment showed consistent benefits for the high-risk population compared to the VRd arm, the outcome comparison between patients with ISS III or HRCA versus ISS I-II or standard risk cytogenetics (SRCG) within the D-VRd group did show slightly inferior results. The patients with ISS III achieved a complete remission (CR) or better rate of 80%, while the group with ISS I and II had a rate of 89.8% and 88.6%, respectively. Similarly, patients with HRCA had a CR or better rate of 82.9%, while patients with SRCG had a rate of 88.6%. Further follow-up will be needed to determine the PFS achieved with this regimen in these patient groups.[28] At this time, the addition of daratumumab to VRd is recommended for high-risk Canadian patients who can access it through private insurance, as it is not yet publicly funded.

High-dose melphalan and ASCT improve outcomes in patients with MM; therefore, ASCT remains a SOC treatment in all patients with a performance status suitable to undergo the procedure. Patients who receive VRd alone have a 53% higher risk of experiencing events like disease progression or death, compared to those who undergo an ASCT after VRd induction.[26]

In contrast, the effectiveness of tandem transplants is not yet fully established. According to the EMN02/HO95 study, in comparison to single ASCT, tandem transplants showed better results in terms of prolonged PFS and OS for both the general patient population and poor prognosis subgroups.[28] The STaMINA trial showed no difference between single and tandem transplants in the overall population, but there appeared to be significantly longer PFS for high-risk patients receiving tandem vs. single transplants.[29]

Tandem transplant remains a suitable option for treating high-risk patients, although it is not universally adopted. Our center (Princess Margaret Cancer Centre, Toronto, ON) conducted a retrospective review, which revealed that patients with high-risk disease who underwent tandem transplantation had a significant improvement in both PFS and OS compared to those who received single ASCT.[30] The median PFS for patients who underwent tandem transplantation was 45 months, and the median OS was 68.5 months. In contrast, patients who received a single ASCT had a median PFS of 24.9 months and a median OS of 29.3 months. It should be noted that this analysis was conducted before the establishment of VRd or D-VRd as induction regimens, and, therefore, it cannot fully evaluate the results of tandem transplants in combination with VRd or quadruplet regimens.

Maintenance treatment plays a crucial role in the treatment of patients with MM, especially in high-risk patients who can achieve deep, but not durable, responses. The Total Therapy 3 (TT3) clinical trial conducted in 2007 was a pioneer in incorporating a proteasome inhibitor (PI), bortezomib, along with the immunomodulatory drug (IMiD) thalidomide as maintenance. When compared to the results of the Total Therapy 2 trial (TT2), patients under 65 years of age and those with gene expression profiling (GEP)-defined high-risk MM showed a significant improvement in the 2-year event-free survival (EFS) and OS with the addition of bortezomib. The TT3 group had a 2-year EFS of 68% and OS of 75%, while the TT2 group had a 2-year EFS of 30% and OS of 50%.[31] The use of dual maintenance (PI/IMiD) is now a SOC practice in treating high-risk MM. A randomized phase 3 trial demonstrated no benefit of adding ixazomib to lenalidomide for maintenance, including in the subgroup of high-risk patients.[32]

Several clinical trials in patients with newly diagnosed MM have incorporated anti-CD38

monoclonal antibodies to lenalidomide during maintenance treatment. However, these studies were not specifically designed to evaluate its efficacy during maintenance and although it is a viable alternative, more information is required before it can be incorporated into day-to-day clinical practice.

What is being investigated for patients with high-risk MM?

The treatment for myeloma is constantly developing, leading to improved patient outcomes across all subgroups. Unfortunately, there remains a discrepancy between patients with high-risk and standard-risk disease. As such, various initiatives aim to overcome these differences.

Carfilzomib and bortezomib are both PIs. Despite their similarities, there are subtle differences in their mechanisms of action. Carfilzomib is an irreversible inhibitor of the 26S proteasome complex, while bortezomib is a reversible inhibitor. Notably, a head-to-head comparison of these drugs demonstrated a significant improvement in OS with carfilzomib over bortezomib in patients with relapsed or refractory MM (RRMM).[33]

This principle has resulted in the inclusion of carfilzomib as a first-line treatment for high-risk patients with newly diagnosed MM. The effectiveness of D-KRd (carfilzomib, lenalidomide, dexamethasone, and daratumumab) for induction/consolidation therapy has been studied in various Phase 2 clinical trials, such as the MASTER and IFM 2018-04 studies, which have demonstrated improved outcomes and feasibility among this patient population.[34,35] Further research is needed to determine its use outside the clinical trial setting.

First-line quintuplet treatments have also been studied as an alternative approach for patients with ultra-high-risk MM. The treatment protocol in the OPTIMUM Phase 2 trial included D-CVRd (cyclophosphamide, bortezomib, lenalidomide, dexamethasone, daratumumab) induction, V-augmented ASCT, extended D-VRd consolidation, and daratumumab-lenalidomide (D-R) maintenance. This trial used the ultra-high-risk patients from the Myeloma XI trial as the external comparator arm. The results showed significant improvement in PFS and OS, with a PFS of 77% compared to 39%, and an OS of 83.5% compared to 73.5% at a 30-month follow-up, for patients treated with this regimen vs. the patients from the Myeloma XI trial, respectively.[36]

Immunotherapies, such as anti-B cell maturation antigen (BCMA) chimeric antigen receptor CAR T-cells and bispecific antibodies, have shown impressive efficacy in heavily pretreated patients with RRMM; however, high-risk subgroups remain a challenge. In the 2-year follow-up of the phase 1b/2 CARTITUDE-1 study of cilta-cel (anti-BCMA CAR T), PFS was shorter in patients with ISS 3, high-risk cytogenetics, plasmacytomas, and high tumour burden as compared to the overall study population.[37] Lower efficacy has also been observed in these subgroups for bispecific antibodies.[38,39] It remains to be seen whether using these therapies earlier in the disease course can abrogate some high-risk features. In the phase 3 CARTITUDE-4 trial, cilta-cel appeared superior to SOC for all high-risk subgroups, but further data are needed to understand the durability of this response compared to standard-risk patients.[40]

Final Recommendations:

- High-risk disease is a dynamic concept. Identifying high-risk features at diagnosis and throughout the course of the disease is crucial for appropriate management.
- Tumor burden, cytogenetic abnormalities, ISS staging, gene expression profile, suboptimal response to treatment, and frailty are all components of high-risk disease.
- Quadruplet induction regimens are preferred over triplet regimens where accessible.
- ASCT remains crucial in the treatment of patients with MM; tandem transplantation can potentially offer improved outcomes when compared to single ASCT.
- Novel approaches to maintenance are being explored, including anti-CD38 antibodies and immunotherapeutic (CAR T-cell and bispecific T cell engager [BiTE]) approaches.
- New immunotherapies, such as anti-BMCA CAR T-cell and BiTEs, have shown positive results in treating patients with high-risk MM. They are currently only used for relapsed/refractory cases. Incorporating these therapies in the first-line setting may help overcome the poor prognosis in this group of patients.

Conclusions

When treating patients with newly diagnosed MM, early detection of high-risk features is crucial to provide treatments that can result in deep and long-lasting remissions. A uniform way of defining

patients with high-risk MM is yet to be developed as there is significant heterogeneity within this group. It is evident that correctly identifying this population requires an evaluation of more factors than just cytogenetics, and high-risk disease is a dynamic entity rather than a single determination performed only at diagnosis.

When selecting a treatment, it is important to not only consider effectiveness but also the potential side effects of the chosen regimen. Additionally, the patient's characteristics and preferences, disease biology, comorbidities, and available treatments and supportive treatments should be considered carefully. These factors are crucial in determining the most appropriate regimen for each scenario. Where available, high-risk patients should be referred for clinical trials.

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Financial Disclosures :

G.L.: None declared.
R.S.: None declared.
K.A.S.H.: None declared.

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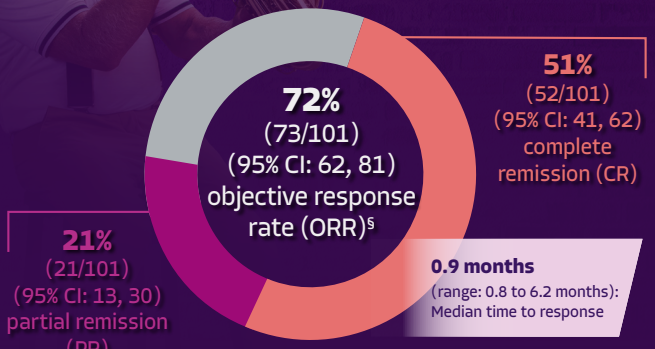
HAVE YOU CONSIDERED YESCARTA AS PART OF THEIR STORYLINE?

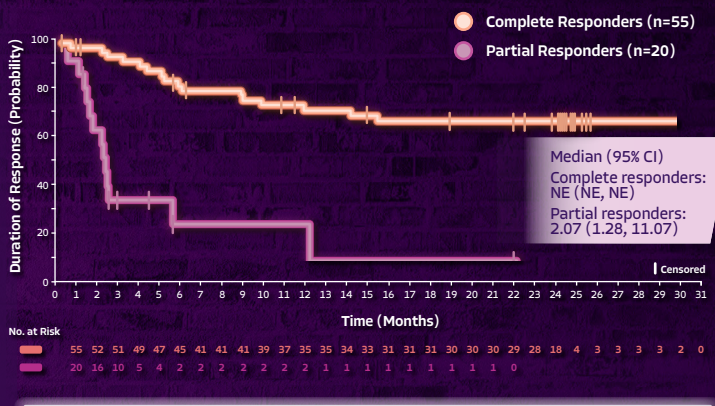
Pr YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

In adult patients with refractory* or relapsed LBCL after two or more lines of systemic therapy, YESCARTA demonstrated an objective response rate in over 7 out of 10 patients treated in the single-arm, open-label 12-month analysis (independent central review)†



0.9 months
(range: 0.8 to 6.2 months): Median time to response

In the 24-month follow-up analysis of the single-arm ZUMA-1 trial, DOR was longer in patients who achieved CR compared to patients with a best response of PR§



YESCARTA, indicated for:

- the treatment of adult patients with relapsed or refractory grade 1, 2 or 3a follicular lymphoma (FL) after two or more lines of systemic therapy

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

NATIONAL COMPREHENSIVE CANCER NETWORK® AS MENTIONED IN NCCN®

- Axicabtagene ciloleucel is considered an option for DLBCL patients:
  - In the 2L setting with relapse within 12 months or primary refractory disease
  - In the 3L setting and subsequent, as a T-cell engager therapy option (CAR T-cell therapy preferred if not previously given)
- For complete recommendations, please refer to the NCCN guidelines

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with:

- diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy;
- relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma.

Most Serious Warnings and Precautions:

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Delay YESCARTA treatment if a patient has active uncontrolled infection or inflammatory disorders, active graft-versus-host disease (GVHD) or unresolved serious adverse reactions from prior therapies. Monitor for CRS after treatment with YESCARTA. Provide supportive care, tocilizumab, or tocilizumab and corticosteroids, as needed.

Neurologic adverse reactions, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or independently of CRS. Monitor for neurologic adverse reactions after treatment with YESCARTA. Provide supportive care, tocilizumab (if with concurrent CRS), or corticosteroids, as needed.

Administration: YESCARTA should be administered by experienced health professionals at specialized treatment centres.

Other Relevant Warnings and Precautions:

- YESCARTA should be administered in a treatment facility with personnel trained in handling and administering YESCARTA and in the management of patients treated with YESCARTA, including monitoring and managing CRS and neurotoxicity. The facility should have immediate access to appropriate emergency equipment and intensive care unit.
- For autologous use only. Under no circumstances should it be administered to other patients.
- Before infusion, the patient's identity must match the patient identifiers on the YESCARTA cassette.
- Safety and efficacy have not been established in patients with central nervous system (CNS) lymphoma.
- Patients should not donate blood, organs, tissues and cells for transplantation.
- Patients should receive life-long monitoring for secondary malignancies.
- Driving, operating machinery, and other hazardous occupations or activities should be avoided in the 8 weeks following YESCARTA infusion.
- Risk of tumour lysis syndrome (TLS).
- Risk of B-cell aplasia and hypogammaglobulinemia.
- Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.
- Allergic reactions may occur with YESCARTA infusion. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.
- Risk of prolonged cytopenias.
- Risk of severe or life-threatening infections. Should not be administered to patients with clinically significant active infections.
- Risk of febrile neutropenia.
- Risk of reactivation of hepatitis B virus (HBV), human polyomavirus 2 (JC virus; the cause of progressive multifocal leukoencephalopathy [PML]) and human herpesvirus 6 (HHV-6).
- Patients must be monitored at least daily for 7 days at the specialized healthcare/clinical facility following infusion for signs and symptoms of CRS and neurologic adverse reactions.
- CRS and neurologic adverse reactions can occur more than 7 days after the infusion. Instruct patients to remain within proximity of the specialized healthcare/clinical facility for at least 4 weeks following infusion. Educate patients and their caregivers for signs and symptoms of CRS and neurologic adverse reactions. Advise patients and their caregivers to immediately contact the designated health professional if CRS or neurologic adverse reactions are suspected.
- YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. Sexually active females of reproductive potential should have a pregnancy test prior to starting treatment and should use effective contraception (methods that result in less than 1% pregnancy rates) after YESCARTA administration. Sexually active males who have received YESCARTA should use a condom during intercourse with females of reproductive potential or pregnant women. See the Product Monographs for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.
- Precaution should be exercised for breastfeeding.
- No data in patients < 18 years old are available to Health Canada: therefore, Health Canada has not authorized an indication for pediatric use.
- No dose adjustment required in patients ≥ 65 years of age.

For More Information:

Please consult the product monograph at https://pdf.hres.ca/dpd_pm/00074215.PDF for important information relating to adverse reactions, interactions, and dosing which has not been discussed in this piece. The product monograph is also available by calling Gilead Sciences Canada, Inc. at 1-866-207-4267.

* Refractory LBCL was defined as progressive or stable disease as the best response to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem cell transplantation (ASCT).

† ZUMA-1 was a phase 2 single-arm, open-label, multicentre trial evaluating the efficacy of YESCARTA in 111 adult patients with relapsed or refractory DLBCL, PMBCL, or TFL after two or more lines of systemic therapies. Eligible patients had refractory disease to the most recent therapy or relapse within 1 year after HSCT. Prior therapies included anti-CD20 antibody therapy and an anthracycline-containing regimen. Following lymphodepleting chemotherapy, YESCARTA was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells). Primary endpoint was ORR, calculated as the combined rates of CR + PR.

‡ As assessed per the revised International Working Group response criteria.

§ Duration of response (DOR) was measured from the date of first objective response to the date of progression or death from relapse or toxicity. DOR was censored for 59% of patients who achieved a complete response or partial response, including those who received a new therapy, had stem cell transplant (SCT), or had an ongoing response. DOR was censored at the time of SCT for patients who received SCT while in response.[1]

CI = confidence interval; LBCL = large B-cell lymphoma; NE = not estimable

Adapted from Data on File and YESCARTA Product Monograph.[1,2]

References:

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2. Data on File, Gilead Sciences Canada, Inc.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. Version 1.2024 – January 18, 2024.

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Treatment of relapsed/refractory chronic lymphocytic leukemia after BTK inhibitor and/or BCL-2 inhibitor failure

Sue Robinson, MD, FRCPC

Introduction

The treatment landscape for first-line and relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) has tremendously advanced with the introduction of Bruton tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL-2i). However, in this new era of targeted therapy for CLL, there is, unfortunately, no evidence yet to guide the optimal sequencing of these drugs. It remains unknown whether treating first-line with a BTKi and relapse with BCL-2i or BCL-2i at first-line followed by BTKi at relapse results in any difference in overall survival (OS). Ibrutinib (BTKi) was first introduced in 2014, and venetoclax (BCL-2i) in 2016, and currently, there are limited prospective data and treatment options for patients who have relapsed after one or both targeted therapies. This article will provide an overview of the approach to treatment for patients with CLL/SLL when BTKi and/or BCL-2i therapy has failed.

Before launching into the treatment of R/R CLL, it is worth noting that guidelines for risk assessment of CLL recommend determining the immunoglobulin heavy chain gene (IGHV) mutational status once, usually before the first treatment, and fluorescence *in situ* hybridization FISH for del(17p) and next-generation sequencing (NGS) before each treatment.[1] Other than *TP53*, NGS-detected mutations are not routinely considered when choosing a therapy, but they may help predict the duration of remission and may become standard of care in the future.

Treatment of R/R CLL after chemoimmunotherapy

Many of our Canadian patients with relapsed CLL have had prior treatment with

chemoimmunotherapy. The RESONATE trial was the first published trial looking at targeted therapy in relapsed disease with the entire population having received first-line chemoimmunotherapy.[2, 3] The median progression-free survival (PFS) for ibrutinib at six years of follow-up was 44.1 months. The alternate arm in this randomized study received ofatumumab, which had inferior results with a PFS of 8.1 months. Therefore, this treatment option was not brought forward for future studies in R/R CLL.

The HELIOS study randomized patients with R/R CLL to ibrutinib alone vs ibrutinib with bendamustine and rituximab.[4] The trial showed similar PFS results in both arms, suggesting there was no advantage of adding chemoimmunotherapy to the BTKi.

Acalabrutinib was the first of the second-generation BTKi's to be studied in R/R CLL. In the ASCEND trial, patients received chemoimmunotherapy as first-line treatment.[5] The median PFS was not reached at 46 months. The comparator arm was idelalisib and rituximab or bendamustine and rituximab (investigator's choice), which resulted in an inferior median PFS of 16.2 months. This study confirmed the superiority in efficacy and safety of acalabrutinib over the other treatments.

The ELEVATE-RR study was a head-to-head comparison of acalabrutinib and ibrutinib in patients who had received a median of two prior treatments.[6] The median PFS was 38.4 months for both BTKi's, at a median follow-up of 40.9 months. Adverse events, especially atrial fibrillation, hypertension, and diarrhea, were less common with the second-generation BTKi acalabrutinib.

Zanubrutinib was the next second-generation BTKi that was developed. The ALPINE study compared zanubrutinib to ibrutinib in patients with a median of one prior treatment.[7] The PFS in the zanubrutinib arm was superior at 78.4% vs. 65.9% at a median follow-up at 29.6 months and 65.8% vs. 54.3 % at a median follow-up at 36.3 months, for zanubrutinib vs. ibrutinib, respectively.[8] Again, the toxicity profile, especially atrial fibrillation, was preferable with zanubrutinib, but the rates of hypertension were similar. Since these two head-to-head comparative studies were published, second-generation BTKi's are favoured over first-generation BTKi mainly because of the superior adverse event profile.

There is no evidence that adding a CD20 monoclonal antibody to ibrutinib improves outcomes, either objective response rate (ORR) or PFS. There is, however, some evidence that adding obinutuzumab to acalabrutinib improves PFS, but this combination is not approved in most of Canada.

The next class of targeted agents studied in R/R CLL was the phosphatidylinositol 4,5-biphosphate 3-kinase catalytic subunit delta inhibitors (PI3Ki). Idelalisib was first studied in combination with rituximab compared to rituximab with placebo. The median PFS was 20.3 months in the PI3Ki arm vs. 5.5 months in the placebo arm, and the study also showed a 6-month OS advantage for the PI3Ki arm. Although the initial results were very promising, the toxicity was high. Idelalisib is available in Canada for combination treatment with rituximab but is not commonly considered an option given the adverse events and better alternatives.

Venetoclax, the first of the BCL-2i, was first studied in 2016 as a single agent given continuously, similar to BTKi. Various studies revealed an ORR of 70-79% for this treatment. With the high rates of undetectable minimal residual disease (uMRD), it was advised that venetoclax could be provided for a fixed duration, with no need for continuous treatment. The addition of rituximab was shown to reduce emerging resistant clones to venetoclax[9] and this resulted in deeper responses with higher complete remission (CR) rates.[10] The MURANO Phase 3 study compared venetoclax with rituximab (VEN-R)with a fixed duration protocol of two years to bendamustine and rituximab (BR).[11] At the 5-year follow-up, the median PFS was 53.6 months for VEN-R and 17 months for BR, confirming that this targeted combination therapy, was superior to chemoimmunotherapy for R/R CLL.[12]

Treatment of R/R CLL previously treated with BTKi

Patients who relapse on a BTKi will most often be switched to venetoclax and rituximab, or less often to venetoclax monotherapy, although published clinical trial data are limited due to small sample sizes. In four early phase studies with venetoclax in R/R CLL, approximately half of the patients receiving the standard 400 mg dose had received a BTKi previously.[13] Adverse factors for attaining a complete remission and durable responses were refractoriness to BTKi, >3 prior treatments, and bulky adenopathy. *TP53*, del(17p), and unmutated IGHV status did not affect the response, but were associated with a shorter PFS.

Switching to another BTKi is not recommended for R/R CLL since approximately 85% of patients will develop resistance by acquiring mutations, most commonly at the C481 position in the BTK kinase domain and less commonly in *PLCG2*.[14] Another option is pirtobrutinib[15], which is a highly selective noncovalent (reversible) BTK inhibitor. The ORR was similar for patients previously treated with ibrutinib, with or without the BTK C481 mutation.

If a patient has discontinued a BTKi due to toxicity, and then relapsed while off treatment, a second BTKi could be considered if the original toxicity was not generic for all BTKi, such as atrial fibrillation or bleeding.

Treatment of R/R CLL previously treated with BCL-2i

Patients previously treated with venetoclax are typically started on a BTKi for R/R disease. Four initial small case series illustrated the effectiveness of BTKi's for R/R CLL after venetoclax treatment, in which the majority of patients were on continuous venetoclax. Patients were heavily pretreated with four median prior treatments, and 76% had mutated *TP53*. Most patients obtained a partial response with the BTKi, and the median PFS was 34 months. Longer PFS was associated with a prior remission duration of >24 months and attainment of a CR.[16-19] In a larger retrospective study, 326 patients who were treated previously with venetoclax were treated with another targeted therapy, including BTKI and PI3Ki.[20] Most of these patients had received venetoclax in the R/R setting and had a median of three therapies prior to venetoclax. The ORR in BTKi-naïve patients was 84% compared to 54% in BTKi-exposed patients. The median PFS was 32 months in patients who had not received BTKi before, while it was not reached in those previously treated with BTKi but who were intolerant to it, and 4 months in those previously BTKi-treated and resistant. In a subset of patients who were BTKi-naïve and had discontinued venetoclax for progressive disease, the estimated median PFS with post-venetoclax BTKi was not reached. With post-venetoclax PI3Ki, the ORR was 46.9% with a short median PFS of 5 months.

Studies of venetoclax resistance have shown that the mechanisms do not overlap with those of BTKi, which supports the effectiveness of BTKi with R/R CLL after venetoclax. A recurrent mutation Gly101Val in BCL-2 has been identified in patients progressing on venetoclax. Resistance tends to occur late (after 19-42 months), and may, therefore, not be relevant for retreatment with venetoclax for patients with relapse after being on fixed-duration venetoclax.[21] In a small study, patients previously treated with venetoclax who acquired the Gly101Val mutation had an effective response to a BTKi at relapse, with the PFS not reached at a median follow-up of 33 months.[22]

Retreatment with venetoclax is also possible if the CLL relapse occurs after venetoclax discontinuation. A five-year follow-up of continuous or limited-duration therapy with venetoclax and rituximab included three patients previously treated with venetoclax. Of these patients, 100% had partial remissions, and the duration of responses ranged from 18.7-40.3 months.[23] The MURANO study included 18 patients who were re-treated with venetoclax, and the ORR was 72.2% with a median treatment duration of 11.4 months (range 0.7-27.6 months).[24] A retrospective study looked at 46 patients receiving a second treatment with venetoclax, which was mostly given as a monotherapy (45.7%), but was also combined with rituximab (28.2%), obinutuzumab (10.9%), and ibrutinib (4.4%) for R/R disease. In most cases, the initial venetoclax treatment was for R/R disease and the median number of prior treatments was two. There was a median of 16 months between completing the first venetoclax treatment and starting the second (range 3-52 months). The ORR was 79.5% with a CR rate of 33.3% and a median PFS of 25 months.[25] It is currently unclear whether the response to retreatment with venetoclax is affected by the duration or depth of response to the initial treatment. Reduced responses to venetoclax have been associated with ≥3 previous lines of therapy, bulky lymphadenopathy, and high-risk molecular results of del(17p), *TP53* mutation, *NOTCH1* mutations, and unmutated IGHV mutational status.[13]

Treatment for R/R CLL previously treated with both BTKi and BCL-2i

A recent review of patients who received prior BTKi and a proportion also being exposed to BCL-2i were treated with pirtobrutinib. The overall response rate for all patients was approximately 82%, similar whether or not they received a prior BCL-2i. The BCL-2i-naïve patients had a longer PFS of 23 months than those previously exposed to BCL-2i of 16 months at a median follow-up of

27.5 months. This could be explained by the more heavily pretreated status of the BCL-2i-exposed group (median prior treatments was 5 for exposed and 3 for naïve).[15,26] Pirtobrutinib was well tolerated with 3.9% of patients requiring dose reduction and 2.5% discontinuing. Some Canadian centers were involved with pirtobrutinib clinical trials; however, this treatment has not yet been approved by Health Canada for standard use.

There is limited experience in Canada with treating patients with combined ibrutinib and venetoclax as first-line therapy and likely no experience with patients who have relapsed after this protocol. This has been approved by Health Canada and is presently available with private insurance or through a clinical trial available in some centres. There is now a 5-year follow-up of the Phase 2 CAPTIVATE study for patients who received a fixed duration of 12 cycles of ibrutinib and venetoclax, which was started after three cycles of ibrutinib; 25% had progressive disease and were re-treated with ibrutinib. The overall response rate was 86%.[27]

Patients with double-refractory CLL are a growing population, and effective treatment options for this group are an unmet need. Although the prognosis of patients with double-refractory CLL who were previously treated with immunochemotherapy is poor, it remains unknown what the outcome is for patients who have only been treated with these two targeted therapies. In one small retrospective analysis of 17 patients with double-refractory progressive disease, the OS was 3.6 months.[28] These patients had high-risk features and were heavily pretreated before receiving the BTKi and BCL-2i. Another real-world study looked at a subgroup in their database who had received both BTKi and BCL-2i (most not continuous), with a small number having received prior immunochemotherapy up until 2021.[29] The majority of the 581 patients had received one of the targeted therapies in the first-line setting and in 83% of patients the BTKi was the first treatment. The most common treatment after both targeted agents contained a BCL2i with or without other treatments. The median time to treatment discontinuation or death was 5.6 months. This outlines the progressive refractoriness and poor prognosis of CLL with increasing lines of therapy and the need for effective treatments post both targeted agents.

Allogeneic stem cell transplant would be a consideration only for young and fit patients who are double-refractory. Long-lasting remissions can occur in 30-50% of transplanted CLL patients.[30] Chimeric antigen receptor (CAR) T-cell therapy[31] will likely be an upcoming option in Canadian clinical trials. Bispecific antibodies[32], bispecific T cell engagers[33], and BTK degraders[34], have also shown early favorable results and, these types of treatments will hopefully be available in clinical trials in Canada in the near future.

For patients experiencing a disease relapse who require bridging to a more definitive treatment, such as an allogeneic stem cell transplant or waiting for an imminent clinical trial, chemoimmunotherapy with bendamustine and rituximab, fludarabine, chlorambucil, or alemtuzumab could be considered as short-term treatment.

Conclusion

With the increased use of BTKi and BCL-2i in the treatment of CLL, the question arises as to what sequence of therapies is preferred, and what therapies are best to follow-up with at the R/R stage. While research remains limited, we have provided the best evidence options for treatment after first-line chemoimmunotherapy, BTKi, BCL-2i, or combined BTKi and BCL-2i. In particular for the patient population progressing to R/R disease after combined use of BTKi and BCL-2i, more research into second and later-line treatment options is warranted.

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Financial Disclosures :

Advisory Boards/Honorarium: AbbVie, AstraZeneca, BeiGene, Celgene, Kite-Gilead, Janssen, Roche;
Grants/Research support: AstraZeneca

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† In a randomized, multi-centre, open-label, Phase 3 trial (ELEVATE-TN) of 535 patients with previously untreated CLL. Patients were randomized to receive either CALQUENCE plus obinutuzumab, CALQUENCE monotherapy, or obinutuzumab plus chlorambucil. CALQUENCE + obinutuzumab: CALQUENCE 100 mg was administered twice daily starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was 28 days. CALQUENCE monotherapy: CALQUENCE 100 mg was administered twice daily until disease progression or unacceptable toxicity. Obinutuzumab and chlorambucil: administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was 28 days. Progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) was per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria with incorporation of the clarification for treatment-related lymphocytosis (Cheson, 2012).[1]

Reference: 1. CALQUENCE (acalabrutinib tablets) Product Monograph. AstraZeneca Canada Inc. February 24, 2023.

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Canadian Hematology Today is published three times per year
in English and French. (ISSN 2816-5152) under the terms of the

VOL. 3
ISSUE 2
Summer 2024

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