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- Fetal/neonatal adverse reactions.
- It is unknown whether BREYANZI cells are excreted in human milk. Women who are breast-feeding should be advised of the potential risk to the breast-fed child.

For more information:
Please consult the BREYANZI Product Monograph for important information relating to adverse reactions, drug interactions, and dosing. The Product Monograph is also available by calling BMS Medical Information at **1-866-463-6267** or by email at medical.canada@bms.com.

Find out more about BREYANZI at Breyanzi.ca

CI: confidence interval; CR: complete response; HDCT: high-dose chemotherapy; HR: hazard ratio; NR: not reached; PR: partial response; SOC: standard of care.

* TRANSFORM was a phase, 3 open-label, randomized, parallel-group, multicentre trial in adult patients with large B-cell lymphoma primary refractory to or relapsed within 12 months from a complete response to initial chemoimmunotherapy, who were candidates for autologous hemopoietic stem cell transplant. 92 patients underwent leukapheresis and 89 patients received a single intravenous infusion of BREYANZI.[1]

† Per the Lugano criteria, as assessed by IRC, and based on primary evidence and analysis for the hypothesis testing purpose (cutoff date: 08 Mar 2021).

‡ Event-free survival was defined as the time from randomization to death from any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization (after 3 cycles of salvage chemotherapy and 5 weeks after BREYANZI infusion) or start of new antineoplastic therapy due to efficacy concerns, whichever occurs first.

§ Based on a stratified Cox proportional hazards model.

¶ *P*-value is compared with 0.012 of the allocated alpha.

** SOC consisted of salvage immunochemotherapy followed by HDCT and autologous HSCT.

†† *P*-value is compared with 0.021 of the allocated alpha.

‡‡ The long-term follow-up study was a single-arm, observational study enrolling patients who had received BREYANZI for relapsed or refractory large B-cell lymphoma in the TRANSFORM study. No further BREYANZI was administered during the follow-up study.[2]

References: 1. BREYANZI Product Monograph. Bristol-Myers Squibb Canada. **2.** Kamdar M, Solomon SR, Arnason JE, et al. Long-term survival with lisocabtagene maraleucel in second-line large B-cell lymphoma from TRANSFORM. *Blood Adv*. 2026.

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About the Authors

Colin Stewart, MD

Dr. Colin Stewart is a Hematologist at the Cross Cancer Institute in Edmonton, Canada. He earned his medical degree from the University of Alberta, followed by residency training in Internal Medicine and Hematology at the University of Calgary and a clinical fellowship in Hematology Oncology at the University of Alberta. Dr. Stewart specializes in the treatment of lymphoma and myeloma. His research interests include lymphoma, the re-appraisal of autologous stem cell transplantation, and health economics.

Affiliations: Cross Cancer Institute & University of Alberta, Edmonton, Canada

Robert Puckrin, MD

Dr. Robert Puckrin is a Hematologist and Clinician Investigator at the Arthur Child Comprehensive Cancer Centre, Alberta Blood and Marrow Transplant Program, and the University of Calgary in Calgary, Canada. Having obtained his medical degree from McGill University, he completed Internal Medicine training at the University of Toronto and subsequent training in Hematology and Hematopoietic Cell Transplantation and Cellular Therapy at the University of Calgary. His main clinical and research interests are in lymphoma, cellular therapy, clinical trials, and real-world data.

Affiliations: Arthur Child Comprehensive Cancer Centre & University of Calgary, Calgary, Canada.

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Current Management of Relapsed or Refractory Classic Hodgkin Lymphoma in Canada

Colin Stewart, MD
Robert Puckrin, MD

Introduction

Classic Hodgkin lymphoma (HL) is a rare B-cell malignancy with approximately 1,150 new cases diagnosed annually in Canada.[1] Outcomes have improved substantially over the past several decades, with HL-related mortality declining by 2.2–3.0% annually since 1984, reflecting advances in both first-line and salvage therapies.[1] Despite this progress, 10–30% of patients develop primary refractory or relapsed (R/R) disease, with risk influenced by stage, treatment regimen, and clinical features.[2-4] Relapse rates are further decreasing with contemporary first-line regimens such as nivolumab, doxorubicin, vinblastine, and dacarbazine (nivolumab-AVD) and brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone (BrECADD), and are now estimated at 5–10% in advanced-stage disease.[5,6] Key adverse prognostic factors at relapse include primary refractory disease, relapse within 12 months, and advanced-stage disease.[7-9]

The introduction of novel targeted therapies, including the anti-CD30 antibody-drug conjugate brentuximab vedotin (BV) and the programmed death-1 (PD-1) inhibitors nivolumab and pembrolizumab, has led to improved outcomes in R/R HL.[8] However, in Canada, access to targeted therapies has been constrained by delays in funding and restrictive approval criteria.[10,11] In this review, we address common challenges and outline our approach to the treatment of adults with R/R HL within the contemporary Canadian context.

Second-Line Treatment in Patients Eligible for ASCT

Role of ASCT

In medically fit patients, the management of R/R HL has traditionally consisted of second-line platinum-based chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT). This approach is supported by two landmark randomized trials demonstrating significant improvements in event-free survival, though not overall survival, with ASCT compared to standard chemotherapy.[12,13] Real-world data from the pre-novel agent era confirm durable remissions in approximately 50–60% of patients with R/R HL undergoing ASCT.[9,14,15] ASCT remains an effective curative modality for fit older patients, as well as for those with primary refractory disease and early or late relapses.[16-18]

Selection of Salvage Regimen

Choice of second-line regimen depends on patient fitness, institutional practice, and funding availability. Retrospective Canadian data support the use of gemcitabine, dexamethasone, and cisplatin (GDP), which has achieved overall response rates (ORR) of 62–71%, computed tomography (CT)-based complete response (CR) rates of 7-9%, transplantation rates of 88–96%, and 1.5-to-2-year progression-free survival (PFS) rates of 58–76%.[19,20] The more intensive dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) regimen, primarily used in Alberta, demonstrated an ORR of 86%, CT-based

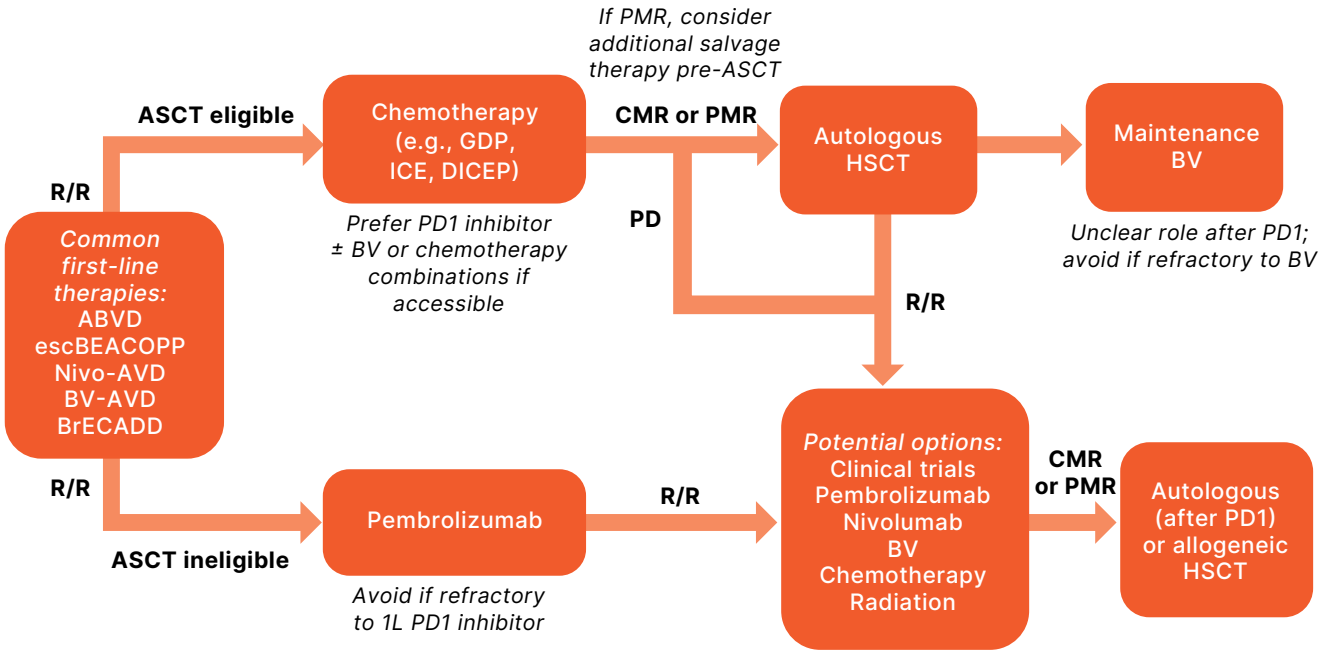

Figure 1. Treatment algorithm for refractory or relapsed Hodgkin lymphoma in Canada; *courtesy of Colin Stewart, MD and Robert Puckrin, MD.*

Abbreviations: ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine; **ASCT:** autologous stem cell transplantation; **BV:** brentuximab vedotin; **BV-AVD:** brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine; **BrECADD:** brentuximab, vedotin, etoposide, cyclophosphamide, doxorubicin, daracrbazine, and dexamethasone; **CMR:** complete metabolic response; **DICEP:** dose-intensive cyclophosphamide, etoposide, cisplatin; **escBEACOPP:** bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; **GDP:** gemcitabine, dexamethasone, and cisplatin; **HSCT:** hematopoietic stem cell transplantation; **HL:** Hodgkin lymphoma; **ICE:** ifosfamide, carboplatin, etoposide; **Nivo-AVD:** nivolumab plus doxorubicin, vinblastine, and dacarbazine; **PD:** progressive disease; **PD1:** programmed death-1; **PMR:** partial metabolic response; **R/R:** refractory or relapsed

CR rate of 18%, transplantation rate of 95%, and 5-year PFS of 61%.[15] Other established regimens include ifosfamide, carboplatin, etoposide (ICE), dexamethasone, cisplatin, cytarabine (DHAP), etoposide, high-dose cytarabine, cisplatinum (ESHAP), and gemcitabine, vinorelbine, doxorubicin (GVD).[21-23]

Pre-Transplant Response Assessment

Historically, patients with R/R HL could proceed to ASCT regardless of their response to salvage chemotherapy, and durable remissions were observed even among a subset with chemorefractory disease,[15,24] although accurate response assessment was limited by CT-based imaging. In the positron emission tomography (PET) era, achieving a complete metabolic response (CMR) prior to ASCT has emerged as a key prognostic factor, with PET-negative patients demonstrating 15–45% higher PFS compared to those with residual PET positivity.[8,25,26] Notably, several studies have reported comparable PFS among patients attaining pre-transplant PET negativity after one versus two lines of salvage therapy, suggesting a potential role for additional salvage treatment to convert a partial metabolic response (PMR) to a CMR before ASCT.[27,28] However, this approach has not been compared in prospective randomized trials against proceeding directly to ASCT in patients with PMR, and it remains unclear whether PET conversion itself causally improves outcomes or simply reflects more favourable disease biology. As such, it remains reasonable to proceed to

ASCT if an adequate PMR has been achieved particularly if alternative novel salvage regimens are unavailable, as over 50% of patients with a positive pre-transplant PET may still achieve durable remission.[8,26]

Impact of Targeted Therapies Before ASCT

The introduction of BV and PD-1 inhibitors has led to multiple single-arm phase II studies evaluating novel second-line regimens before ASCT. BV-based sequential or concurrent chemotherapy combinations (e.g., BV with bendamustine, gemcitabine, ICE, DHAP, or ESHAP) have demonstrated promising outcomes, with ORRs of 68–100%, CMR rates of 62–81% transplantation rates of 73–96%, and 2-to-3 year PFS rates of 63–82%.[28-32] Importantly, a randomized phase II trial demonstrated that the addition of BV to ESHAP increased CMR rates from 48% to 70%.[33]

PD-1-based strategies have shown particularly promising activity in the pre-ASCT setting, with retrospective data demonstrating superior 2-year PFS among patients undergoing ASCT after PD-1 inhibitor therapy (88%) compared to BV (70%) or chemotherapy (67%).[26] Phase II studies of PD-1 inhibitors ± BV or chemotherapy (e.g., GVD, ICE, gemcitabine and oxaliplatin [GemOx]) have reported ORRs of 85–100%, CMR rates of 67–97%, transplantation rates of 79–95%, and 2-to-3 year PFS rates of 72–96% among all patients and >90% among those undergoing ASCT.[34-39] Intriguingly, favourable 18-month PFS rates of 81% have been observed even among heavily pretreated, chemorefractory patients undergoing ASCT after third- or later-line PD-1 blockade, suggesting a paradoxical synergy between immune checkpoint inhibition and ASCT through deepened responses and/or resensitization to chemotherapy.[40]

Despite these encouraging data, second-line BV and PD-1 inhibitors are not currently funded in Canada for patients eligible for ASCT. Additionally, the future role of BV or PD-1-based salvage regimens is unclear given the increasing incorporation of these agents into the first-line setting.[5,6] Patients who are refractory to a targeted agent-containing regimen may be switched to an alternative novel agent and/or chemotherapy at relapse, whereas those with late relapse may be candidates for retreatment. Indeed, Canada's Drug Agency has endorsed retreatment with BV and PD-1 inhibitors for selected patients who relapse >6-12 months after treatment,[11,41] and small datasets support this approach in R/R HL.[42-44] The phase II CCTG HD11 trial, which randomized patients to BV plus pembrolizumab versus GDP prior to ASCT, has completed accrual and is expected to inform optimal salvage strategies in the Canadian context, including for patients with prior exposure to BV and PD-1 inhibitors.

Can ASCT be Omitted?

The efficacy of PD-1-based regimens has prompted interest in the potential for omitting ASCT in the era of novel agents. In a provocative phase II study, 24 patients who achieved CMR with pembrolizumab plus GVD received pembrolizumab maintenance without ASCT, resulting in a 2-year PFS of 60%. Outcomes were inferior in patients with stage IV disease, with a 2-year PFS of 37% versus 72% in those with stage I-III disease, although most patients who relapsed were successfully rescued with ASCT.[45] Another prospective trial reported a 2-year PFS rate of 79% among 73 patients with CMR after ESHAP ± BV who received maintenance BV instead of ASCT.[33] In addition, several pediatric studies also reported favourable outcomes with consolidative radiotherapy in lieu of ASCT in selected patients with low-risk relapse.[46-48] Although promising, these findings are preliminary in nature and insufficient to alter standard practice, particularly given the established curative potential of ASCT and its manageable safety profile in a generally fit population. However, ongoing randomized studies are evaluating whether ASCT can be safely omitted or deferred in selected patients.

Maintenance Therapy After ASCT

Post-transplant maintenance with 16 cycles (48 weeks) of BV is funded in Canada based on the AETHERA trial, which demonstrated a significant improvement in 5-year PFS (59% vs 41%) among high-risk patients who received ASCT for R/R HL, including those with primary refractory disease, early relapse within 12 months, or extranodal involvement.[7,49] However, BV maintenance has not been shown to improve overall survival, may represent overtreatment for some patients already cured by ASCT, and is associated with risks of neuropathy (67%), neutropenia (35%), gastrointestinal toxicity (>20%), and premature treatment discontinuation due to intolerance (33%). Its use should therefore be individualized, with the greatest benefit observed in patients with a positive pre-transplant PET or ≥2 enrolment risk factors.

Real-world data suggest the PFS benefit of maintenance BV is maintained despite dose reductions or early discontinuation.[50] Importantly, the AETHERA trial was conducted before the routine incorporation of targeted agents into first and second-line therapy. While there is conflicting retrospective data regarding the utility of maintenance BV among patients previously exposed to targeted agents,[51,52] there is no evidence to support its use among those refractory to BV. Maintenance BV does not appear to be necessary for those undergoing ASCT after PD-1-containing regimens, given the high cure rates with this strategy.[52]

Patients Ineligible for ASCT

Transplant ineligibility may result from advanced age, comorbidities, poor performance status, chemorefractory disease, or inadequate stem cell mobilization. Prior to the availability of BV and PD-1 inhibitors, outcomes for this population with conventional chemotherapy were poor.[53] In the randomized KEYNOTE-204 trial, which enrolled 304 adults with R/R HL who were either ineligible for (63%), or who had relapsed after (37%) ASCT, pembrolizumab was associated with a higher ORR (66% vs 54%) and a significantly improved PFS compared with BV (median 13 vs 8 months).[54] Pembrolizumab now represents the preferred funded second-line option for transplant-ineligible patients without prior PD-1 inhibitor resistance. BV is generally reserved for patients who are intolerant of or refractory to PD-1 inhibitors; however, in most Canadian provinces, its funding is restricted to the post-ASCT setting.

Of note, response assessment during PD-1 therapy may be challenging due to false-positive PET findings and pseudoprogression related to immune cell infiltration.[55] In cases of equivocal response, treatment continuation with repeat imaging and/or biopsy is appropriate to clarify disease status.[55] Data also support continuation of PD-1 blockade beyond progression in selected patients with asymptomatic, indolent relapse to maximize the clinical benefit of this therapy.[56,57]

Multiply Relapsed Disease

Post-ASCT Relapse

Outcomes for patients relapsing after ASCT have improved in the current era of PD-1 inhibitors and BV, with 4-year overall survival rising from 43% to 71%.[8] Both agents are broadly funded in Canada for patients relapsing after ASCT, and the superiority of PD-1 inhibitors over BV was confirmed in post-ASCT relapses in the KEYNOTE-204 trial.[54] While the median PFS with these agents is in the range of 9–15 months, long-term follow-up demonstrates 5-year PFS rates of 14–22%, suggesting a curative potential in a subset of patients.[58-60] Among patients who relapse while off treatment, rechallenge with PD-1 inhibitors or BV is associated with an ORR of >50–60% and a median PFS of 6–13 months.[44]

Double-Refractory Disease

Ultimately, a subset of patients develop resistance to both BV and PD-1 inhibitors ("double-refractory disease"), representing an area of high unmet need with limited evidence to guide therapy. Radiotherapy can be an effective option for localized relapses, although most patients will eventually relapse outside the irradiated field.[61] Emerging data suggest that epigenetic therapies may restore sensitivity to PD-1 inhibitors.[62] Other palliative-intent strategies include chemotherapy (e.g., bendamustine, vinblastine, gemcitabine) or everolimus, though responses are typically partial and short-lived.[63-65] Whenever possible, enrolment in clinical trials should be sought, as there are encouraging results from early-phase studies of CD30-directed CAR T-cell therapy, allogeneic natural killer cells, bispecific antibodies, and novel antibody-drug conjugates and immune checkpoint inhibitors.[66-69]

Contemporary Outcomes of Allogeneic HSCT

Allogeneic hematopoietic stem cell transplantation (HSCT) remains an underappreciated but important curative option for patients with multiply relapsed disease who have exhausted other options. Several contemporary studies have reported remarkably high PFS rates of 69–84% following allogeneic HSCT after PD-1 therapy in heavily pretreated patients, suggesting a PD-1-mediated enhancement of the graft-versus-lymphoma effect.[70,71] The safety profile of allogeneic HSCT has improved with the adoption of reduced-intensity conditioning and post-transplant cyclophosphamide.[70,72,73] However, because pre-transplant exposure to PD-1 therapy has been associated with increased risks of acute graft-versus-host disease, a washout period of 4–12 weeks is recommended prior to transplantation owing to the long half-lives of these agents.[72,74]

Given the prognostic importance of achieving adequate disease control prior to allogeneic HSCT,[70,72] the timing of transplantation should be individualized, taking into account the disease course, patient preferences, and anticipated availability of bridging therapies. Referral for allogeneic HSCT is recommended by the time of initiation of a second targeted therapy in multiply relapsed patients. Patients with high-risk features, such as refractory disease or short remission durations, may benefit from consolidation with allogeneic HSCT while responding to a second targeted agent, whereas others may defer transplantation until progression on both agents, followed by re-induction with chemotherapy prior to transplant. Donor lymphocyte infusion may be considered in the setting of post-transplant relapse, with reported ORR of 56–79%.[75,76]

Conclusions

Outcomes in R/R HL have become increasingly favourable due to the integration of targeted therapies across multiple lines of treatment. However, this progress has introduced new uncertainties, including the impact of novel first-line regimens on salvage strategies, the evolving role of ASCT, and the optimal management of patients with double-refractory disease.

In Canada, the most immediate challenge remains access. Despite robust evidence, targeted therapies are inconsistently funded, particularly in the pre-transplant and transplant-ineligible settings, creating a gap between evidence and practice. Addressing these disparities will be essential to ensure that advances in therapy translate into meaningful improvements in patient outcomes.

Correspondence

Robert Puckrin, MD
Email: Robert.Puckrin@albertahealthservices.ca

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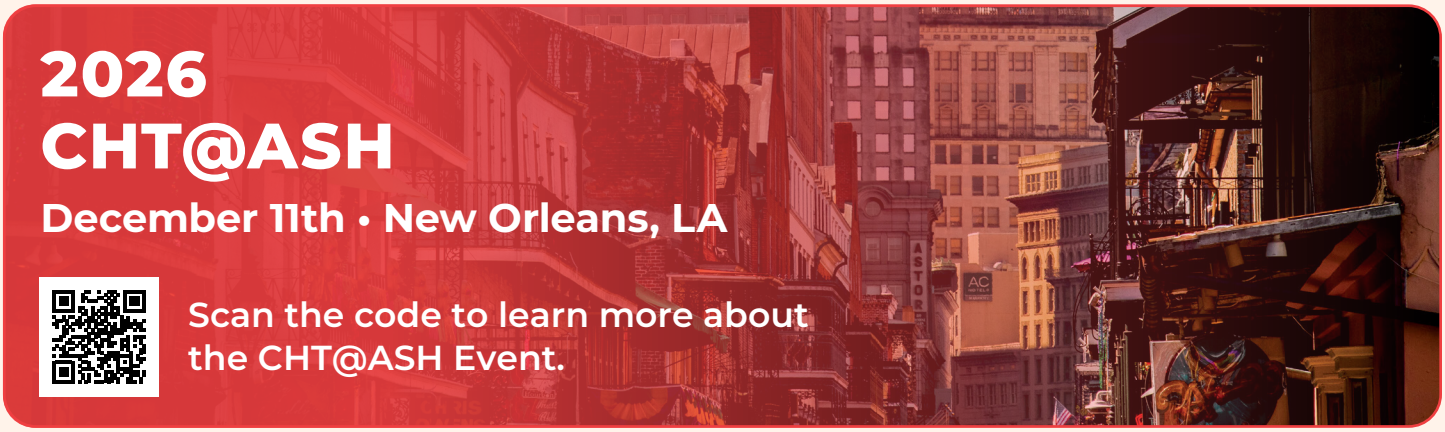

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About the Authors

Cristiano Machado de Freitas, MD

Dr. Cristiano Freitas is a Brazilian-trained hematologist and current Leukemia & MPN Clinical Fellow at Princess Margaret Cancer Centre / University Health Network and the University of Toronto. His clinical focus is malignant hematology, with expertise in acute leukemias, myelodysplastic syndrome, myeloproliferative neoplasms, and bone marrow failure syndromes. He is actively involved in clinical research such as real-world studies on azacitidine/venetoclax outcomes. His academic interests include translational research in AML and myelofibrosis, medical education, and improving outcomes for patients with hematologic malignancies.

Affiliations: Princess Margaret Cancer Centre, Toronto, Canada

Guillaume Richard-Carpentier, MD

Dr. Guillaume Richard-Carpentier is a Staff Hematologist in the Leukemia Program at the Princess Margaret Cancer Centre in Toronto, Ontario. His clinical focus is the care of patients with acute leukemia, myelodysplastic syndromes (MDS) and bone marrow failure syndromes. Dr Richard-Carpentier is interested in the development of biomarkers in acute myeloid leukemia (AML) and in clinical trials evaluating novel targeted and combination therapies for patients with high-risk MDS or AML. He is actively involved in leading and conducting early-phase clinical trials for clinical drug development in MDS and AML.

Affiliations: Princess Margaret Cancer Centre, Toronto, Canada

Approach to Patients with Acute Myeloid Leukemia in First Relapse: A Practical Guide for Canadian Hematologists

Cristiano Machado de Freitas, MD
Guillaume Richard-Carpentier, MD

Introduction

Acute myeloid leukemia (AML) is an aggressive and heterogeneous type of blood cancer associated with significant morbidity and mortality. Despite major improvements in the treatment of AML over the last decade, many patients unfortunately present with relapsed or refractory (R/R) disease after first-line standard treatment.[1]

With traditional high-intensity induction chemotherapy (IC) for AML, such as

the 7+3 regimen, complete remission (CR) rates are about 75–80%, and in those who achieve remission, the relapse rate is approximately 40–50%.[2] With less intensive regimens, such as azacitidine plus venetoclax (Aza-Ven), composite CR rates are about 65–70%, and in those who respond, about half will relapse within 2 years.[3] Relapses mainly result from the survival of leukemia stem cells (LSCs), which may acquire additional mutations under the selective pressure of therapy and expand to drive disease recurrence.[4] The majority of patients with R/R AML present with adverse-risk genetic features, which are associated with a lower median overall survival (OS) of less than 6 months. With second-line therapy for R/R AML, the overall response rates (ORRs) ranged between 20%–45%,[5] underscoring the unmet need regarding the best therapeutic approach for these patients.

This review aims to help the reader quickly identify the most common current standard salvage chemotherapy regimens and targeted agents used in the first relapse setting of AML and discuss the ongoing challenges in treating this patient population.

Genetic Landscape Upon Relapse

As shown by Nuno *et al*., relapse in AML is often not driven by new genetic mutations but by epigenetic evolution, in which leukemia cells alter gene regulation and chromatin states to become more resistant to therapy, with different clones converging toward similar resistant phenotypes.[6] It unfortunately still remains poorly understood how these epigenetic changes drive chemo-resistance and how this could be overcome to achieve remission.[7] Despite the relative stability of genetic features in R/R AML, certain gene mutations (*FLT3*, *IDH1/2, NPM1*) and cytogenetic abnormalities (*KMT2A* rearrangement) warrant retesting at relapse, since targeted agents may be used in patients harbouring these genetic abnormalities. For example, approximately 10% of patients with AML will present with changes in their *FLT3* mutational status at the time of R/R disease and should therefore be retested so that *FLT3* inhibitors, such as gilteritinib, may be considered for treatment.

General Approach and Goals of Care

Selecting optimal salvage therapy in relapsed AML requires a balanced, patient-centred approach. Disease biology should be reassessed, as repeat genetic profiling at relapse may identify new actionable targets. Patient-related factors—including performance status, comorbidities (especially active infections), and goals of care—must also be carefully considered. Finally, transplant eligibility is critical, as allogeneic hematopoietic stem cell transplant (HSCT) remains key to achieving durable remission and potential cure after relapse.

Because R/R AML remains a clinically unmet need, clinical trials evaluating novel drugs or combination therapy should always be considered if available, especially in biologically high-risk disease (e.g., *TP53*-mutated) or after venetoclax failure, where conventional approaches have limited efficacy.[8]

Many patients with R/R AML are not fit for curative treatment. Even low-intensity therapies can cause significant toxicity and impair quality of life. In these cases, a palliative approach with cytoreduction (e.g., hydroxyurea or low-dose cytarabine) and transfusion support may best optimize quality of life and time at home.

Available Salvage Regimens for R/R AML

FLAG-IDA

FLAG-IDA (fludarabine, cytarabine, granulocyte colony-stimulating factor [G-CSF], and idarubicin) is a commonly used regimen for patients with R/R AML deemed fit for IC (**Table 1**). It was evaluated by Pastore *et al*. in 46 patients with R/R AML. This study demonstrated a CR rate of 52%, with similar efficacy in both relapsed and refractory settings.[9] Median OS was 11 months, and disease-free survival was 12 months, with better outcomes observed in patients who had a lower blast burden and favourable cytogenetics. Treatment was associated with acceptable toxicity, including a low induction mortality of 6.6%, although infectious complications and mucositis were common. Importantly, a substantial proportion (46%) of responders was able to proceed to stem cell transplantation, supporting FLAG-IDA as an effective salvage regimen and a bridge to transplant in R/R AML.

FLAG-IDA plus Venetoclax

DiNardo et al., conducted a phase IIB study of 61 patients with R/R AML treated with FLAG-IDA plus venetoclax, demonstrating high efficacy (**Table 1**).[10] In the R/R cohort, the regimen achieved a composite CR rate of 64%, with minimal residual

disease (MRD)-negativity in 74% of responders. Survival outcomes were favourable, with a 3-year OS of 32%, particularly among patients in first salvage with *TP53* wild-type disease (3-year OS of 51%). Notably, 57% of R/R patients proceeded to HSCT, supporting its role as an effective salvage bridge-to-transplant strategy with an acceptable safety profile. Molecular subgroups known to be sensitive to venetoclax-based therapy, including *NPM1, IDH1*, and *IDH2*, demonstrated excellent outcomes, with a composite CR rate of 100% and a 12-month OS of 83% in the R/R AML setting. In contrast, mutations in tumour suppressor genes, such as *TP53, WT1, FBXW7*, and *PHF6*, which are more common in non-responders and associated with treatment resistance, were linked to significantly lower composite CR rates (38% vs. 77%; P=0.021), demonstrating the ongoing challenge of treating these subgroups of patients.

Based on this phase II trial,[10] and retrospective studies,[11] adding venetoclax to FLAG-IDA for R/R AML appears to be associated with higher rates of deep remission than IC alone. However, no randomized trial has yet addressed this question, and the availability of venetoclax in this setting can be a challenge. Addition of venetoclax could be considered particularly in patients with *NPM1*- or *IDH1/2*-mutated disease or *TP53* wild-type status, and in the first salvage setting in patients aiming for a curative intent who are likely eligible for HSCT. Previous exposure to venetoclax and the availability of more appropriate biology-directed treatment options should also be considered.

MEC

The MEC regimen (mitoxantrone, etoposide, and cytarabine) is also commonly used for R/R AML (**Table 1**). The phase II study by Amadori et al. evaluated MEC in 32 patients with high-risk R/R AML, including primary refractory disease, early relapse, and post-transplant relapse.[12] The regimen produced a high CR rate of 66%, with better responses in younger patients and those in early relapse, while patients with primary refractory disease had lower response rates. Despite this activity, remissions were short (median 16 weeks), and OS was limited (median 36 weeks). Treatment was associated with universal severe myelosuppression and a high rate of infectious complications (91%), but early mortality was relatively low at 6%, and non-hematologic toxicity was generally manageable. Overall, MEC demonstrated significant anti-leukemic activity with acceptable toxicity in a poor-risk population, supporting its role as a salvage regimen, although without evidence of durable long-term benefit.

Among IC regimens, there is no universally superior regimen for patients with R/R AML. MEC and FLAG-IDA appear broadly comparable based on retrospective data,[13] but this has not yet been confirmed in a head-to-head randomized trial. Although larger studies have been performed with FLAG-IDA plus venetoclax, MEC has also been reported as a backbone to add venetoclax in the R/R setting.

Hypomethylating Agents (HMAs) Plus Venetoclax

HMAs, such as azacitidine, in combination with venetoclax, have become the standard of care for patients with newly diagnosed AML who are ineligible for IC, based on the VIALE-A trial (**Table 1**).[3] In R/R settings, HMAs (azacitidine or decitabine) plus venetoclax are also increasingly used, with several retrospective studies describing the use of this combination. As shown by Aldoss *et al.*,[14] in a retrospective cohort of 90 patients with R/R AML treated with venetoclax plus HMA, the composite CR rate was 46%, with many responses occurring early and frequently achieving MRD-negativity. Patients who achieved CR/complete remission with incomplete count recovery (CRi) had significantly improved OS compared to non-responders (median OS 16.6 vs. 5.1 months), while the median OS for the overall cohort was 7.8 months, highlighting the clinical benefit of response to venetoclax-based therapy in this high-risk population.

Additionally, as shown by Unglaub and colleagues, venetoclax plus azacitidine is an effective and less toxic salvage strategy in relapsed AML, achieving higher response rates than standard IC and enabling successful bridging to HSCT in approximately 70% of patients.[15] However, no prospective clinical trials have yet confirmed the added benefit of venetoclax in this challenging-to-treat population.

Beyond fitness, the choice between IC and HMA plus venetoclax in R/R AML may be guided by disease biology, aggressiveness of the relapse, prior exposure to venetoclax, and transplant intent. When rapid cytoreduction is required in a fit patient in first salvage with a clear plan to proceed to HSCT, IC with or without venetoclax is likely a preferred approach. Conversely, Aza–Ven may

Chemotherapy Regimen	Dosage and Schedule	ORR (*%, n*)	mOS rate (*months*)	Reference
FLAG-IDA	• Fludarabine 30 mg/m^2 IV over 30 min, D 1–5 • Cytarabine, 2000 mg/m^2 IV over 4 h, D 1–5[A] • Idarubicin 10 mg/m^2 IV, D 1–3 • G-CSF (Filgrastim) 5 mcg/kg SC D 6-until ANC recovery	52 (24/46)	11 (1–25)	[12]
FLAG-IDA plus Venetoclax	• Fludarabine 30 mg/m^2 IV , D 2–6 • Cytarabine,1500 mg/m^2 IV, D 2–6 • Idarubicin, 6 mg/m^2 IV, D4–5[B] • G-CSF (Filgrastim) 5 mcg/kg SC, D1–7 • Venetoclax 400 mg PO daily, D 1–7[C]	67 (41/61)	12 (9–34)	[13]
MEC	• Mitoxantrone 6 mg/m^2 IV, D 1–6[D] • Etoposide 80 mg/m^2 IV, D 1–6 • Intermediate-dose Cytarabine 1000 mg/m^2 IV D 1–6	66 (21/32)[E]	4 (0.5–29.5)[F]	[14]
Azacitidine plus Venetoclax	• Azacitidine,75mg/m^2 SC daily for 7 days • Venetoclax PO 100mg D1, 200mg D2, 400mg D3–28[F]	46 (41/90)	7.8 (5.9–15.5)	[3,15]
Gilteritinib	• Gilteritinib 120 mg PO, D 1–28[G]	68, (167/247)	9.3 (7.7–10.7)	[17]
Ivosidenib	• Ivosidenib 500 mg PO, D 1–28	42, (52/125)	8.8 (6.7–10.2)	[18]

Table 1. Salvage Therapies for Relapsed/Refractory AML; *courtesy of Cristiano Machado de Freitas, MD and Guillaume Richard-Carpentier, MD.*

Abbreviations: Ara-C: Cytarabine; **D:** days; **G-CSF:** granulocyte colony-stimulating factor; **h:** hours; **IV:** intravenous; **mOS:** median overall survival; **ORR:** overall response rate; **PO:** *per os* (by mouth); **SC:** subcutaneous.

[A]Four hours after fludarabine infusion
[B]The idarubicin dose and duration differ for the newly diagnosed (8 mg/m^2 D4–6) and R/R (6 mg/m^2 D4–5) cohorts
[C]Venetoclax is given for 7 days each cycle and requires dose adjustment with concurrent administration of CYP3A4 inhibitors
[D]The 6-hour infusion of Ara-C is preceded by a short infusion (1 hour) of etoposide and followed, 3 hours later, by a bolus of mitoxantrone. Dosing for MEC may also be as follows: mitoxantrone 8 mg/m^2 IV x 5 days, etoposide 100 mg/m^2 x 5 days and cytarabine 1000 mg/m^2 x 5 days
[E]CR rate, not ORR
[F]Venetoclax requires dose adjustment with concurrent administration of CYP3A4 inhibitors
[G]Gilteritinib dose can be escalated up to 200 mg daily if no response after the first cycle

be preferred when a less toxic salvage strategy is desired, particularly in patients with more indolent disease kinetics, venetoclax-sensitive biology (e.g., *IDH1/2*-mutated AML), or when transplant eligibility is uncertain. Importantly, *TP53*-mutated and adverse-risk AML remain poor-risk entities regardless of the chosen strategy; in these cases, enrollment in clinical trials should be prioritized whenever feasible.[9,10,14,15]

Targeted Therapies

FLT3-mutated AML

In the phase III ADMIRAL trial, adults with R/R *FLT3*-mutated AML were randomized to receive gilteritinib or salvage chemotherapy (including regimens such as MEC and FLAG-IDA). Gilteritinib significantly improved OS (median 9.3 vs. 5.6 months; HR, 0.64; 95% confidence interval [CI], 0.49–0.83; P < 0.001) and achieved higher

remission rates (CR/complete remission with partial hematologic recovery [CRh] 34% vs. 15%) than chemotherapy, with a consistent benefit across subgroups. Importantly, more patients proceeded to HSCT in the gilteritinib arm, yet the survival advantage persisted even with censoring at the time of HSCT. Overall, toxicity was more favourable with gilteritinib, with lower rates of severe adverse events than with chemotherapy. These results established gilteritinib as a standard of care in R/R *FLT3*-mutated AML.[16]

Early-phase data support the combination of gilteritinib with venetoclax, with or without azacitidine, showing high response rates (around 70%–75%) and deep molecular responses. However, these data remain limited and investigational, and *FLT3* inhibitor-based combination therapies are not widely available in Canada outside clinical trials.[17,18]

IDH1- and *IDH2*-mutated AML

Although ivosidenib is available in Canada for the treatment of newly diagnosed *IDH1*-mutated AML in combination with azacitidine, ivosidenib and olutasidenib (*IDH1* inhibitors) and enasidenib (*IDH2* inhibitor) are not approved and available for the treatment of R/R AML.

In the phase I study of ivosidenib in *IDH1*-mutated R/R AML, clinically meaningful responses were observed in a heavily pre-treated population. Among patients with R/R disease, the combined CR and CRh rate was 30%, while the CR rate alone was 22%. The ORR was 39%, reflecting additional responses, such as CRi and morphologic leukemia-free state. The 18-month survival rate was 50% among patients with CR or CRh (median not reached at the data cut-off date).[19] Therefore, ivosidenib could be considered for patients with *IDH1*-mutated R/R AML, although access in Canada remains limited.

Outcomes with enasidenib are similar in *IDH2*-mutated R/R AML. However, it has been withdrawn from the Canadian market following negative results from the study by de Botton *et al.*, which failed to meet its primary endpoint.[20]

KMT2A Rearrangement (KMT2Ar) and *NPM1*-mutated AML

Menin inhibitors are a new class of targeted agents with activity in AML with *NPM1* mutations or *KMT2A* gene rearrangements located at 11q23. The first menin inhibitor, revumenib, was investigated in the AUGMENT-101 study, a phase I/II, open-label, multicentre clinical trial that led to its US Food and Drug Administration (FDA) approval.[21] The study included patients with *KMT2Ar* R/R acute leukemia and *NPM1*-mutated AML. Results from the phase II, registration-enabling portion in patients with *KMT2Ar* showed a CR/CRh rate of 23% and an ORR of 63%, allowing a quarter of patients in this study to proceed to HSCT.

Bleximenib is another potent and selective menin inhibitor currently under study as monotherapy or in combination regimens. In the phase I dose-finding study, bleximenib at the recommended phase II dose (RP2D) of 100 mg BID (twice/day) was associated with a composite CR (CR/CRh/CRi) rate of 40% and an ORR of 50%.[22] Menin inhibitors are currently only available in Canada through clinical trials, but will hopefully be approved and funded in the future.

HSCT and Donor Lymphocyte Infusion (DLI)

HSCT is considered the only potentially curative therapy for R/R AML. Most commonly, complete morphological remission with less than 5% bone marrow blasts is required before proceeding with HSCT to optimize post-transplant outcomes. Data show that the deeper the remission status is, the better the OS will be post-transplant.[23] However, this concept has been challenged by the ASAP trial, a multicentre, open-label, randomized controlled trial evaluating the non-inferiority of IC followed by immediate HSCT using reduced-intensity conditioning (RIC) compared with salvage chemotherapy intended to induce CR followed by HSCT. The trial showed no clear benefit of salvage chemotherapy and confirmation of CR before HSCT, while demonstrating higher rates of toxicity-related complications and longer hospitalization associated with salvage regimens. The 3-year OS was 59% (95% CI, 48–69) for patients undergoing IC with immediate RIC-based HSCT and 64% (95% CI, 49-76) for patients receiving salvage chemotherapy to achieve CR before proceeding to HSCT.[24]

DLI may also provide benefit as part of a salvage strategy in patients who relapse after HSCT. Reported OS rates at 1, 2, and 5 years were 67%, 34%, and 34%, respectively, among those receiving pre-emptive DLI, compared with 43%, 20%, and 20% in patients treated at overt relapse, as shown by Accorsi Buttini *et al*.[25]

Conclusion

AML is a heterogeneous disease, and responses to treatment vary based on disease features, with some patient subsets presenting with high rates of relapse. It is important to thoroughly characterize the genetic landscape at relapse, as this allows appropriate selection of salvage therapy, including targeted agents. Whenever possible, patients should be enrolled in clinical trials and referred for HSCT at the earliest opportunity. Lastly, it is of utmost importance to consider the patients' goals of care and to ensure early referral to the palliative care team to provide a holistic approach to this complex disease.

Correspondence

Guillaume Richard-Carpentier, MD
Email: Guillaume.Richard-Carpentier@uhn.ca

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Data from the CEPHEUS study

A phase 3, open-label, multicentre, randomized, active-controlled study in patients with NDMM for whom ASCT was not planned as initial therapy or who were not eligible for ASCT: D-VRd (n=197) vs. VRd (n=198)

Primary endpoint: At a median follow-up of **22.3 months**, D-VRd demonstrated a statistically significant improvement in overall MRD-negativity rate* vs. VRd at the primary MRD analysis (53.3% [105/197] vs. 35.4% [70/198]; RR 1.51; 95% CI: 1.20, 1.90;† p=0.0004)

At a median follow-up of **58.7 months**, overall MRD-negativity rates were 60.9% (95% CI: 53.7, 67.8) and 39.4% (95% CI: 32.5, 46.6), respectively (RR 1.55; 95% CI: 1.26, 1.90†)

Secondary endpoint: At a median follow-up of **58.7 months**, **sustained MRD-negativity rates‡§ were 48.7% with D-VRd** (n=96/197; 95% CI: 41.6, 55.9) and 26.3% with VRd (n=52/198; 95% CI: 20.3, 33.0; RR 1.86; 95% CI: 1.41, 2.44†)

Scan here to learn more about the CEPHEUS trial

* Patients achieved both MRD negativity (threshold of at or below 10^{-5}) and CR or better.
† RR is D-VRd vs. VRd.
‡ Based on intention-to-treat population.
§ Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.

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SC=subcutaneous; NDMM=newly diagnosed multiple myeloma; ASCT=autologous stem cell transplant; D-VRd=DARZALEX® SC (daratumumab) + Velcade® (bortezomib) + Revlimid® (lenalidomide) + dexamethasone; VRd=Velcade® (bortezomib) + Revlimid® (lenalidomide) + dexamethasone; MRD=minimal residual disease; RR=risk ratio; CI=confidence interval; CR=complete response; NYHA=New York Heart Association; CBC=complete blood count; IgG=immunoglobulin G.

CEPHEUS Study parameters: A phase 3, open-label, multicentre, randomized, active-controlled study in patients with NDMM for whom ASCT was not planned as initial therapy or who were not eligible for ASCT. Patients were randomized 1:1 to receive D-VRd or VRd. All patients received eight 21-day cycles of VRd, consisting of SC bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11), oral lenalidomide (25 mg on Days 1–14), and oral or intravenous dexamethasone (20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 [Days 1, 4, 8, and 11 if aged >75 years or body mass index <18.5 kg/m^2], after which point bortezomib was discontinued per protocol and patients continued to receive 28-day cycles of Rd, consisting of oral lenalidomide (25 mg on Days 1–21) and oral dexamethasone (40 mg on Days 1, 8, 15, and 22 [20 mg weekly if aged >75 years or body mass index <18.5 kg/m^2]) until progression or unacceptable toxicity. Patients in the D-VRd group also received SC daratumumab (1800 mg co-formulated with recombinant human hyaluronidase PH20 (2000 U/mL) weekly in cycles 1–2, every 3 weeks in cycles 3–8), and every 4 weeks thereafter until progression or unacceptable toxicity.[1,2]

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About the Authors

Rina Latscha, MD

Dr. Rina Latscha is a Clinical Research Fellow in the Lymphoma, Myeloma and Transplant Program at the Princess Margaret Cancer Centre in Toronto. She completed medical school in Hamburg, Germany, and is board-certified in Internal Medicine and Hematology, with specialist training in Switzerland. Her work focuses on patient-centered clinical research, as well as medical education and curriculum development across the healthcare continuum, including nurses, trainees, residents, fellows, patients, and caregivers.

Affiliations: Department of Medical Oncology Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Sita Bhella, MD

Dr. Sita Bhella is a staff hematologist at Princess Margaret Cancer Centre. She specializes in malignant hematology, with a primary clinical focus on lymphoma, myeloma, autologous stem cell transplantation and cellular t therapies. She is an Assistant Professor within the Department of Medicine at the University of Toronto and is the Autologous Stem Cell Transplant Medical Director at Princess Margaret Cancer Centre.

Affiliations: Department of Medical Oncology Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

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Upfront Therapy for Non-transplantable Multiple Myeloma in 2026: Decision-making in an Increasingly Complex Therapeutic Landscape

Rina Latscha, MD
Sita Bhella, MD

Introduction

Multiple myeloma (MM) is an age-related disease with a median age at diagnosis of approximately 70 years.[1] While quadruplet regimens, such as daratumumab, bortezomib, lenalidomide, and dexamethasone (Dara-VRd), followed by autologous hematopoietic stem cell transplantation (HSCT), as demonstrated in the Perseus trial, have recently become a standard for transplant-eligible patients, optimal first-line therapy remains challenging in older, frail individuals with comorbidities and reduced functional reserve. This challenge is driven less by biological differences in the disease and more by heterogeneity in treatment tolerance, comorbidity burden, and real-world care conditions.[1-3]

Historically, non-transplant-eligible patients were treated with doublets, such as melphalan/prednisone or lenalidomide/dexamethasone (Rd). With the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs), triplet regimens, including VRd and later DRd (daratumumab, lenalidomide, dexamethasone), became the new standard of therapy.[1,2]

A major advance was the incorporation of monoclonal CD38 antibodies. Network meta-analyses have shown that anti-CD38 monoclonal antibody-based combinations significantly improve progression-free survival (PFS) and response rates compared with regimens lacking anti-CD38 therapy.[4] However, increasing efficacy has also led to greater treatment complexity and toxicity, which is particularly relevant for older and frail patients.

For this population, first-line therapy must balance effective disease control with minimizing treatment-related morbidity and preserving quality of life. In addition, regional differences in access to modern therapies—especially to anti-CD38 monoclonal antibodies and quadruplet combinations—further widen the gap between evidence-based recommendations and real-world practice.[3]

This review provides practical guidance on selecting first-line therapy for patients with MM who are not eligible for transplantation, focusing on efficacy, toxicity profiles, and key clinical decision factors.

What Role Does Frailty Play in Choosing First-line Therapy?

Although age was once the main determinant of treatment decisions, this paradigm has shifted substantially. A landmark International Myeloma Working Group (IMWG) analysis identified frailty as an independent predictor of mortality, treatment discontinuation, and severe adverse events. The three-year overall survival (OS) was 84% in fit patients but declined to 57% in frail individuals.[5]

A systematic review further confirmed that geriatric impairments—particularly in mobility, cognition, polypharmacy, and activities of daily living—are associated with higher mortality, increased toxicity, and reduced treatment feasibility.[6]

While the IMWG frailty score is the most extensively validated tool, its complexity limits routine use. Simplified models incorporating age, Eastern Cooperative Oncology Group (ECOG) performance status, and comorbidities show comparable prognostic value and greater clinical practicality.[5,7-9]

Frailty is also increasingly viewed as a dynamic concept. Integrating geriatric

assessment with hematopoietic parameters improves prediction of treatment-related toxicities and underscores the need for repeated frailty evaluation throughout therapy, not only at baseline.[10] This is particularly relevant with modern continuous treatment strategies, as functional status may improve or deteriorate over time (**Table 1**).

Which Patients Benefit from Quadruplet Regimens?

The introduction of quadruplet regimens represents a major advance in MM therapy, enabling deeper remissions and more durable disease control than established triplets (**Table 2**). This is particularly relevant for transplant-ineligible patients, as a substantial proportion will not receive second- or third-line therapy during their disease course.[11] Consequently, the effectiveness of first-line treatment has a disproportionate impact on long-term prognosis.

The phase III CEPHEUS trial compared Dara-VRd with VRd in patients unsuitable for or deferring transplantation, demonstrating a significant 43% reduction in the risk of progression or death (hazard ratio [HR]: 0.57). The remission depth was markedly improved, with minimal residual disease (MRD)-negativity rates of 60.9% versus 39.4% in favour of the quadruplet. These findings support Dara-VRd as a potential new standard for functionally fit patients without immediate transplant intent. However, higher rates of hematologic toxicity were observed, particularly grade 3/4 neutropenia (44.2% vs. 29.7%), and pneumonia was the most frequent serious adverse event (13.7% vs. 12.8%). Importantly, discontinuation due to toxicity remained lower with Dara-VRd than with VRd alone (7.6% vs. 15.9%), indicating overall feasibility in selected patients.[12]

Similar results were reported in the IMROZ study, which evaluated Isa-VRd (isatuximab, bortezomib, lenalidomide, dexamethasone) versus VRd in transplant-ineligible patients. After nearly five years of follow-up, the estimated 60-month PFS rate was 63.2%, compared with 45.2%, respectively, corresponding to a 40% risk reduction (HR: 0.60). Higher complete response and MRD-negativity rates were also achieved. As with other quadruplet therapies, this benefit came at the cost of increased toxicity, including higher rates of severe infections (grade ≥3: 44.9% vs. 38.1%) and grade 3/4 neutropenia (54.4% vs. 37.0%). Notably, infection rates were lower in patients receiving antibiotic prophylaxis, underscoring the importance of supportive measures.[13]

Peripheral neuropathy remains a key limitation of bortezomib-based quadruplets. In the French BENEFIT study comparing Isa-VRd with Isa-Rd, neuropathy occurred in 52% of Isa-VRd-treated patients, with 27% having grade ≥2 neuropathy. Ten percent discontinued bortezomib due to neurologic toxicity, highlighting the need for caution in patients with pre-existing neuropathy or diabetic comorbidities.[14]

Renal dysfunction represents another important clinical scenario, as lenalidomide-based regimens often require dose reduction or delay. In this context, bortezomib/cyclophosphamide-based quadruplets provide an alternative. The Dara-VCD (Dara-CyBorD; daratumumab, cyclophosphamide, bortezomib, dexamethasone) study demonstrated that weekly bortezomib was tolerable in elderly and frail patients, with peripheral neuropathy rates of only 28% and no grade 3/4 events. Infections, particularly upper respiratory tract infections and pneumonia, were more frequent with daratumumab, emphasizing the need for close monitoring. Dara-VCD may therefore be particularly attractive in renal myeloma requiring rapid cytoreduction.[15]

Beyond PI/IMiD-based approaches, alkylator-containing quadruplets remain clinically relevant, particularly for very elderly patients or those with renal impairment. In the ALCYONE trial, Dara-VMP (daratumumab, bortezomib, melphalan, prednisone) significantly improved OS compared with VMP alone (83.0 vs. 53.6 months; HR: 0.65). Approximately one-third of participants were aged ≥75 years, supporting applicability in older populations. Severe neutropenia occurred in ~40% of patients, and infections were more frequent, although discontinuation rates remained below 10%, suggesting feasibility with appropriate geriatric assessment.[16,17]

Which Patients Benefit from Triplet Regimens?

Quadruplet regimens are mainly reserved for functionally fit patients with the goal of achieving the deepest possible remission, while triplet therapies remain more appropriate for many transplant-ineligible individuals. Triplets provide substantially improved disease control compared with doublets, without the added toxicity burden associated with four-drug combinations.

Consequently, they often represent the most pragmatic first-line option for a large proportion of patients with non-transplant-eligible myeloma.

The phase III MAIA trial established DRd as a reference regimen in this setting. After a median follow-up of more than five years, DRd significantly prolonged PFS compared with Rd alone (median 61.9 vs. 34.4 months; HR: 0.55) and also conferred an OS advantage (HR: 0.66). Importantly, this benefit was consistent across all age groups, including patients aged ≥80 years, in whom the PFS improvement remained substantial (HR: 0.48).[18] These results explain why DRd is widely regarded as the preferred triplet for many transplant-ineligible patients in routine practice.

However, the MAIA study also highlighted that increased efficacy may be accompanied by higher rates of infections and cytopenias. While treatment discontinuation due to adverse events was lower with DRd than with Rd (15.7% vs. 24.4%), careful monitoring remains essential, particularly in more vulnerable patients.[18]

Beyond anti- CD38 monoclonal antibody-based triplets, the proteasome inhibitor/IMiD-based VRd regimen remains a key cornerstone of first-line therapy. In the randomized phase III SWOG S0777 trial, VRd significantly improved both PFS (41 vs. 29 months; HR: 0.74) and OS (not reached vs. 69 months; HR: 0.71) compared with Rd. This benefit persisted after adjustment for age, confirming the effectiveness of VRd beyond the transplant population.[19]

Nevertheless, full-dose VRd is not always feasible in older patients, largely due to cumulative neuropathy toxicity. This underscores the importance of frailty-adapted approaches in optimizing triplet therapy for less robust individuals.

Frailty-adapted Triplets: VRd-lite and Dexamethasone Reduction: A Bridge Between Intensity and Tolerability

VRd-lite represents a particularly relevant option for the large group of intermediately fit patients who are too vulnerable for quadruplets yet too resilient for doublet therapy. This dose-adapted regimen was designed to preserve the efficacy of a proteasome inhibitor–based triplet while substantially reducing toxicity.

In the phase II RVD lite study, median PFS reached 35.1 months, with a very low incidence of severe neuropathy (grade ≥3: 2%). Most neuropathic symptoms remained mild, underscoring the clinical attractiveness of this approach in older patients.[20] VRd-lite therefore provides an important balance between efficacy and tolerability, especially for individuals who require PI-based therapy but cannot tolerate full-dose VRd.

Another key insight in optimizing triplet therapy is the recognition that both drug selection and steroid exposure strongly influence tolerability. In frail patients, steroid-related toxicities—including delirium, muscle weakness, hyperglycemia, and infections—are often the primary limiting factor.

In this context, the phase III IFM2017-03 trial is particularly practice-changing. Conducted in a frail population with a median age of 81 years, it evaluated a dexamethasone-sparing regimen of daratumumab and lenalidomide, with dexamethasone restricted to the first two cycles only. This strategy significantly prolonged PFS compared with standard Rd (53.4 vs. 22.5 months; HR: 0.51), without additional safety concerns.[21]

These findings demonstrate that frailty-adapted de-escalation does not necessarily compromise efficacy but may instead improve long-term treatment feasibility. For vulnerable patients, reducing steroid intensity can, therefore, translate into meaningful clinical benefit, marking an important shift toward more individualized first-line strategies.

Will Rd Still be Relevant in 2026?

In an era of highly effective CD38-based triplet and quadruplet regimens, classic doublets such as lenalidomide and dexamethasone (Rd) may appear largely outdated. Indeed, the first-line standard for transplant-ineligible patients has evolved substantially. Nevertheless, Rd remains clinically relevant—not as the default option, but within a clearly defined, patient-centred context.

The historical role of Rd is largely based on the pivotal phase III FIRST trial, which compared Rd with melphalan-based regimens. Rd significantly prolonged OS versus MPT (melphalan, prednisone, thalidomide; median OS 59.1 vs. 49.1 months; HR: 0.78), establishing it as a long-standing standard for non-transplant-eligible patients. Importantly, long-term follow-up revealed no new safety concerns.[22]

Frailty Tool / Approach	Key Components	Clinical Output	Strengths	Limitations	Practical Use in First-line Decision-Making
IMWG Frailty Index[5]	Age (≤75, 76-80, >80 years); Charlson Comorbidity Index (CCI ≤1 or ≥2); ADL (>4 or ≤4); IADL (>5 or ≤5)	Score 0-5: Fit (0), Intermediate (1), Frail (≥2)	Most widely validated in MM; predicts OS, PFS, toxicity, and treatment discontinuation; 3-year OS: fit 84-91%, intermediate 74-77%, frail 47–57%; online calculator available	Requires ADL/IADL assessment not routinely collected; heavily weighs age (no fit patients >75 years); time-consuming in busy clinics; limited ability to distinguish toxicity risk between fit and intermediate-fit patients	Gold standard for MM frailty assessment; guides treatment intensity and dose modifications
Simplified Frailty Scale (ECOG-based)[7]	Age; CCI; ECOG PS	Frail vs. non-frail classification	Easy to implement using readily available clinical data; validated in FIRST trial; predicts OS, PFS, and grade 3/4 AEs; improves prognostic assessment when combined with ISS	Less granular than IMWG (2 vs. 3 categories); may miss nuanced functional impairments	Most user-friendly for daily practice; can be calculated immediately at bedside; useful for rapid treatment stratification
Revised Myeloma Comorbidity Index (R-MCI)[8]	Renal, lung, and Karnofsky performance impairment; age; cytogenetics	Risk stratification for fit vs. frail	Strong prognostic value for OS and PFS; 3-year OS differences: fit 90%, intermediate 74%, frail 43%; complements IMWG score; superior to age-based subgroups for treatment tailoring	Requires cytogenetic data, which may delay assessment; more complex scoring	Useful when cytogenetic data are available; particularly valuable for comprehensive risk stratification combining disease and patient factors; guides initial dose reduction decisions
Hemo-IMWG GA (Combined Model)[10]	IMWG GA components plus HS: hemoglobin, platelet count, absolute neutrophil count	Dynamic frailty assessment with integrated hematologic risk	Superior predictive performance for total toxicity (C-index 0.615) and non-hematological toxicity (C-index 0.605); HS strongly stratifies hematological AEs (HR=9.91); allows dynamic reassessment across treatment cycles	Requires serial assessment; more complex than single-timepoint tools; relatively new with limited external validation	Optimizes prediction of chemotherapy tolerance by combining functional and hematopoietic dimensions; particularly useful for predicting hematological toxicity; enables personalized treatment adjustments during therapy

Frailty Tool / Approach	Key Components	Clinical Output	Strengths	Limitations	Practical Use in First-line Decision-Making
G8 Questionnaire[9]	8 items derived from Mini Nutritional Assessment	Score 0–17; ≤14 abnormal	Widely validated across cancers including hematologic malignancies; high sensitivity (73-81%); quick screening tool; predicts survival, treatment tolerance, hospitalization	Lower specificity (44–80%); screening tool, not comprehensive assessment	First-line screening to identify who needs full GA; takes 5 minutes; recommended by NCCN for older adults with cancer; validated in hematology populations
Vulnerable Elders Survey-13 (VES-13)[9]	13 self-reported items on age, self-rated health, physical function, ADL	Score 1–10; ≥3 vulnerable	Self-administered in 5 minutes; high specificity (70-100%); predicts survival, toxicity, treatment tolerance	Lower sensitivity (46–69%) vs. G8; may miss some vulnerable patients	Efficient self-administered screening; useful when staff time is limited; validated for treatment outcome prediction in hematology

Table 1. Validated frailty assessment tools used in transplant-ineligible patients with newly-diagnosed multiple myeloma, outlining key components and their implications for first-line treatment selection; *courtesy of Rina Latscha, MD and Sita Bhella, MD*.

Frailty classification (fit, intermediate, frail, or vulnerable) predicts survival, treatment-related toxicity, and feasibility of therapy intensity.

Abbreviations: ADL: Activities of Daily Living; **AEs:** adverse events; **CCI:** Charlson Comorbidity Index; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **GA:** Geriatric Assessment; **HS:** Hematopoietic Score; **IADL:** Instrumental Activities of Daily Living; **IMWG:** International Myeloma Working Group; **ISS:** International Staging System; **MM:** multiple myeloma; **NCCN:** National Comprehensive Cancer Network; **OS:** overall survival; **PFS:** progression-free survival; **R-MCI:** Revised Myeloma Comorbidity Index.

Study	Study Type	Population	Treatment	Response Rate	PFS	OS	Key Toxicity
CEPHEUS[12]	Phase III, randomized	Transplant-ineligible or transplant-deferred NDMM (n=395)	D-VRd vs. VRd (8 cycles) followed by D-Rd or Rd	≥CR: 81.2% vs. 61.6%; MRD-neg: 60.9% vs. 39.4%	Median not reached vs. NR; HR: 0.57 (95% CI 0.41-0.79)	Median follow-up 58.7 months; OS data immature	Higher neutropenia, thrombocytopenia, peripheral neuropathy; but consistent with known safety profiles
IMROZ[13]	Phase III, randomized	Transplant-ineligible NDMM, age 18–80 (n=446)	Isa-VRd vs. VRd (3:2 randomization	≥CR: 74.7% vs. 64.1%; MRD-neg + CR: 55.5% vs. 40.9%	60-month PFS: 63.2% vs. 45.2%; HR: 0.60 (98.5% CI: 0.41-0.88)	Median follow-up 59.7 months; OS data immature	Neutropenia (54.4% vs. 37.0% grade ≥3), infections (44.9% vs. 38.1%; grade ≥3); no new safety signals
BENEFIT[14]	Phase III, randomized	TI NDMM age 65–79 (n=270)	Isa-VRd (12 cycles) followed by Isa-Rd vs. Isa-Rd	≥CR: 65.4% vs. 47.1% (p=0.002); MRD-neg (10^{-5}): 53.6% vs. 26.8%; Sustained MRD-neg ≥12 months: 42.5% vs. 18.3%	Median: Not reached vs 47.0 months; HR 0.54 (95% CI: 0.36–0.81, p=0.003);	Median follow-up: 42.5 months; OS data immature; HR 0.75 (95% CI 0.44–1.28, p=0.29)	Neutropenia: 50.3% vs. 39.9% (grade ≥3); infections: 50.3% vs. 48.4% (any grade), 22.2% vs. 19.6% (grade ≥3); peripheral neuropathy: 44.4% vs. 26.8% (any grade), 3.3% vs. 0.7% (grade ≥3);
ALCYONE[16]	Phase III, randomized	TI NDMM ≥65 or comorbidities (n=706)	D-VMP vs. VMP	≥CR: 42.6% vs. 24.4%; MRD-neg: 22.3% vs. 6.2%	Median 18.1 months (primary); HR: 0.50 (95% CI: 0.38-0.65)	Median 83.0 vs 53.6 months; HR 0.65 (95% CI 0.53–0.80) at 86.7 months follow-up	Neutropenia (40% vs. 39% grade 3/4), thrombocytopenia (35% vs. 38%), anemia (18% vs. 20%)
AMaRC3-16[15]	Phase II/III randomized	TI NDMM (n=121)	D-VCD vs. VCD	ORR: 86% vs. 65% (p=0.007); ≥VGPR: 52% vs. 28% (p=0.009)	25.8 months (95% CI: 19.9-33.5) vs. 16.8 months (95% CI: 15.3-21.7); HR: 0.67; PFS 30 months: 41% vs. 27% (p=0.0001)	Not reported in final analysis	72% completed 9 cycles of induction; no grade 3/4 peripheral neuropathy; well tolerated with no new safety signals
MAIA[18]	Phase III, randomized	TI NDMM (n=737)	D-Rd vs. Rd	≥CR: 51.1% vs. 30.1%; MRD-neg: 32.1% vs. 11.1%	Median 61.9 vs. 34.4 months; HR: 0.55 (95% CI: 0.45-0.67)	Median NR vs. 65.5 months; HR: 0.66 (95% CI: 0.53-0.83) at 64.5 months follow-up	Neutropenia (54% vs. 37% grade ≥3), pneumonia (19% vs. 11%), anemia (17% vs. 22%)

Study	Study Type	Population	Treatment	Response Rate	PFS	OS	Key Toxicity
SWOGS0777[19]	Phase III, randomized	NDMM without intent for early ASCT (n=460)	VRd (8 cycles) vs. Rd (6 cycles) followed by Rd maintenance	≥CR: 15.7% vs. 8.4%; ORR: 82% vs. 72%	Median 43 vs. 30 months; HR: 0.712 (96% CI: 0.56–0.906)	Median 75 vs. 64 months; HR: 0.709 (95% CI: 0.524–0.959)	Neuropathy risk increased with bortezomib Grade ≥3 AEs: 82% vs. 75%; discontinuation due to AEs: 23% vs. 10%
RVD-lite[20]	Phase II, single-arm	TI NDMM (n=50)	Modified RVd: R 15mg days 1–21, V 1.3mg/m² weekly SC, D 20mg (35-day cycles)	ORR: 86%; ≥VGPR: 66%	Median 35.1 months (95% CI: 30.9–NR)	Median not reached at 30 months follow-up	Peripheral neuropathy: 62% (only 1 grade 3); well-tolerated
IFM2017-03[21]	Phase III, randomized	Frail NDMM, age ≥65 years, ECOG frailty score ≥2 (n=295)	D-Rd (dex only 2 cycles) vs. Rd (2:1 randomization	≥CR: 47.5% vs. 28.4%; MRD-neg at 12 months: 24% vs. 9%	Median 53.4 vs. 22.5 months; HR: 0.51 (95% CI: 0.37–0.70)	Median follow-up 46.3 months; OS data immature	Neutropenia (55% vs. 24% grade 3–5), infections (19% vs. 21%); serious AEs: 63% vs. 69%
FIRST Trial[22]	Phase III, randomized	TI NDMM (n=1623)	Rd continuous vs. Rd18 vs. MPT (72 weeks)	≥CR: higher with Rd continuous vs MPT	Median 26 vs. 21 vs. 21 months (Rd continuous vs. Rd18 vs. MPT); HR: 0.69 vs. MPT	Median 59.1 vs. 62.3 vs. 49.1 months (Rd continuous vs. Rd18 vs. MPT); HR: 0.78 vs. MPT	No new safety concerns; no increased risk of secondary malignancies; steroid-related AEs relevant in elderly

Table 2. Major clinical trials evaluating modern CD38 antibody–based quadruplet and triplet regimens in transplant-ineligible or transplant-deferred patients with newly diagnosed multiple myeloma; *courtesy of Rina Latscha, MD and Sita Bhella, MD.*

Reported outcomes include depth of response, PFS, OS, and key treatment-related toxicities. These data highlight the balance between improved efficacy with intensified regimens and the increased risk of hematologic and infectious adverse events in older or frail populations.

Abbreviations: AEs: adverse events; **ASCT:** autologous stem cell transplant; **CI:** confidence interval; **CR:** complete response; **D-Rd:** daratumumab + lenalidomide + dexamethasone; D-VCD: daratumumab + bortezomib + cyclophosphamide + dexamethasone; **D-VMP:** daratumumab + bortezomib + melphalan + prednisone; **D-VRd:** daratumumab + bortezomib + lenalidomide + dexamethasone; **HR:** hazard ratio; **Isa-VRd:** isatuximab + bortezomib + lenalidomide + dexamethasone; **MPT:** melphalan + prednisone + thalidomide; **MRD-neg:** minimal residual disease negativity; **NDMM:** newly-diagnosed multiple myeloma; **NR:** not reached; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; Rd: lenalidomide + dexamethasone; RVd: lenalidomide + bortezomib + dexamethasone; **TI:** transplant-ineligible; **VGPR:** very good partial response; **VCD:** bortezomib + cyclophosphamide + dexamethasone; **VRd:** bortezomib + lenalidomide + dexamethasone.

First bispecific antibody indicated in the treatment of the triple-class exposed patients with RRMM[1,2*]

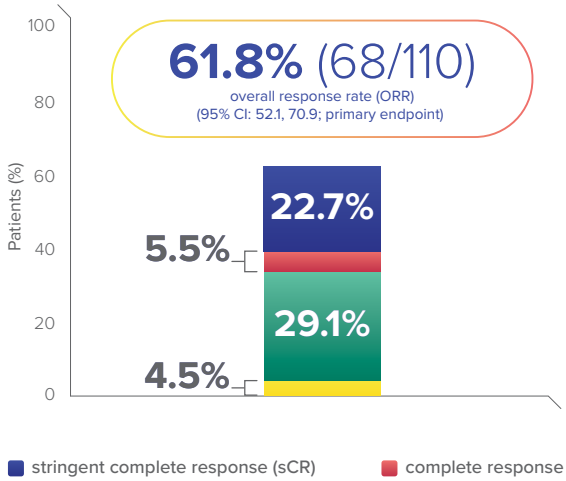
TECVAYLI® has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.[1]

TECVAYLI® (teclistamab injection) is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[1]

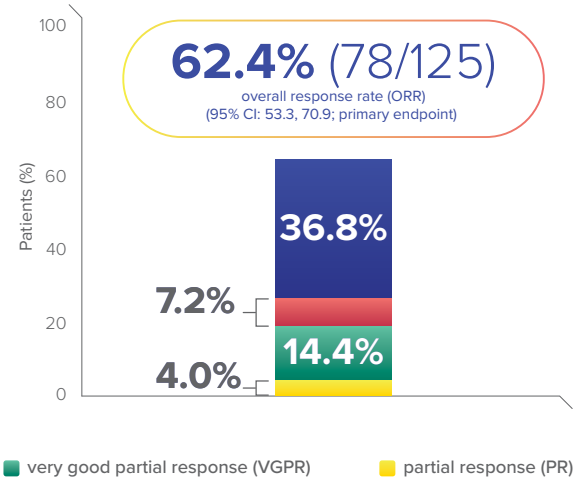
TURN TO THE POWER OF TECVAYLI®

Efficacy profile investigated in the open-label MajesTEC-1 trial:[1†‡§]

At 8.8 months (primary analysis; n=110):[¶]



At 29.5 months (follow-up analysis; n=125):[1]



stringent complete response (sCR) · complete response (CR) · very good partial response (VGPR) · partial response (PR)

Adapted from TECVAYLI® Product Monograph[1]

Primary analysis: median time to first response (n=68): 1.2 months (range: 0.2–5.5) for responders
- Median duration of response: NE (95% CI: 9.0, NE)

Follow-up analysis: median duration of response (n=78): 21.6 months (95% CI: 14.9 months, NE) for responders

55.1% of the 78 responders in the MajesTEC-1 trial switched from weekly to biweekly dosing during the study[1]

With the incorporation of daratumumab into first-line therapy, Rd has increasingly served as the control arm in modern trials. As expected, it was clearly inferior to DRd in the MAIA study, yet still achieved a median OS of 65.5 months. This highlights that less intensive therapy can provide durable disease control, particularly in patients able to tolerate continuous treatment.[18]

Therefore, the key issue is not maximal efficacy alone, but the appropriateness of treatment intensity. For some individuals—especially very frail older patients with limited physiological reserve, significant comorbidity burden, or restricted life expectancy—continuous triplet therapy may be impractical despite its benefits. In such cases, Rd remains an important alternative due to its outpatient administration, oral convenience, and manageable toxicity profile, while prioritizing quality of life and patient autonomy.

Side Effects as a Key Tool for Managing Treatment

For patients who are not eligible for transplantation, first-line therapy for MM will be less a purely regimen-based decision and increasingly a question of treatment feasibility under real geriatric conditions. Although quadruplet and triplet regimens can significantly prolong PFS, clinical practice remains characterized by a persistent tension between efficacy and toxicity. As treatment intensity increases, so does the overall toxicity burden, which often limits therapy in older patients.[3]

Hematological toxicities, such as neutropenia and thrombocytopenia, as well as the resulting hospitalizations, are particularly relevant because they are not merely adverse events but often mark the beginning of functional decline. Infections in older patients can rapidly lead to loss of mobility, delirium, or the need for nursing care—outcomes that are not adequately captured by traditional trial endpoints.

RRMM=relapsed or refractory multiple myeloma; CD38=cluster of differentiation 38; CI=confidence interval; NE=non estimable; SC=subcutaneous(ly); q2w=every 2 weeks; IRC=Independent Review Committee; IMWG=International Myeloma Working Group.

* Comparative clinical significance unknown.

† Phase 1/2, single-arm, open-label, multicentre study in adults with RRMM who had received ≥3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg administered SC, followed by 1.5 mg/kg SC once-weekly thereafter until disease progression or unacceptable toxicity. Patients who had a CR or better for ≥6 months were eligible to reduce dosing frequency to 1.5 mg/kg SC q2w until disease progression or unacceptable toxicity. Efficacy population treated at the pivotal study dose in phase 2 had a median duration of follow-up of 8.8 months at the primary analysis.

‡ ORR was a composite of sCR + CR + VGPR + PR as determined by the IRC assessment using IMWG 2016 criteria.

§ Follow-up analysis included 15 additional patients since the primary analysis.

¶ Efficacy population treated at the pivotal dose in phase 2.

** Clinical significance unknown.

†† Based on sales data (up to August 31, 2025), it is estimated that approximately 19,177 patients have been exposed to teclistamab in the post-marketing setting. An estimated total of 2,821 participants were exposed to teclistamab in the Company-sponsored and collaborative interventional clinical trials.[3]

More than 21,900 patients have been treated worldwide with TECVAYLI®[3]††**

Clinical use:

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): Of the 165 patients treated with TECVAYLI® in Study MajesTEC-1 at the recommended dose, 48% were 65 years of age or older, and 15% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Most serious warnings and precautions:

Cytokine release syndrome (CRS): CRS, including life-threatening or fatal reactions, can occur in patients receiving TECVAYLI®. Initiate treatment with TECVAYLI® step-up dosing schedule to reduce the risk of CRS. Monitor patients for signs or symptoms of CRS. Withhold TECVAYLI® until CRS resolves, provide supportive care and treatment as needed, or permanently discontinue based on severity.

Neurologic toxicities: Serious, life-threatening or fatal neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS), can occur following treatment with TECVAYLI®. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Monitor patients for signs or symptoms of neurologic toxicity, including ICANS, during treatment. Withhold TECVAYLI® until neurologic toxicity resolves or permanently discontinue based on severity.

Other relevant warnings and precautions:

- Driving and operating machinery during and for 48 hours after completion of TECVAYLI® step-up dosing schedule and in the event of new onset of any neurological symptoms
- Hypogammaglobulinemia
- Neutropenia and febrile neutropenia
- Severe, life-threatening, or fatal infections
- New/reactivated viral or opportunistic infections
- Progressive multifocal leukoencephalopathy (PML), which can be fatal
- Hepatitis B virus reactivation
- Immune response to vaccines may be reduced
- Live viral vaccines are not recommended
- Not recommended for women who are pregnant or breastfeeding
- Patients should use effective contraception
- ICANS, including fatal outcome, occurred in post-marketing experience
- Potential for immunogenicity

For more information:

Please consult the Product Monograph at jnj.com/innovativemedicine/canada/our-medicines for important information relating to contraindications, adverse reactions, drug interactions, and dosing/administration that has not been discussed in this piece.

The Product Monograph is also available by calling 1-800-567-3331.

References: 1. TECVAYLI® (teclistamab injection) Product Monograph. Janssen Inc. June 26, 2025. **2.** Data on file, Johnson & Johnson. October 13, 2023. **3.** Data on file, Johnson & Johnson. October 31, 2025.

The image depicted contains models and is being used for illustrative purposes only.

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TECVAYLI (teclistamab) Injection for subcutaneous use 10 mg/mL and 90 mg/mL

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Another frequently underestimated factor is steroid-associated toxicity. Dexamethasone remains part of many standard regimens, yet its side effects—including sleep disturbances, delirium, muscle weakness, hyperglycemia, and an increased risk of falls—are highly clinically relevant in geriatric patients. Reviews of treatment in older myeloma populations emphasize that steroid toxicity is often underestimated, despite its major contribution to treatment discontinuation rates.[10]

A substantial proportion of patients present with impaired renal function at diagnosis. The IMWG highlights that up to 50% of patients with myeloma have renal involvement, which is associated with higher early mortality and poorer OS. This has direct therapeutic implications: bortezomib-based regimens remain the cornerstone of treatment in this setting, as they induce rapid responses and improve the likelihood of renal recovery.[23]

Beyond renal impairment, individual neuropathy risk is another decisive factor. Although bortezomib-containing regimens such as VRd or VRd-based quadruplets are highly effective, they may cause peripheral neuropathy with a substantial impact on quality of life in older patients. The *American Society of Clinical Oncology (ASCO)–Ontario Health Living Guideline* therefore emphasizes that, outside of emergency situations, twice-weekly bortezomib should be avoided, as weekly administration provides comparable efficacy with significantly lower neuropathy rates.[23]

Patients with pre-existing polyneuropathy, diabetes, or a tendency to fall often benefit from PI-free strategies, such as DRd or Rd. However, in aggressive disease or in the presence of renal involvement, the benefits of including a PI may outweigh the neuropathy risk.

Conclusion

First-line therapy for transplant-ineligible MM has fundamentally evolved and is now characterized by substantial therapeutic diversity. Anti-CD38 monoclonal-based triplet and quadruplet regimens have significantly improved PFS and, in several studies, OS. As a result, even older patients can achieve long-term disease control to an extent previously observed mainly in transplant-eligible populations.

However, these advances have also increased clinical complexity. Treatment decisions are no longer driven solely by maximal efficacy, but by the question of which regimen is feasible, safe, and sustainable for an individual patient. In transplant-ineligible patients, treatment tolerance is often the primary limiting factor rather than lack of therapeutic effectiveness.

Frailty has, therefore, become a central guiding principle. Geriatric assessment–based classifications (fit, intermediate, frail) predict survival, treatment discontinuation, and therapy-related toxicity more accurately than age or ECOG status alone. Impairments in daily functioning, cognition, or nutritional status strongly correlate with infection risk, mortality, and reduced treatment feasibility, even in patients with preserved performance status. Dynamic frailty models, such as the integration of IMWG geriatric assessment with hematopoietic scoring, further improve the prediction of severe adverse events and support adaptive treatment strategies over time.

Consequently, first-line decisions must systematically incorporate multiple dimensions, including frailty, comorbidities, organ function, neuropathy risk, infection vulnerability, and the practicality of continuous regimens. In this population, adverse events are not merely side effects but often determine whether therapy can be delivered effectively.

Overall, first-line treatment of transplant-ineligible myeloma requires a structured, pragmatic, and patient-centred approach. The key lies not in a universal standard regimen, but in individualized adjustment of treatment choice and intensity, with regular reassessment throughout the disease course.

Correspondence

Rina Latscha, MD
Email: rina.latscha@uhn.ca

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S.B.: None declared.

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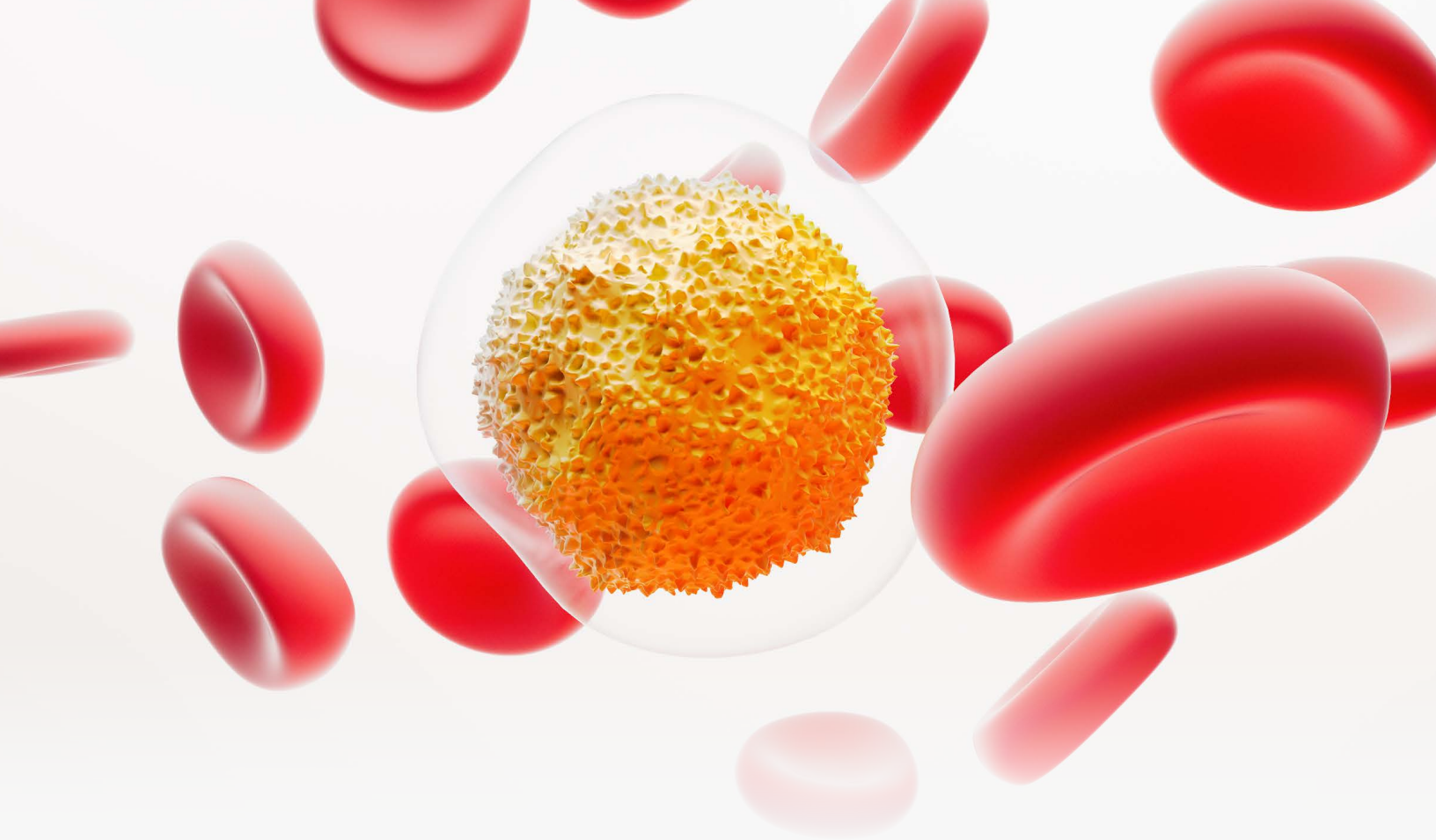

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About the Authors

Stephanie Craig, MD

Dr. Stephanie Craig is a Hematology Fellow at Dalhousie University. She earned her Master of Public Health from Memorial University of Newfoundland and completed her medical degree from Dalhousie University. She pursued internal medicine residency training at the Northern Ontario School of Medicine. Her clinical and academic interests focus on malignant hematology.

Affiliations: Dalhousie University, Halifax, NS, Canada

Shannon Murphy, MD

Dr. Shannon Murphy is a Hematologist and Assistant Professor at Dalhousie University and practices at the QEII Health Sciences Centre in Halifax, NS. Prior to joining the Division of Hematology and Hematologic Oncology in Halifax, Dr. Murphy completed her internal medicine and hematology training at Dalhousie University, followed by a 1-year clinical lymphoma fellowship with BC Cancer in Vancouver. Her practice focuses on lymphoma and chronic lymphocytic leukemia.

Affiliations: Dalhousie University, Halifax, NS, Canada
Nova Scotia Health, Halifax, NS, Canada

Is Continuous Therapy Becoming Finite? The Evolving Landscape of CLL Treatment in 2026

Stephanie Craig, MD
Shannon Murphy, MD

Introduction

The front-line treatment landscape for chronic lymphocytic leukemia (CLL) is rapidly evolving, with several new therapeutic options emerging. Traditionally, chemoimmunotherapy (CIT) formed the foundation of front-line treatment. However, over the past decade, targeted therapies have transformed the management of CLL, replacing CIT as the backbone of front-line treatment.

Table 1 summarizes pivotal trials that have advanced CLL treatment.

As a result of these advances, clinicians now have multiple highly effective frontline options. The challenge is no longer selecting the most efficacious regimen but rather selecting the optimal strategy for each individual patient. To address this evolving landscape, this review highlights current evidence and key practical considerations shaping frontline CLL management in Canada.

Trial	Regimen	Duration	Population	High-risk patients included?	Median Follow-up	Progression-Free Survival
Amplify[13]	Acalabrutinib + venetoclax or acalabrutinib + venetoclax + obinutuzumab or CIT	Fixed-duration	≥18 yr and ECOG PS 0–2	No	40.8 mo	Est. 36 mo, 76.5% for acalabrutinib + venetoclax; 83.1% for acalabrutinib + venetoclax + obinutuzumab; 66.5% for CIT
ALLIANCE[3]	Ibrutinib or ibrutinib + rituximab or BR	Continuous	≥65 yr	Yes	55 mo	Estimated 48 mo, 47% for BR; 76% for ibrutinib; 76% for ibrutinib + rituximab
CLL13/GAIA[10]	Venetoclax + obinutuzumab or venetoclax + obinutuzumab + ibrutinib or venetoclax + rituximab or CIT (FCR for pts ≤65 yr; BR for pts >65 yr)	Fixed-duration	≥18 yr and ECOG PS 0–2 and CIRS ≤6 or a single score of 4 or lower	No	63.8 mo	Est. 60 mo, 69.8% for venetoclax + obinutuzumab; 81.3% for venetoclax + obinutuzumab + ibrutinib; 57.4% for venetoclax + rituximab; 50.7% for CIT
CLL14[9]	Venetoclax + obinutuzumab or Clb-O	Fixed-duration	≥65 yr, or CIRS >6, or creatinine clearance <70 mL/min	Yes	76.4 months	Est. 72 mo, 76.2 mo (53.1%) for venetoclax + obinutuzumab; 36.4 mo (21.7%) for Clb-O
CLL17[17]	Ibrutinib or venetoclax + obinutuzumab or ibrutinib + venetoclax	Continuous vs. Fixed-duration	≥18 yr	Yes	34.2 mo	Est. 36 mo, 81.1% for venetoclax–obinutuzumab; 81.0% for ibrutinib; 79.4% for ibrutinib-venetoclax
ELEVATE-TN[5]	Acalabrutinib +/- obinutuzumab or Clb-O	Continuous	≥65 yr, or 18-65 yr with comorbidities (CIRS >6 or creatinine clearance 30–69 mL/min)	Yes	74.5 mo	Est. 72 mo, 78.0% for acalabrutinib-obinutuzumab; 61.5% for acalabrutinib; 17.2% for Clb-O
GLOW[11]	Ibrutinib-venetoclax or Clb-O	Fixed-duration	≥65 yr or CIRS >6 or creatinine clearance <70 mL/min	No	46 mo	Est. 42 mo, 74.6% for ibrutinib + venetoclax; 24.8% for Clb-O
RESONATE-2[2]	Ibrutinib or Clb-O	Continuous	≥65 yr	No	9.6 yr	Est. 8.9 yr for ibrutinib vs. 1.3 yr for Clb-O
SEQUOA[6]	Zanubrutinib vs. BR	Continuous	≥65 or ≥18 yr + comorbidities	No	61.2 mo	Est. 60 mo, 75.8% for zanubrutinib; 40.1% for BR

Table 1. Pivotal Trials in Front-line CLL Management; *courtesy of Stephanie Craig, MD and Shannon Murphy, MD.*

Abbreviations: BR: Bendamustine-rituximab; **CIRS:** Cumulative Illness Rating Scale; **CIT:** chemoimmunotherapy; **Clb-O:** chlorambucil-obinutuzumab; **ECOG PS:** Eastern Cooperative Oncology Group Performance Score; **est:** estimated; **FCR:** fludarabine, cyclophosphamide, and rituximab; **mo:** months; **pts:** patients; **yr:** years.

Risk Stratification in the Targeted Therapy Era: What Still Matters?

While historically numerous prognostic markers informed risk stratification in CLL, their relevance has evolved as the field has transitioned toward targeted therapies. In the modern era, molecular disease characteristics, particularly immunoglobulin heavy chain variable region (*IGHV*) mutational status and the presence of del(17p) and/or *TP53* aberrations, have emerged as the most clinically relevant predictors of outcome. In contrast, traditional factors, such as clinical stage and age, now play a more limited role in treatment decisions.[1]

Unmutated IGHV is associated with more aggressive disease and inferior overall survival (OS), particularly in the CIT era. Similarly, del(17p)/*TP53* aberrations remain one of the strongest adverse prognostic factors, historically associated with poor response to CIT and inferior outcomes. Importantly, targeted therapies have significantly improved outcomes in these high-risk groups, with multiple phase III trials demonstrating superior efficacy compared with CIT, reinforcing the role of molecular and cytogenetic characteristics in guiding front-line treatment selection.[1]

Front-line Treatment Strategies in CLL

Continuous Bruton's Tyrosine Kinase Inhibitor (BTKi) Therapy: The Foundation of Modern Therapy

Continuous BTKi therapy remains a cornerstone of front-line CLL management. This approach was established by ibrutinib, the first-in-class agent, which showed durable efficacy across multiple trials. The RESONATE-2 trial provides the longest phase III follow-up data for any targeted CLL therapy. In the final analysis, with a median follow-up of 9.6 years, front-line ibrutinib demonstrated a median progression-free survival (PFS) of 8.9 years compared with 1.3 years for chlorambucil. This benefit was largely preserved in high-risk subgroups, with a median PFS of 8.4 years with ibrutinib versus 0.7 years with chlorambucil.[2] Similarly, follow-up from the ALLIANCE A041202 trial demonstrated continued efficacy in patients with and without high-risk aberrations, with superior PFS for ibrutinib-containing regimens compared with bendamustine-rituximab (BR).[3]

In current practice, the second-generation BTKis acalabrutinib and zanubrutinib have largely replaced ibrutinib due to improved safety profiles and lower discontinuation rates.[4] The ELEVATE-TN trial compared acalabrutinib-obinutuzumab and acalabrutinib monotherapy to chlorambucil-obinutuzumab (Clb-O) in patients ≥65 years, or 18–65 years with comorbidities. At a median follow-up of 74.5 months, acalabrutinib-containing regimens demonstrated superior PFS compared to Clb-O (78.0% for acalabrutinib-obinutuzumab vs. 61.5% for acalabrutinib vs. 17.2% for Clb-O), irrespective of *IGHV* or TP53 status.[5] The SEQUOIA study similarly demonstrated superior PFS for zanubrutinib over BR with an estimated 60-month PFS rate of 75.8% and 40.1% in zanubrutinib- and BR-treated patients, respectively.[6]

While no phase III trials have directly compared ibrutinib with second-generation BTKis in previously untreated patients, evidence in the relapsed/refractory setting supports second-generation agents as the standard of care. The ALPINE and ELEVATE-RR trials demonstrated improved tolerability with second-generation BTKis, with the ALPINE trial additionally showing superior PFS for zanubrutinib, supporting their preferential use.[7,8]

Fixed-Duration Venetoclax-Obinutuzumab

Ushering in the era of fixed-duration targeted therapy, venetoclax-obinutuzumab (VenO) was the first targeted fixed-duration treatment combination, proving to be well-tolerated while achieving deep and durable remissions in previously untreated patients.

Its efficacy has been demonstrated across multiple phase III randomized trials in both fit and unfit populations. Established in the CLL14 trial, the VenO regimen demonstrated a substantial improvement in outcomes, with a median PFS of 76.2 months compared with 36.4 months for Clb-O. Notably, the 6-year time-to-next-treatment (TTNT) rate was 65.2%, indicating that nearly two-thirds of patients remained free of subsequent therapy for more than 5 years after completing a single year of treatment. While outcomes were best in low-risk patients, those with del(17p)/*TP53* aberrations still demonstrated a median PFS and TTNT of 51.9 months and 57.3 months, respectively.[9]

The Phase III GAIA/CLL13 trial also showed that VenO outperformed CIT, with superior PFS in fit patients without *TP53* aberrations (5-year PFS 69.8% vs. 50.7%). Importantly, patient-reported outcomes from CLL13 showed more rapid and clinically meaningful improvements in quality of life with VenO, likely reflecting the advantages of fixed-duration treatment and reduced treatment-related symptoms.[10]

VenO has been reimbursed in Canada since 2022 and is established as a front-line standard of care for CLL. A substantial body of evidence supports its efficacy as a fixed-duration regimen, offering durable remissions and clinically meaningful treatment-free intervals.

Ibrutinib-Venetoclax: The First All-Oral Fixed-Duration Doublet

Building on the success of fixed-duration venetoclax-based therapy, the combination of ibrutinib and venetoclax (Ibr–Ven) represents the first all-oral, fixed-duration regimen combining BTK and BCL-2 inhibition as an alternative treatment strategy. This combination has regulatory approval in Canada and is currently publicly reimbursed in select provinces. The Ibr-Ven regimen was evaluated against Clb-O in the randomized phase III GLOW trial, which included patients without del(17p)/*TP53* aberrations who were ≥65 years old, or those younger with comorbidities. At a median follow-up of 46 months, Ibr-Ven demonstrated a significant PFS advantage, with an estimated 42-month PFS of 74.6% versus 24.8% with Clb-O. This benefit was consistent across subgroups, including older patients, those with comorbidities, and *IGHV* mutational status.[11] Similarly, in younger, fit patients treated with Ibr–Ven, the phase II CAPTIVATE trial demonstrated a 5.5-year PFS rate of 70% among patients without high-risk mutations, at a median follow-up of 68.9 months.[12]

Next-Generation Doublet: Acalabrutinib-venetoclax

For patients seeking an all-oral, fixed-duration approach but for whom cardiac history may limit the use of ibrutinib-based regimens, acalabrutinib–venetoclax (AV) may be an attractive alternative. As a second-generation BTKi, acalabrutinib provides a more favourable cardiac safety profile while maintaining the convenience of a chemotherapy-free, time-limited approach. Based on the phase III AMPLIFY trial, AV is the newest fixed-duration, all-oral doublet approved in Canada. In this study, the 3-year PFS for AV was 76.5%, compared with 83.1% for AV plus obinutuzumab and 66.5% for CIT in previously untreated patients with CLL without del(17p)/*TP53* aberrations. Notably, OS at 36 months was highest in the AV arm, despite higher rates of undetectable measurable residual disease (MRD) in the triplet arm, likely reflecting increased toxicity with the addition of obinutuzumab.[13]

From a practical standpoint, access remains a key limitation. While approved by Health Canada, AV is currently under review for reimbursement by the Canadian Drug Agency for use, and access is currently dependent on private insurance or special access pathways.

Chemoimmunotherapy: The End of an Era?

In Canada, CIT remains available and funded but plays a small role in contemporary front-line CLL management. Although fludarabine, cyclophosphamide, and rituximab (FCR) can produce durable remissions in select younger patients with favourable-risk disease, this benefit is offset by long-term toxicity, including an increased risk of second primary malignancies, and by the availability of more effective targeted options.[14] Phase III trials such as ECOG-E1912, FLAIR, AMPLIFY, and GAIA/CLL13 have shown that targeted therapies can outperform FCR with a more acceptable safety profile, while acknowledging that neither comparator regimen perfectly mirrors modern clinical practice.[10,13,15,16] Outcomes with CIT are particularly poor in patients with *TP53* aberrations or unmutated *IGHV*, further limiting its applicability.[5,6,9-11] Given broad Canadian access to front-line targeted therapies, CIT is best viewed as largely obsolete, reserved only for rare situations where targeted agents are inaccessible.

Fixed-Duration vs. Continuous Therapy: Defining the Optimal Approach

Perhaps the most relevant question in front-line CLL management today is not which therapy is most effective, but rather how long to treat. Fixed-duration and continuous treatment strategies have each demonstrated remarkable efficacy, yet until recently, no randomized trial had directly compared them. The CLL17 trial provided the first head-to-head comparison, randomizing treatment-naïve patients to fixed-duration VenO or Ibr-Ven versus continuous ibrutinib. At a median follow-up of 34.2 months, both fixed-duration arms demonstrated noninferior PFS compared with continuous ibrutinib, with 3-year PFS rates

of approximately 80% across all arms. However, outcomes among high-risk subgroups were more nuanced. Patients with *TP53* aberrations and complex karyotype appeared to derive greater benefit from continuous BTKi therapy, although these findings are limited by small numbers and a relatively short follow-up. Conversely, fixed-duration therapy performed particularly well in *IGHV*-mutated disease, with no clear disadvantage in unmutated *IGHV*.[17] While fixed-duration strategies offer the appeal of time-limited therapy with durable remissions for many patients, continuous BTKi therapy may remain preferable for select high-risk populations until more mature data are available.

Putting it All Together: A Shift Toward Individualized Care

As multiple targeted strategies demonstrate comparable disease control in front-line CLL, treatment selection has shifted from an efficacy-driven decision to an individualized one, incorporating several key factors (**Figure 1**).

Molecular disease characteristics remain a key driver of front-line treatment selection. Current evidence suggests that patients with del(17p)/*TP53* aberrations derive more durable disease control with continuous BTKi–based strategies or BTKi–venetoclax combinations than with VenO alone. In contrast, patients with mutated *IGHV* often experience favourable outcomes with fixed-duration venetoclax-based regimens, supporting their use in individuals seeking a time-limited approach.

Beyond disease characteristics, patient-specific factors further influence treatment selection. BTKis carry increased risks of atrial fibrillation, hypertension, and bleeding, warranting caution in patients with pre-existing cardiac disease or those requiring anticoagulation. While fixed-duration BTKi–venetoclax combinations limit cumulative BTKi exposure and cardiovascular events often improve after treatment cessation, cardiac toxicity may still occur during the active treatment period. In patients for whom even time-limited BTKi exposure poses unacceptable risk, a venetoclax-based strategy without a BTKi may be preferred. Venetoclax-based regimens, however, carry their own risks, including an increased susceptibility to tumour lysis syndrome (TLS), particularly in patients with renal impairment, and higher rates of neutropenia. Patient preferences further shape decision-making, as some patients prioritize the predictability of a time-limited approach and the potential for treatment-free intervals, whereas others favour the simplicity and psychological reassurance of continuous oral therapy.

Logistical factors and economic considerations can also influence treatment selection. Continuous BTKi therapy offers the convenience of oral-only administration and easier treatment initiation, without the need for intravenous infusions or intensive laboratory monitoring. In contrast, VenO requires intravenous obinutuzumab infusions and close laboratory monitoring to mitigate TLS risk. From an economic perspective, continuous therapies impose a considerable financial burden on the Canadian healthcare system due to their high costs and indefinite administration. Fixed-duration regimens may alleviate this burden by reducing cumulative treatment expenditures and resource utilization, offering a more sustainable care model without compromising clinical outcomes.[18]

Future Directions: Emerging Therapies and Evolving Strategies

As the CLL treatment landscape continues to evolve, novel agents are being explored in the front-line setting. Pirtobrutinib, a highly selective, noncovalent BTKi, is currently approved, though not funded, in Canada for relapsed/refractory CLL after at least two prior lines of therapy. Recent phase III data suggest a potential role in earlier lines of therapy. In treatment-naïve CLL, pirtobrutinib achieved better 24-month PFS than BR[19] and had a noninferior overall response rate to ibrutinib with favourable early PFS trends.[20] Both trials demonstrated a favourable safety profile, with lower rates of atrial fibrillation, hypertension, and treatment discontinuation in the pirtobrutinib groups.[19,20] These findings support the potential expansion of pirtobrutinib into earlier lines of therapy.

Beyond novel agents, MRD-guided strategies represent another emerging frontier, offering the potential to individualize treatment duration based on depth of response. Although included in international guidelines, adoption in Canadian clinical practice remains limited and largely confined to use in clinical trials and specialized centres.

Decision Point	Favours Continuous Therapy	Favours Finite-based Therapy
Disease Biology	Patients with *TP53*/del(17p) aberrations; concerns about durability of finite therapy	Mutated *IGHV*; standard-risk biology
Patient Preference	Reassurance of continuous therapy	Treatment-free interval
Patient Comorbidities		
Cardiac	Prefer second-generation BTKi if used	Pre-existing cardiac history present
Renal	Pre-existing renal dysfunction	No pre-existing renal dysfunction
Bleeding/Anticoagulation	Caution with BTKi therapy	Preferred in patients requiring anticoagulation or increased bleed risk
Infection	No neutropenia risk	Neutropenia risk
Logistics	Avoids infusion requirements and TLS ramp-up; advantageous for patients living remotely	Preferred if long-term adherence a concern
Economic burden	Lower upfront resource utilization but higher long-term costs	Higher upfront resource utilization but long-term cost savings

Figure 1. Fixed-Duration vs. Continuous Therapy in Front-line CLL: A Comparative Framework; *courtesy of Stephanie Craig, MD and Shannon Murphy, MD.*

Abbreviations: IGHV: immunoglobulin heavy chain variable region; **BTKi:** Bruton's tyrosine kinase inhibitor; **TLS:** tumour lysis syndrome

Conclusion

In summary, the front-line treatment paradigm of CLL continues to evolve, leading to substantial improvements in PFS and OS for patients. While continuous therapy may not be finite, the key decision is no longer simply what works, but rather what is best for the individual patient, underscoring the importance of a shared decision-making approach. This approach must thoughtfully integrate disease biology, patient comorbidities, treatment preferences, and practical considerations to optimize patient outcomes.

Correspondence

Stephanie Craig, MD
Email: StephanieE.Craig@nshealth.ca

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BCL2 =B-cell lymphoma 2.

* Comparative clinical significance is unknown.

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About the Authors

Andrew J. Cowan, MD

Dr. Andrew J. Cowan is Associate Professor of Medicine in the Division of Medical Oncology at the University of British Columbia and BC Cancer Agency, Vancouver, specializing in multiple myeloma, AL amyloidosis, and plasma cell disorders. He joined BCCA in November 2025 after establishing a robust clinical and research program at Fred Hutchinson Cancer Center and the University of Washington (2016–2025). Dr. Cowan's research has focused on novel immunotherapies for myeloma, particularly CAR T-cell therapies and bispecific antibodies. He served as principal investigator on the first-in-human trial combining gamma-secretase inhibition with fully human BCMA-directed CAR T cells, published in *The Lancet Oncology* (2023). His work spans clinical trials, global epidemiology, and AI applications in oncology, with 100+ peer-reviewed publications in journals including *NEJM, Blood, JAMA*, and *The Lancet*. Dr. Cowan serves as Deputy Editor of *ASH Clinical News* (2026–2028) and **hemonc.org**, where he leads development of structured oncology knowledge infrastructure and AI governance initiatives. He co-authored WHO Classification chapters on plasma cell myeloma and plasmacytoma, and published the landmark Global Burden of Disease analysis for multiple myeloma in *JAMA Oncology* (2018). He holds leadership positions with the International Myeloma Working Group (Immunotherapy Working Group), Canadian Myeloma Research Group (Clinical Trials Committee), and Worldwide Network for Blood & Marrow Transplantation. He is an active reviewer for major hematology journals including *NEJM, Blood*, and *Blood Advances*. Dr. Cowan received his MD from the University of Washington and completed fellowship training in Hematology-Oncology at Fred Hutchinson Cancer Center.

Affiliations: Division of Medical Oncology, BC Cancer Agency, Vancouver, B.C.
University of British Columbia, Vancouver, B.C.

Kevin Song, MD

Dr. Kevin Song is a Clinical Professor in the Division of Hematology at the University of British Columbia and Director of the Hematology Research Program at the Vancouver Coastal Health Research Institute. He serves as Medical Director of the Leukemia/Bone Marrow Transplant Program of British Columbia, where he oversees the province's largest malignant hematology group. Dr. Song completed his hematology training and leukemia/bone marrow transplant fellowship in Vancouver (1998–2001), followed by additional transplant training in Toronto before joining the Leukemia/BMT Program as attending staff in 2002. His clinical and research interests focus on the treatment of multiple myeloma and other plasma cell dyscrasias, and the use of hematopoietic stem cell transplantation to treat non-Hodgkin's lymphoma. He has been instrumental in establishing Vancouver's Hematology Research Unit, which provides patients access to cutting-edge clinical trials including CAR T-cell therapy and other novel treatments for blood cancers.

Affiliations: Division of Hematology, Leukemia and Bone Marrow Transplant Program of BC, Vancouver General Hospital, Vancouver, B.C.
University of British Columbia, Vancouver, B.C

Florian Kuchenbauer, MD

Dr. Florian Kuchenbauer is a Senior Scientist in the Terry Fox Laboratory and Clinical Scientist in the Leukemia and Bone Marrow Transplant Program of BC, as well as Associate Professor of Medicine at the University of British Columbia. He received his MD from Ludwig-Maximilians-University in Munich, Germany (2001), and completed his PhD at the Terry Fox Laboratory under Dr. Keith Humphries (2009). After establishing a successful research and clinical program at the Bone Marrow Transplantation Unit at the University of Ulm in Germany, he returned to Vancouver in 2018. Dr. Kuchenbauer's translational research program focuses on acute myeloid leukemia and multiple myeloma, utilizing preclinical animal models to better understand disease pathophysiology and develop novel treatments. He is internationally recognized for his work on APOBEC-driven disease mechanisms in multiple myeloma and has developed predictive scoring tools to improve patient stratification. He was awarded BC Cancer's Patient Care Champion Award in 2021 and the Outstanding Academic Performance Award in 2022, reflecting his dedication to both cutting-edge research and compassionate patient care.

Affiliations: Division of Hematology, Leukemia and Bone Marrow Transplant Program of BC, Vancouver General Hospital, Vancouver, B.C.
University of British Columbia, Vancouver, B.C.

Christopher P. Venner, MD

Dr. Christopher P. Venner is a hematologist at BC Cancer – Vancouver Centre, where he leads the Plasma Cell Dyscrasias Program. He completed his medical training at the University of Calgary and University of Alberta, followed by sub-specialty training in Hematology at the University of British Columbia. He pursued a Plasma Cell Dyscrasias Fellowship jointly through the Leukemia/Bone Marrow Transplant Program of British Columbia, St. Bartholomew's Hospital, the London School of Medicine, and the National Amyloidosis Centre in London, UK, where he subsequently served as a staff physician. From 2012 to 2021, he led the Malignant Hematology Program and Myeloma/Plasma Cell Dyscrasias group at the Cross Cancer Institute in Edmonton, where he pioneered Alberta's first province-wide clinical database for multiple myeloma to track treatment outcomes and inform clinical decisions. His clinical research focuses on plasma cell dyscrasias, examining the evolution of therapy in these diseases and the impact of real-world treatment outcomes. He serves on the NCI Myeloma Steering Committee and the Board of Directors of the Canadian Myeloma Research Group.

Affiliations: Division of Medical Oncology, BC Cancer Agency, Vancouver, B.C.
University of British Columbia, Vancouver, B.C.

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High-Risk Multiple Myeloma in 2026: Evolving Definitions and Therapeutic Options

Andrew J. Cowan, MD
Kevin Song, MD
Florian Kuchenbauer, MD
Christopher P. Venner, MD

Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by osteolytic bone disease, anemia, kidney disease, and hypercalcemia, resulting in significant morbidity compared to age-matched controls.[1] Treatment has advanced considerably over the past 20 years; the current standard of care involves treatment with quadruplet regimens combining a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and dexamethasone, with a CD38 monoclonal antibody.[2] Eligible and fit patients will proceed with autologous stem cell transplantation (ASCT), and, following initial therapy, all patients receive maintenance therapy, typically lenalidomide and a CD38 monoclonal antibody.[2] For elderly or frail patients, regimens such as daratumumab plus lenalidomide, or lenalidomide plus bortezomib, with or without dexamethasone, may be considered, but most patients will tolerate four drug regimens well.[3] These treatment combinations have resulted in dramatic improvements in both progression-free survival (PFS) and overall survival (OS); the phase III PERSEUS trial reported a 2-year PFS of 84.3%.[4] Even with the use of older triplet regimens and ASCT, real-world data document a median OS of ~10 years.[5,6]

However, not all patients will achieve these outcomes. A subset of patients with MM has poorer outcomes even with state-of-the-art treatment with quadruplet regimens, which is broadly defined as high-risk multiple myeloma (HRMM).[7] Patients with HRMM have earlier relapses, more aggressive disease biology, and shorter remissions with standard-of-care treatments. They can also be more prone to the development of aggressive presentations, such as extramedullary plasmacytomas (EMP), anaplastic morphology, and secondary plasma cell leukemia. The hallmark of all these subtypes is treatment refractoriness—defined as a lack of durable responses to standard effective treatments.

Herein, we review the definition of HRMM, outcomes with standard treatment, and preferred treatment approaches for a patient with *de novo* or functional HRMM in the Canadian treatment landscape.

Risk Factors

HRMM can be broadly thought of in two ways: one, through well-defined "classical" chromosomal changes or pathologic findings that increase risk of aggressive disease and early relapse; or, *dynamic* risk assessment (sometimes called functional HRMM) based on the early onset of progressive disease, often among patients without traditional high-risk markers.[8,9] It is likely that, with improved genomic risk assessments, many patients who were considered standard-risk MM may be better classified as HRMM, thereby improving the *a priori* risk assessment of newly diagnosed MM.[10,11]

In this review, we explore these concepts and develop a unified definition of HRMM before addressing the treatment approach to high-risk disease.

Current High-Risk Definitions

Chromosomal Factors

The most frequently used tool for MM risk assessment is chromosomal analysis by fluorescent in situ hybridization (FISH). The chromosomal changes considered to be high risk

Chromosomal Abnormalities	Details
Loss of *TP53*: chromosome 17	**Deletion 17p:** Deletion of the long arm of chromosome 17, resulting in loss of *TP53*[34] *TP53* mutations: mutations causing deactivation of the *TP53* gene[34] ***Must be present in ≥20% of nucleated cells to be significant, as per recent IMWG/IMS guidelines[8]
***IGH* translocations: chromosome 14, immunoglobulin heavy-chain locus at 14q32**	**t(4;14):** *FGFR3-IGH* translocation – deregulation of fibroblast growth factor[35] **t(14;16):** *MAF-IGH* translocation - deregulation of *c-MAF* proto-oncogene[36] **t(14;20):** *MAFB-IGH* translocation – deregulation of *MAFB* oncogene[37] **t(8;14):** *MYC-MAF* translocation – uncommon, results in rearrangement of MYC oncogene[38]
Chromosome 1 abnormalities	**1q+:** Gain (2 copies) vs. amplification (>3 copies); CKS1B – activation of cyclin dependent kinase, deregulation of cell cycle control[39] **Del(1p):** Several genes implicated; however, the underlying driver remains unknown[39]
Complex karyotype	≥3 chromosomal abnormalities on a conventional karyotype with G banding; associated with worse prognosis in many series[40]
Biologic Features	
Beta-2 microglobulin	Serum marker of tumor burden in newly diagnosed MM, with elevated values portending worse prognosis; may be affected by underlying kidney function[8] *New IMWG/IMS guidelines restrict this to patients with normal creatinine (<1.2 mg/dl or <106 µmol/L).
Lactate dehydrogenase (LDH)	Marker of cell turnover; elevated values above the upper limit of normal associated with more rapidly proliferative disease. Incorporated into the Revised ISS staging system[15]
Circulating tumour cells	Plasma cell leukemia – extreme example of this, defined as >5% circulating plasma cells on manual differential[17] The presence of any circulating plasma cells at the time of diagnosis, and prior to ASCT, has been shown to be a negative prognostic indicator in retrospective series[41]
Anaplastic morphology	Uncommon presentation, more commonly seen in relapsed multiple myeloma, treatment resistant and poor prognosis. Characterized by pathologic finding of poorly differentiated, pleomorphic, and significantly enlarged plasma cell[16]
Extramedullary disease	Generally defined as plasmacytomas arising outside the bone marrow, without direct connection to the bones. When presenting in a patient with newly diagnosed or relapsed disease, portends poor outcomes[42]

Table 1. High-Risk Features in Newly Diagnosed Multiple Myeloma; *courtesy of Andrew J. Cowan, MD, Kevin Song, MD, Florian Kuchenbauer, MD, and Christopher P. Venner, MD.*

Abbreviations: ASCT: autologous stem cell transplant; **HRMM:** high-risk multiple myeloma; **IMWG/IMS:** International Myeloma Working Group and International Myeloma Society

Criteria for HRMM[8]
Del(17p)* and/or *TP53* mutation**
IGH translocations: t(4;14), t(14;16), or t(14;20), co-occurring with 1q+ and/or del(1p32)
Monoallelic del(1p32) with 1q+, or biallelic del(1p32)
High beta-2 microglobulin (>5.5 mg/dL) with normal creatinine (<106 µmol/L)

Table 2. IMWG/IMS Consensus Genomic Criteria for High-Risk Multiple Myeloma; *adapted from Avet-Louiseau et al., JCO 2025.*[8]

*Cancer clonal fraction ≥20% by analyses of CD138-positive cells
**Assessed by a next-generation sequencing-based method

Abbreviations: HRMM: high-risk multiple myeloma; **1q+:** gain (3 copies) or amplification (>=4 copies) of the long arm of chromosome 1

in MM include chromosome 14 immunoglobulin heavy chain locus (*IGH*) translocations, including t(14;16), t(4;14), t(14;20); the deletion 17p resulting in loss of *TP53*; and chromosome 1 changes, such as the 1q gain or 1p deletion (**Table 1**).[8] Additionally, TP53 mutations have been associated with worse outcomes.[12] These risk factors form part of the recently published guidelines for determining high-risk disease.[8] Although many of these were originally defined in the context of doublet or triplet upfront treatment combinations, recent data continue to show the negative impact of these high-risk chromosomal changes, albeit with some nuance, and dramatically improved outcomes with quadruplet-based regimens.[13] Based on recent analyses of patients treated with quadruplet regimens in newly diagnosed MM, the presence of two or more high-risk cytogenetic features appears to confer the highest risk for early disease progression.[14]

Biologic Risk Factors

Several other surrogate markers can help understand which patients are more prone to aggressive disease biology (**Table 1**). Beta-2 microglobulin, included in the Revised International Staging System (R-ISS) for M15, is a surrogate marker of MM tumour volume. Further, anaplastic morphology, which can occur *de novo* but is more frequently described among patients with heavily treated MM, confers treatment resistance and poor outcomes.[16]

Plasma cell leukemia (PCL) is a high-risk subtype of MM, defined by the presence of >5% circulating plasma cells on the peripheral smear differential.[17] Although considered a separate diagnosis, it is just the leukemic phase of MM, representing a more advanced form of the disease. It may be present at diagnosis (primary PCL) or with relapse (secondary PCL). Patients with PCL have much poorer outcomes in general, even with the advent of modern therapies. The translocation t(11;14) is present in approximately half of patients with primary PCL and appears to be associated with improved prognosis.[18] Despite PCL being on the MM spectrum of disease, reflecting the most aggressive clinical phenotype, it is often excluded from trials, thereby limiting data that could contribute to optimizing treatment approaches.

Expert Driven High-Risk Criteria: The 2025 IMW/IMS High-Risk Classification

Recently, the International Myeloma Working Group and International Myeloma Society (IMW/IMS) published the results of a working group recommendation for the definition of HRMM. Considering the significant progress in treating newly diagnosed MM, the group aimed to improve on the previous International Staging System (ISS) and the revised ISS (R-ISS), which were developed using older datasets and treatments that are less relevant now. In summary, the group determined a new set of criteria, the Consensus Genomic Staging (CGS) of HRMM (**Table 2**).[8] These new criteria build on the R-ISS but also emphasize the importance of co-occurring chromosome 1 abnormalities and the significance of beta-2 microglobulin in patients with normal kidney function.

Primary Refractory/Functional HRMM

A different way to examine HRMM is not as an *a priori* determination, but rather as a dynamic assessment of risk over time. Several analyses have confirmed that patients who experience early relapse (often called functional HRMM [FHRMM]) have much more aggressive, treatment-resistant disease and poorer survival compared to other patients.[19-21] In the MRC XI trial, patients who experienced relapse within 12 months of ASCT had a 3-year OS of 28% compared to 53% amongst those who did not, with similar results reported in a French analysis.[22,23] In a subanalysis of the adaptive trial MASTER, which utilized daratumumab, carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) as front-line treatment, patients who relapsed within 36 months were a subset who fared poorly even with the successful use of salvage regimens.[24] Thus, patients who experience early relapse after successful front-line induction with triplets (<24 months) or quadruplet regimens (<36 months), should also be considered as having FHRMM irrespective of initial chromosomal abnormalities. Indeed, up to 44% of patients in the MASTER cohort who relapsed within 36 months did not have high-risk chromosomal changes at the time of diagnosis.

Identification of HRMM: Future Directions

Although we have refined our classification of HRMM using the recent IMWG/IMS CSG criteria, as evidenced by the emerging recognition of FHRMM, not all patients are accurately identified as having HRMM at the time of diagnosis. Better tools are needed to accurately identify these patients. Gene expression profiling (GEP) has been used to more accurately risk-stratify patients at diagnosis and has shown some success in categorizing patients better than traditional chromosomal analysis.[10,25] Two such tools are available: the GEP70/UAMS70 and the EMC92 assays; however, neither is broadly available in Canada, nor is it currently funded through public means.[25] For example, in one analysis of 94 patients using the GEP70/UAMS70 assay, relapse rates were 28% among patients with a high-risk GEP70 result but only 2% among those classified as low risk.[26] Additionally, early relapse was documented in 30% of patients with high-risk GEP70 scores and low-risk chromosomal abnormalities, but there were no patients with low-risk GEP70 scores and high-risk chromosomal changes who had early relapse.

Recent analyses have also implicated genomic signatures from the apolipoprotein B mRNA-editing catalytic polypeptide-like (APOBEC) family of deaminases as potentially driving MM progression, which may also help better classify HRMM at diagnosis. In a recent publication, APOBEC classifiers were shown to help improve MM risk assessment.[27] In another recent analysis of newly diagnosed MM in the CoMMpass study, high APOBEC mRNA expression was associated with hyper-APOBEC mutations and was more common in MM cells with genomic instability and increased replication stress.[28]

Taken together, gene expression profiling and a better understanding of the importance of APOBEC expression patterns may be promising modalities for improved risk assessment. At present, GEP panels are limited globally, so further efforts are needed to expand access across all MM treatment centres.

Therapeutic Options

One of the major challenges in treating HRMM has been the lack of high-quality, randomized, prospective trials in this patient population. As such, guidance for the management of HRMM has often been based on expert opinion, sometimes informed by retrospective analyses and datasets. In general, however, the treatment of newly diagnosed HRMM, as defined above, would involve applying the standard treatment algorithms for newly diagnosed MM in Canada. Presently, this would be with a quadruplet regimen containing an anti-CD38 monoclonal antibody, IMiD, PI, and dexamethasone, with ASCT in eligible patients, followed by consolidation quadruplet therapy, after which the patient will receive anti-CD38 antibody and lenalidomide maintenance. For years, older trials, such as the HOVON-65 trial, demonstrated the apparent superiority of bortezomib in patients with certain high-risk chromosomal abnormalities, leading some expert recommendations to advise the use of PIs for maintenance in HRMM.[29] However, the data that support these recommendations are not consistent with modern treatment paradigms. These studies had control arms ranging from observation, steroids, or thalidomide treatment. There is no prospective comparison of bortezomib and lenalidomide, and more contemporary approaches suggest that multi-agent maintenance is the most beneficial for these patients. This could be achieved with prolonged PI-IMiD combinations

(challenging given long-term neuropathy risk, time toxicity, and general tolerability) or, more recently, with an anti-CD38 antibody and lenalidomide. The latter are now recommended based on large, randomized trials, such as PERSEUS, CEPHEUS, GMMG-HD7, and IMROZ.[4,30-32]

For patients who experience early relapse, the next line of therapy must consider the refractoriness status to previously used therapies. Looking ahead, these patients have usually been exposed to and are almost universally resistant to both anti-CD38 antibodies and lenalidomide. In a recent analysis of patients with FHRMM from the MASTER trial (all of whom received front-line quadruplet therapy), the best results appeared to be achieved with T cell-engaging therapies (TCE), such as bispecific antibodies or chimeric antigen receptor (CAR) T-cell therapy.[24] Presently, many jurisdictions await funding of CAR T-cell therapy for early relapse. Even when available, these high-risk patients face a challenging path to treatment given the potential of high tumour burden and rapidly progressing disease prior to CAR T-cell infusion. While bispecific antibodies are more accessible, access is often restricted to patients who have reached the 4th treatment line or beyond. Ideally, if access were not an issue, these patients should be sequenced early in relapse. Both retrospective (*post-hoc* analysis of MASTER) and prospective (MajesTEC3) data highlight the impressive depth of responses and encouraging PFS regardless of cytogenic risk.[33] More data are needed on the durability of the response in FHRMM. However, it is important to reiterate that outcomes with more traditional regimens in either a primary refractory or early relapse setting after lenalidomide + anti-CD38 are abysmal.

Summary

Although definitions have evolved over the years, specific chromosomal abnormalities and combinations, as well as elevated beta-2 microglobulin, remain the cornerstone of defining HRMM. Patients with MM who meet the new CSG criteria for high-risk disease, or those who have early relapse (FHRMM), fare poorly compared to other patients. Although benefits from modern MM treatment with quadruplet regimens, ASCT, and dual CD38/IMiD maintenance are observed, a proportion of patients have less durable remissions or outright refractoriness. These patients require novel approaches after establishing triple-class-exposed/refractory status. Early use of TCE therapies should be considered and advocated for. Overall, better tools are necessary to *a priori* define these high-risk patient populations with definitions tailored to the specific therapeutic context.

Correspondence

Andrew J. Cowan, MD
Email: andrew.cowan@bccancer.bc.ca

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Count on CALQUENCE's Experience

5 indications combined across CLL and MCL[1,2]

- **2019:** Previously untreated CLL, as monotherapy or with obinutuzumab
- **2019:** Previously treated CLL, as monotherapy
- **2019:** Previously treated MCL, as monotherapy
- **2025:** Previously untreated CLL, with venetoclax
- **2025:** Previously untreated MCL, with bendamustine + rituximab

5+ years of market availability in Canada (as CLL monotherapy)[3†]

5 Phase 3 trials: AMPLIFY, ELEVATE-TN, ASCEND, ELEVATE-RR, ECHO[1,4]

Visit **calquence.ca** to access more resources, information, and patient materials.

CALQUENCE (acalabrutinib tablets) is indicated:

- in combination with obinutuzumab or as monotherapy for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- in combination with venetoclax for the treatment of patients with previously untreated CLL
- as monotherapy for the treatment of patients with CLL who have received at least one prior therapy
- in combination with bendamustine and rituximab for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous stem cell transplant
- as monotherapy for the treatment of patients with MCL who have received at least one prior therapy

Please consult the Product Monograph at calquence-tablet-en.azpm.ca for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling us at 1-800-668-6000.

† Clinical significance has not been established.

References: 1. CALQUENCE (acalabrutinib tablets) Product Monograph. AstraZeneca Canada Inc. **2.** Data on file – CALQUENCE indication dates. October 20, 2025. **3.** Health Canada Notice of Compliance Database. CALQUENCE (2019-08-23). Accessed at: https://health-products.canada.ca/noc-ac/nocInfo?no=22572. **4.** Byrd JC, *et al*. Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. *J Clin Oncol*. 2021;39(31):3441-3452.

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