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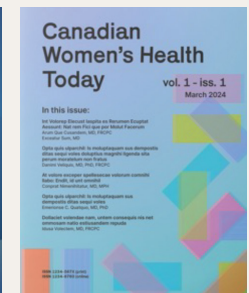
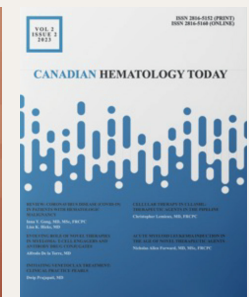
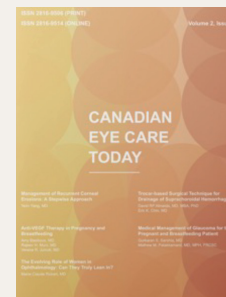
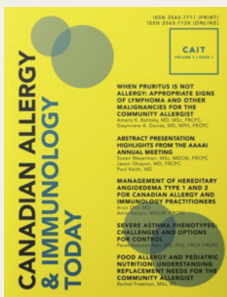
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About the Authors



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.

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

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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References

1. Canadian Cancer Statistics Advisory Committee in collaboration with the Canadian Cancer Society, Statistics Canada and the Public Health Agency of Canada. Canadian Cancer Statistics 2025. Toronto, ON: Canadian Cancer Society; 2025 [accessed 2026 Apr 6]. Available from: cancer.ca/Canadian-Cancer-Statistics-2025-EN
2. Rodday AM, Evens AM, Maurer MJ, Upshaw JN, Counsell N, Rossetti S, et al. An individualized prediction model for early-stage classic Hodgkin's lymphoma. *NEJM Evid.* 2025;4(9):EVIDoa2500115. doi:10.1056/EVIDoa2500115
3. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med.* 1998;339(21):1506–1514. doi:10.1056/NEJM199811193392104
4. Moccia AA, Donaldson J, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ, et al. International Prognostic Score in advanced-stage Hodgkin's lymphoma: altered utility in the modern era. *J Clin Oncol.* 2012;30(27):3383–3388. doi:10.1200/JCO.2011.41.0910
5. Borchmann P, Ferdinandus J, Schneider G, Moccia A, Greil R, Hertzberg M, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. *Lancet.* 2024;404(10450):341–352. doi:10.1016/S0140-6736(24)01315-1
6. Herrera AF, LeBlanc M, Friedberg JW. Nivolumab+AVD in advanced-stage classic Hodgkin's lymphoma. Reply. *N Engl J Med.* 2025;392(1):102. doi:10.1056/NEJMc2414269
7. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;385(9980):1853–1862. doi:10.1016/S0140-6736(15)60165-9
8. Spinner MA, Sica RA, Tamaresis JS, Lu Y, Chang C, Lowsky R, et al. Improved outcomes for relapsed/refractory Hodgkin lymphoma after autologous transplantation in the era of novel agents. *Blood.* 2023;141(22):2727–2737. doi:10.1182/blood.2022018827
9. Bröckelmann PJ, Müller H, Gillesen S, Yang X, Koeppel L, Pilz V, et al. Clinical outcomes of relapsed and refractory Hodgkin lymphoma patients after contemporary first-line treatment: a German Hodgkin Study Group analysis. *Leukemia.* 2022;36(3):772–780. doi:10.1038/s41375-021-01442-8
10. Davies GA, Orav JE, Brantley KD. Survival Outcomes for US and Canadian patients diagnosed with Hodgkin lymphoma before and after brentuximab vedotin approval for relapsed/refractory disease: a retrospective cohort study. *Curr Oncol.* 2024;31(7):3885–3894. doi:10.3390/curroncol31070287
11. Canada's Drug Agency. CADTH reimbursement recommendation pembrolizumab (Keytruda). Canadian Journal of Health Technologies. 2021;1(11):1–16. Available from: <https://www.cda-amc.ca/sites/default/files/DRR/2021/PC0236%20Keytruda%20-%20CADTH%20Final%20Rec%20Final.pdf>

12. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341(8852):1051–1054. doi:10.1016/0140-6736(93)92411-I
13. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359(9323):2065–2071. doi:10.1016/S0140-6736(02)08938-9
14. Sureda A, Genadieva Stavrik S, Boumendil A, Finel H, Khvedelidze I, Dietrich S, et al. Changes in patients population and characteristics of hematopoietic stem cell transplantation for relapsed/refractory Hodgkin lymphoma: an analysis of the Lymphoma Working Party of the EBMT. *Bone Marrow Transplant*. 2020;55(11):2170–2179. doi:10.1038/s41409-020-0929-y
15. Shafey M, Duan Q, Russell J, Duggan P, Balogh A, Stewart DA. Double high-dose therapy with dose-intensive cyclophosphamide, etoposide, cisplatin (DICEP) followed by high-dose melphalan and autologous stem cell transplantation for relapsed/refractory Hodgkin lymphoma. *Leuk Lymphoma*. 2012;53(4):596–602. doi:10.3109/10428194.2011.624227
16. Desai SH, Spinner MA, Sykora A, Bachanova V, Evens AM, Goyal G, Kahl BS, Dorritie K, Azzi J, Kenkre VP, Chang C. Outcomes of autologous stem cell transplant in older adults with relapsed/refractory classic Hodgkin lymphoma. *Blood*. 2024;144 (Supplement 1):570. <https://doi.org/10.1182/blood-2024-199845>
17. Epperla N, Huang Y, Cashen AF, Vaughn JL, Hanel W, Badar T, et al. Evaluation of prognostic factors in patients with high-risk classical Hodgkin lymphoma undergoing autologous transplantation. *Blood Adv*. 2024;8(21):5458–5466. doi:10.1182/bloodadvances.2024013743
18. Bröckelmann PJ, Goergen H, Kohnhorst C, von Tresckow B, Moccia A, Markova J, et al. Late relapse of classical Hodgkin lymphoma: an analysis of the German Hodgkin Study Group HD7 to HD12 Trials. *J Clin Oncol*. 2017;35(13):1444–1450. doi:10.1200/JCO.2016.71.3289
19. Moccia AA, Hitz F, Hoskins P, Klasa R, Power MM, Savage KJ, et al. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. *Leuk Lymphoma*. 2017;58(2):324–332. doi:10.1080/10428194.2016.1193852
20. Kuruvilla J, Nagy T, Pintilie M, Tsang R, Keating A, Crump M. Similar response rates and superior early progression-free survival with gemcitabine, dexamethasone, and cisplatin salvage therapy compared with carmustine, etoposide, cytarabine, and melphalan salvage therapy prior to autologous stem cell transplantation for recurrent or refractory Hodgkin lymphoma. *Cancer*. 2006;106(2):353–360. doi:10.1002/cncr.21587
21. Moskowitz CH, Nimer SD, Zelenetz AD, Trippett T, Hedrick EE, Filippa DA, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. *Blood*. 2001;97(3):616–623. doi:10.1182/blood.v97.3.616
22. Josting A, Rudolph C, Reiser M, Mapara M, Sieber M, Kirchner HH, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. *Ann Oncol*. 2002;13(10):1628–1635. doi:10.1093/annonc/mdf221
23. Bartlett NL, Niedzwiecki D, Johnson JL, Friedberg JW, Johnson KB, van Besien K, et al. Gemcitabine, vinorelbine, and pegylated liposomal doxorubicin (GVD), a salvage regimen in relapsed Hodgkin's lymphoma: CALGB 59804. *Ann Oncol*. 2007;18(6):1071–1079. doi:10.1093/annonc/mdm090
24. Gerrie AS, Power MM, Shepherd JD, Savage KJ, Sehn LH, Connors JM. Chemoresistance can be overcome with high-dose chemotherapy and autologous stem-cell transplantation for relapsed and refractory Hodgkin lymphoma. *Ann Oncol*. 2014;25(11):2218–2223. doi:10.1093/annonc/mdu387
25. Moskowitz AJ, Yahalom J, Kewalramani T, Maragulia JC, Vanak JM, Zelenetz AD, et al. Pretransplantation functional imaging predicts outcome following autologous stem cell transplantation for relapsed and refractory Hodgkin lymphoma. *Blood*. 2010;116(23):4934–4937. doi:10.1182/blood-2010-05-282756
26. Desai SH, Moskowitz AJ, Merryman RW, Shah H, Pederson LD, Geyer SM, et al. PD-1-based combinations before autologous transplant are associated with improved outcomes in classical Hodgkin lymphoma. *Blood*. 2026;147(10):1125–1134. doi:10.1182/blood.2025030151
27. Moskowitz CH, Matasar MJ, Zelenetz AD, Nimer SD, Gerecitano J, Hamlin P, et al. Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. *Blood*. 2012;119(7):1665–1670. doi:10.1182/blood-2011-10-388058
28. Moskowitz AJ, Schöder H, Yahalom J, McCall SJ, Fox SY, Gerecitano J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. *Lancet Oncol*. 2015;16(3):284–292. doi:10.1016/S1470-2045(15)70013-6
29. LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. *Blood*. 2018;132(1):40–48. doi:10.1182/blood-2017-11-815183
30. Chen R, Palmer JM, Martin P, Tsai N, Kim Y, Chen BT, et al. Results of a multicenter phase ii trial of brentuximab vedotin as second-line therapy before autologous transplantation in relapsed/refractory Hodgkin lymphoma. *Biol Blood Marrow Transplant*. 2015;21(12):2136–2140. doi:10.1016/j.bbmt.2015.07.018
31. Stamatoullas A, Ghesquières H, Feugier P, André M, Le Bras F, Gac AC, et al. Final results of brentuximab vedotin combined with ifosfamide-carboplatin-etoposide in first refractory/relapsed Hodgkin lymphoma: a lymphoma study association phase I/II study. *Leuk Lymphoma*. 2022;63(13):3063–3071. doi:10.1080/10428194.2022.2107204

32. Kersten MJ, Driessen J, Zijlstra JM, Plattel WJ, Morschhauser F, Lugtenburg PJ, et al. Combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC Transplant BRaVE study. *Haematologica*. 2021;106(4):1129–1137. doi:10.3324/haematol.2019.243238
33. Balari AM, Cespedes JN, Castera MJ, Hernandez FM, Domenech ED, De la Cruz Vicente F, et al. The addition of brentuximab vedotin to ESHAP significantly increases the rate of metabolic complete remissions vs chemotherapy alone. in patients with relapsed/refractory classical Hodgkin's lymphoma. Final results of a phase iib prospective randomized clinical trial (BRESELIBET). *Blood*. 2024;144 (Supplement 1):3049. <https://doi.org/10.1182/blood-2024-211527>
34. Moskowitz AJ, Shah G, Schöder H, Ganesan N, Drill E, Hancock H, et al. Phase II trial of pembrolizumab plus gemcitabine, vinorelbine, and liposomal doxorubicin as second-line therapy for relapsed or refractory classical Hodgkin lymphoma. *J Clin Oncol*. 2021;39(28):3109–3117. doi:10.1200/JCO.21.01056
35. Bryan LJ, Casulo C, Allen PB, Smith SE, Savas H, Dillehay GL, et al. Pembrolizumab added to ifosfamide, carboplatin, and etoposide chemotherapy for relapsed or refractory classic Hodgkin lymphoma: a multi-institutional phase 2 investigator-initiated nonrandomized clinical trial. *JAMA Oncol*. 2023;9(5):683–691. doi:10.1001/jamaoncol.2022.7975
36. Mei MG, Lee HJ, Palmer JM, Chen R, Tsai NC, Chen L, et al. Response-adapted anti-PD-1-based salvage therapy for Hodgkin lymphoma with nivolumab alone or in combination with ICE. *Blood*. 2022;139(25):3605–3616. doi:10.1182/blood.2022015423
37. Mei M, Palmer J, Lee HJ, Isufi I, Chen R, Tsai NC, et al. Nivolumab plus ifosfamide, carboplatin, and etoposide are a highly effective first salvage regimen in high-risk relapsed/refractory Hodgkin lymphoma. *Hemasphere*. 2025;9(5):e70126. doi:10.1002/hem3.70126
38. Advani RH, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood*. 2021;138(6):427–438. doi:10.1182/blood.2020009178
39. Ding K, Liu H, Ma J, Yang H, Cao L, Wang H, et al. Tislelizumab with gemcitabine and oxaliplatin in patients with relapsed or refractory classic Hodgkin lymphoma: a multicenter phase II trial. *Haematologica*. 2023;108(8):2146–2154. doi:10.3324/haematol.2022.282266
40. Merryman RW, Redd RA, Nishihori T, Chavez J, Nieto Y, Darrah JM, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. *Blood Adv*. 2021;5(6):1648–1659. doi:10.1182/bloodadvances.2020003556
41. Canada's Drug Agency. CADTH reimbursement recommendation brentuximab vedotin (Adcetris). *Canadian Journal of Health Technologies*. 2024;4(9):1–24. Available from: <https://www.cda-amc.ca/sites/default/files/DRR/2024/PC0371REC-Adcetris.pdf>
42. Nishimura Y, Han Y, Toumeh N, Janda G, Fujiwara Y, Durani U, et al. Outcomes of immune checkpoint inhibitor rechallenge in relapsed/refractory Hodgkin lymphoma. *Blood Neoplasia*. 2025;2(3):100134. doi:10.1016/j.bneo.2025.100134
43. Bazarbachi A, Boumendil A, Finel H, Mohty M, Castagna L, Blaise D, et al. Brentuximab vedotin for recurrent Hodgkin lymphoma after allogeneic hematopoietic stem cell transplantation: a report from the EBMT Lymphoma Working Party. *Cancer*. 2019;125(1):90–98. doi:10.1002/cnrc.31755
44. Voorhees TJ, McLaughlin EM, Torka P, Florindez J, Kim NH, Moyo TK, et al. Outcomes in patients with classic Hodgkin lymphoma refractory or intolerant to brentuximab vedotin and anti-PD-1 therapy: a real world analysis from 15 U.S. academic centers. *Blood Cancer J*. 2025;15(1):45. doi:10.1038/s41408-025-01257-1
45. Moskowitz A, Shah GL, Ganesan N, Chang T, Drill E, Davey T, Hancock H, Munayirji B, Douglas M, Santarosa AM, Casper E. Pembrolizumab maintenance instead of autologous hematopoietic cell transplantation for patients with relapsed or refractory Hodgkin lymphoma in complete response after pembrolizumab, gemcitabine, vinorelbine, and liposomal doxorubicin.
46. Hoppe BS, Milgrom SA, Renfro LA, Wu Y, Schwartz CL, Constine LS, et al. Transplant-free salvage therapy for low-risk relapsed pediatric Hodgkin lymphoma: a nonrandomized clinical trial. *JAMA Oncol*. 2025;11(3):340–342. doi:10.1001/jamaoncol.2024.5648
47. Daw S, Claviez A, Kurch L, Stoevesandt D, Attarbaschi A, Balwierz W, et al. Transplant and nontransplant salvage therapy in pediatric relapsed or refractory Hodgkin lymphoma: The EuroNet-PHL-R1 phase 3 nonrandomized clinical trial. *JAMA Oncol*. 2025;11(3):258–267. doi:10.1001/jamaoncol.2024.5636
48. Daw S, Cole PD, Hoppe BS, Hodgson D, Beishuizen A, Garnier N, et al. Transplant-free approach in relapsed Hodgkin lymphoma in children, adolescents, and young adults: a nonrandomized clinical trial. *JAMA Oncol*. 2025;11(3):249–257. doi:10.1001/jamaoncol.2024.5627

49. Moskowitz CH, Walewski J, Nademanee A, Masszi T, Agura E, Holowiecki J, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. *Blood*. 2018;132(25):2639–2642. doi:10.1182/blood-2018-07-861641
50. Wagner CB, Boucher K, Nedved A, Micallef IN, Desai S, Hatic H, et al. Effect of cumulative dose of brentuximab vedotin maintenance in relapsed/refractory classical Hodgkin lymphoma after autologous stem cell transplant: an analysis of real-world outcomes. *Haematologica*. 2023;108(11):3025–3032. doi:10.3324/haematol.2023.282780
51. Martínez C, Khvedelidze I, Fekom M, Deau Fischer B, Marouf A, Ghesquière H, et al. Outcomes of patients with Hodgkin lymphoma receiving Brentuximab Vedotin (BV) as maintenance therapy after ASCT according to previous exposure to BV. A retrospective analysis of the EBMT Lymphoma Working Party in collaboration with GELTAMO, FIL, LYSA, and Turkish Lymphoma Group. *Bone Marrow Transplant*. 2025;60(6):879–887. doi:10.1038/s41409-025-02568-4
52. Falade AS, Redd R, Desai SH, Moskowitz AJ, Shah HR, Geyer S, et al. Impact of Novel Therapies on the Efficacy of Post-Transplantation Brentuximab Vedotin Maintenance in Hodgkin Lymphoma. *Blood Adv*. Published online March 27, 2026. doi:10.1182/bloodadvances.2025018683
53. Böll B, Goergen H, Arndt N, Meissner J, Krause SW, Schnell R, et al. Relapsed hodgkin lymphoma in older patients: a comprehensive analysis from the German hodgkin study group. *J Clin Oncol*. 2013;31(35):4431–4437. doi:10.1200/JCO.2013.49.8246
54. Kuruvilla J, Ramchandren R, Santoro A, Paszkiewicz-Kozik E, Gasiorowski R, Johnson NA, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol*. 2021;22(4):512–524. doi:10.1016/S1470-2045(21)00005-X
55. Cheson BD, Ansell S, Schwartz L, Gordon LI, Advani R, Jacene HA, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. *Blood*. 2016;128(21):2489–2496. doi:10.1182/blood-2016-05-718528
56. Merryman RW, Carreau NA, Advani RH, Spinner MA, Herrera AF, Chen R, et al. Impact of Treatment Beyond Progression with Immune Checkpoint Blockade in Hodgkin Lymphoma. *Oncologist*. 2020;25(6):e993–e997. doi:10.1634/theoncologist.2020-0040
57. Cohen JB, Engert A, Ansell SM, Younes A, Trneny M, Savage KJ, Ramchandren R, Collins G, Fanale MA, Armand P, Zinzani PL. Nivolumab treatment beyond investigator-assessed progression: outcomes in patients with relapsed/refractory classical Hodgkin lymphoma from the phase 2 Checkmate 205 study. *Blood*. 2017;130 (Supplement 1):650. https://doi.org/10.1182/blood.V130.Suppl_1.650.650
58. Armand P, Zinzani PL, Lee HJ, Johnson NA, Brice P, Radford J, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. *Blood*. 2023;142(10):878–886. doi:10.1182/blood.2022019386
59. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study. *Blood Adv*. 2023;7(20):6266–6274. *Blood Adv*. 2024;8(4):829–831. doi:10.1182/bloodadvances.2023012353. Erratum for: *Blood Adv*. 2023 Oct 24;7(20):6266–6274. doi:10.1182/bloodadvances.2023010334
60. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. *Blood*. 2016;128(12):1562–1566. doi:10.1182/blood-2016-02-699850
61. Josting A, Nogová L, Franklin J, Glossmann JP, Eich HT, Sieber M, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: a retrospective analysis from the German Hodgkin Lymphoma Study Group. *J Clin Oncol*. 2005;23(7):1522–1529. doi:10.1200/JCO.2005.05.022
62. Mei M, Chen L, Godfrey J, Song J, Egelston C, Puverel S, et al. Pembrolizumab plus vorinostat induces responses in patients with Hodgkin lymphoma refractory to prior PD-1 blockade. *Blood*. 2023;142(16):1359–1370. doi:10.1182/blood.2023020485
63. Moskowitz AJ, Hamlin PA, Perales MA, Gerecitano J, Horwitz SM, Matasar MJ, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2013;31(4):456–460. doi:10.1200/JCO.2012.45.3308
64. Johnston PB, Inwards DJ, Colgan JP, Laplant BR, Kabat BF, Habermann TM, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. *Am J Hematol*. 2010;85(5):320–324. doi:10.1002/ajh.21664
65. Fehniger TA, Larson S, Trinkaus K, Siegel MJ, Cashen AF, Blum KA, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. *Blood*. 2011;118(19):5119–5125. doi:10.1182/blood-2011-07-362475
66. Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T Cell Therapy in Relapsed and Refractory Hodgkin Lymphoma. *J Clin Oncol*. 2020;38(32):3794–3804. doi:10.1200/JCO.20.01342
67. Nieto Y, Banerjee P, Kaur I, Basar R, Li Y, Daher M, et al. Allogeneic NK cells with a bispecific innate cell engager in refractory relapsed lymphoma: a phase 1 trial. *Nat Med*. 2025;31(6):1987–1993. doi:10.1038/s41591-025-03640-8

68. Herrera AF, Ansell SM, Zinzani PL, Radford J, Maddocks K, Pinto A, et al. Camidanlumab tesirine for relapsed or refractory classic Hodgkin lymphoma: a phase 2 study. *Blood Adv*. 2025;9(23):6205–6217. doi:10.1182/bloodadvances.2024015600
69. Timmerman J, Lavie D, Johnson NA, Avigdor A, Borchmann P, Andreadis C, et al. Favezelimab (anti-LAG-3) plus pembrolizumab in patients with relapsed or refractory (R/R) classical Hodgkin lymphoma (cHL) after anti-PD-1 treatment: an open-label phase 1/2 study [Abstract]. *J Clin Oncol*. 2022;40(16 suppl). doi:10.1200/JCO.2022.40.16_suppl.7545
70. Perales MA, Awan FT, Boumendil A, Patel J, Castagna L, Angelucci E, et al. Outcomes of allogeneic HCT in Hodgkin lymphoma in the era of checkpoint inhibitors: a joint CIBMTR and EBMT analysis. *Blood*. 2025;146(8):1011–1029. doi:10.1182/blood.2024027197
71. Tabbara N, Zahurak M, Sterling CH, Trutzer IM, Jedrych J, Swinnen LJ, et al. Improved overall survival with checkpoint inhibition and allogeneic transplantation in relapsed Hodgkin lymphoma. *Blood Adv*. 2025;9(5):1202–1209. doi:10.1182/bloodadvances.2024015048
72. Merryman RW, Castagna L, Giordano L, Ho VT, Corradini P, Guidetti A, et al. Allogeneic transplantation after PD-1 blockade for classic Hodgkin lymphoma. *Leukemia*. 2021;35(9):2672–2683. doi:10.1038/s41375-021-01193-6
73. Montoro J, Ngoya M, Kulagin A, Giebel S, Broers AEC, Bramanti S, et al. PTCy vs CNL-based GVHD prophylaxis in HLA-matched transplants for Hodgkin lymphoma: a study of the LWP of the EBMT. *Blood Adv*. 2024;8(15):3985–3992. doi:10.1182/bloodadvances.2024013328
74. Ahmed S, Kumar A, Carpenter P, Herrera A, Kelly K, Pinnix C, et al. American Society of Transplantation and Cellular Therapy Clinical Practice Recommendations for Transplantation in Classical Hodgkin Lymphoma. *Transplant Cell Ther*. 2026;32(3):250–260. doi:10.1016/j.jtct.2025.12.944
75. Peggs KS, Kayani I, Edwards N, Kottaridis P, Goldstone AH, Linch DC, et al. Donor lymphocyte infusions modulate relapse risk in mixed chimeras and induce durable salvage in relapsed patients after T-cell-depleted allogeneic transplantation for Hodgkin's lymphoma. *J Clin Oncol*. 2011;29(8):971–978. doi:10.1200/JCO.2010.32.1711
76. Peggs KS, Hunter A, Chopra R, Parker A, Mahendra P, Milligan D, et al. Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation. *Lancet*. 2005;365(9475):1934–1941. doi:10.1016/S0140-6736(05)66659-7

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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 cyto-reduction (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/m² IV over 30 min, D 1–5 - Cytarabine, 2000 mg/m² IV over 4 h, D 1–5^A - Idarubicin 10 mg/m² 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/m² IV , D 2–6 - Cytarabine, 1500 mg/m² IV, D 2–6 - Idarubicin, 6 mg/m² 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/m² IV, D 1–6^D - Etoposide 80 mg/m² IV, D 1–6 - Intermediate-dose Cytarabine 1000 mg/m² IV D 1–6	66 (21/32) ^E	4 (0.5–29.5) ^F	[14]
Azacitidine plus Venetoclax	- Azacitidine, 75 mg/m² 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.

^AFour hours after fludarabine infusion

^BThe idarubicin dose and duration differ for the newly diagnosed (8 mg/m² D4–6) and R/R (6 mg/m² D4–5) cohorts

^CVenetoclax is given for 7 days each cycle and requires dose adjustment with concurrent administration of CYP3A4 inhibitors

^DThe 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/m² IV x 5 days, etoposide 100 mg/m² x 5 days and cytarabine 1000 mg/m² x 5 days

^ECR rate, not ORR

^FVenetoclax requires dose adjustment with concurrent administration of CYP3A4 inhibitors

^GGilteritinib 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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References

- Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood*. 2022;140(12):1345-1377.
- Burnett AK, Russell NH, Hills RK, Kell J, Cavenagh J, Kjeldsen L, et al. A randomized comparison of daunorubicin 90 mg/m² vs 60 mg/m² in AML induction: results from the UK NCRI AML17 trial in 1206 patients. *Blood*. 2015;125(25):3878-3885. doi:10.1182/blood-2015-01-623447.
- DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629. doi:10.1056/NEJMoa2012971
- Ding L, Ley TJ, Larson DE, Miller CA, Koboldt DC, Welch JS, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature*. 2012;481(7382):506-510. doi:10.1038/nature10738.
- Bataller A, Kantarjian H, Bazinet A, Kadia T, Daver N, DiNardo CD, et al. Outcomes and genetic dynamics of acute myeloid leukemia at first relapse. *Haematologica*. 2024;109(11):3543-3556. doi:10.3324/haematol.2024.285057.
- Nuno K, Azizi A, Koehnke T, Lareau C, Ediriwickrema A, Ryan Corces M, et al. Epigenetic evolution and convergent chromatin states in relapsed acute myeloid leukemia. *eLife*. 2024;13:e93019. doi:10.7554/eLife.93019.
- Esposito MT, So CWE. DNA damage accumulation and repair defects in acute myeloid leukemia: implications for pathogenesis, disease progression, and chemotherapy resistance. *Chromosoma*. 2014;123(6):545-61.
- Short NJ, Konopleva M, Kadia TM, Daver N. How I treat refractory and relapsed acute myeloid leukemia. *Blood*. 2024;143(1):11-24.
- Pastore D, Specchia G, Carluccio P, Liso A, Mestice A, Rizzi R, et al. FLAG-IDA in the treatment of refractory/relapsed acute myeloid leukemia: single-center experience. *Ann Hematol*. 2003;82(4):231-5. doi:10.1038/s41375-025-02531-8
- DiNardo CD, Jen WY, Takahashi K, Kadia TM, Loghavi S, Daver NG, et al. Long-term results of venetoclax combined with FLAG-IDA induction and consolidation for newly diagnosed and relapsed or refractory acute myeloid leukemia. *Leukemia*. 2025;39(4):854-863. doi:10.1038/s41375-025-02531-8
- Shahswar R, Beutel G, Gabdoulline R, Schwarzer A, Kloos A, Koenecke C, et al. Fludarabine, cytarabine, and idarubicin with or without venetoclax in patients with relapsed/refractory acute myeloid leukemia. *Haematologica*. 2024;109(1):72-83.
- Amadori S, Arcese W, Isacchi G, Meloni G, Petti MC, Monarca B, et al. Mitoxantrone, etoposide, and intermediate-dose cytarabine: an effective and tolerable regimen for the treatment of refractory acute myeloid leukemia. *J Clin Oncol*. 1991;9(7):1210-1214.
- Silva WF, Da Rosa LI, Seguro FS, Silveira DRA, Nardinelli L, Buccheri V, et al. Retrospective comparison between MEC and FLAG-Ida regimens for refractory or relapsed acute myeloid leukemia in adults. *Blood*. 2019;134(Suppl_1):1354.
- Aldoss I, Yang D, Pillai R, Sanchez JF, Mei M, Aribi A, et al. Association of leukemia genetics with response to venetoclax and hypomethylating agents in relapsed/refractory acute myeloid leukemia. *Am J Hematol*. 2019;94(10):E253-E255.
- Unglaub JM, Schlenk RF, Middeke JM, Krause SW, Kraus S, Einsele H, et al. Venetoclax-based salvage therapy as a bridge to transplant is feasible and effective in patients with relapsed/refractory AML. *Blood Adv*. 2025;9(2):375-386.
- Perl AE, Martinelli G, Cortes JE, Neubauer A, Berman E, Paolini S, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
- Short NJ, Daver N, DiNardo CD, Kadia T, Nasr LF, Macaron W, et al. Azacitidine, venetoclax, and gilteritinib in newly diagnosed and relapsed or refractory FLT3-mutated acute myeloid leukemia. *J Clin Oncol*. 2024;42(13):1499-1508. doi:10.1200/JCO.23.01911.

18. Daver N, Perl AE, Maly J, Levis M, Ritchie E, Litzow M, et al. Venetoclax plus gilteritinib for FLT3-mutated relapsed or refractory acute myeloid leukemia. *J Clin Oncol*. 2022;40(35):4048-4059. doi:10.1200/JCO.22.00602.
19. DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory acute myeloid leukemia. *N Engl J Med*. 2018;378(25):2386-2398.
20. de Botton S, Montesinos P, Schuh AC, Papayannidis C, Vyas P, Wei AH, et al. Enasidenib vs conventional care in older patients with late-stage mutant-IDH2 relapsed/refractory AML: a randomized phase 3 trial. *Blood*. 2023;141(2):156-167.
21. Issa GC, Aldoss I, Thirman MJ, DiPersio J, Arellano M, Blachly JS, et al. Menin inhibition with revumenib for KMT2A-rearranged relapsed or refractory acute leukemia (AUGMENT-101). *J Clin Oncol*. 2025;43(1):75-84. doi:10.1200/JCO.24.00826.
22. Searle E, Recher C, Abdul-Hay M, Abedin S, Aldoss I, Alfonso Pierola A, et al. Bleximenib dose optimization and determination of recommended phase 2 dose (RP2D) from a phase 1 study in relapsed/refractory acute leukemia patients with KMT2A and NPM1 alterations. *Blood*. 2024;144(Suppl 1):212-214. doi:10.1182/blood-2024-207106.
23. Weisdorf D. Allogeneic transplantation for advanced acute leukemia. *Hematology Am Soc Hematol Educ Program*. 2022;2022(1):534-8.
24. Stelljes M, Middeke JM, Bug G, Wagner-Drouet EM, Müller LP, Schmid C, et al. Remission induction versus immediate allogeneic haematopoietic stem cell transplantation for patients with relapsed or poor responsive acute myeloid leukaemia (ASAP): a randomised, open-label, phase 3, non-inferiority trial. *Lancet Haematol*. 2024;11(5):e324-35.
25. Accorsi Buttini E, Doran C, Malagola M, Radici V, Galli M, Rubini V, et al. Donor lymphocyte infusion in the treatment of post-transplant relapse of acute myeloid leukemias and myelodysplastic syndromes significantly improves overall survival: a French-Italian experience of 134 patients. *Cancers (Basel)*. 2024;16(7):1278. doi:10.3390/cancers16071278.

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

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 $\sim 40\%$ 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.

Frailty Tool / Approach	Key Components	Clinical Output	Strengths	Limitations	Practical Use in First-line Decision-Making
IMWG Frailty Index⁵	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 Questionnaire⁹	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 ⁻⁹): 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
SWOGS0777¹⁹	Phase III, randomized	NMM 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-lite²⁰	Phase II, single-arm	TI NMM (n=50)	Modified RVd: R 15mg days 1–21, V 1.3mg/m ² 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
IFM2017-03²¹	Phase III, randomized	Frail NMM, 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 Trial²²	Phase III, randomized	TI NMM (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; **NMM:** 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.

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

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.

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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References

1. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. *JAMA*. 2022;327(5):464-77.
2. Abdallah N, Kumar SK. Up-front treatment of elderly (age ≥ 75 years) and frail patients with multiple myeloma. *J Natl Compr Canc Netw*. 2024;22(9).
3. Hicks LK, Messersmith HJ, Al Hadidi S, Banerjee R, Derman BA, Kumar S, et al. Treatment of multiple myeloma: ASCO-Ontario Health (Cancer Care Ontario) living guideline. *J Clin Oncol*. 2026;Jco2502587.
4. Souto Filho JTD, Cantadori LO, Crusoe EQ, Hungria V, Maiolino A. Survival impact of anti-CD38-based quadruplet regimens in transplant-ineligible newly diagnosed multiple myeloma: a network meta-analysis and reconstructed individual patient data meta-analysis. *Blood Cancer J*. 2025;15(1):212.
5. Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-74.
6. Scheepers ERM, Vondeling AM, Thielen N, van der Griend R, Stauder R, Hamaker ME. Geriatric assessment in older patients with a hematologic malignancy: a systematic review. *Haematologica*. 2020;105(6):1484-93.
7. Facon T, Dimopoulos MA, Meuleman N, Belch A, Mohty M, Chen WM, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia*. 2020;34(1):224-33.
8. Scheubeck S, Ihorst G, Schoeller K, Holler M, Möller MD, Reinhardt H, et al. Comparison of the prognostic significance of 5 comorbidity scores and 12 functional tests in a prospective multiple myeloma patient cohort. *Cancer*. 2021;127(18):3422-36.
9. Dotan E, Walter LC, Browner IS, Clifton K, Cohen HJ, Extermann M, et al. NCCN Guidelines® insights: older adult oncology, version 1.2021. *J Natl Compr Canc Netw*. 2021;19(9):1006-19.
10. Chen Y, He F, Chen Y, He Z, Wu D, An H, et al. Combining IMWG GA and hematopoietic score to optimize the evaluation of dynamic chemotherapy tolerance in multiple myeloma. *Ann Med*. 2025;57(1):2558127.

11. McCurdy A, Mian H, LeBlanc R, Jimenez-Zepeda VH, Su J, Masih-Khan E, Visram A, Louzada M, Song K, White D, Sebag M, Stakiw J, Reiman A, Aslam M, Bergstrom D, Kotb R, Kaedbey R, Gul E, Reece D, Venner CP. Redefining attrition in multiple myeloma (MM): a Canadian Myeloma Research Group (CMRG) analysis. *Blood Cancer J.* 2023 Jul 20;13(1):111. doi: 10.1038/s41408-023-00883-x. Erratum in: *Blood Cancer J.* 2023 Aug 28;13(1):129. doi: 10.1038/s41408-023-00888-6. PMID: 37474492; PMCID: PMC10359388.
12. Usmani SZ, Facon T, Hungria V, Bahlis NJ, Venner CP, Braunstein M, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med.* 2025;31(4):1195-202.
13. Facon T, Dimopoulos MA, Leleu XP, Beksac M, Pour L, Hájek R, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med.* 2024;391(17):1597-609.
14. Leleu X, Hulin C, Lambert J, Bobin A, Perrot A, Karlin L, et al. Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial. *Nature Medicine.* 2024;30(8):2235-41.
15. Mollee P, Reynolds J, Janowski W, Quach H, Campbell P, Gibbs S, et al. Daratumumab, cyclophosphamide, bortezomib, and dexamethasone for transplant-ineligible myeloma: AMaRC 03-16. *Blood Adv.* 2024;8(14):3721-30.
16. Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet.* 2020;395(10218):132-41.
17. Mateos MV, San-Miguel J, Cavo M, Suzuki K, Jakubowiak A, Knop S, et al. Bortezomib, melphalan, and prednisone with or without daratumumab in transplant-ineligible patients with newly diagnosed multiple myeloma (ALCYONE): final analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol.* 2025;26(5):596-608.
18. Facon T, Moreau P, Weisel K, Goldschmidt H, Usmani SZ, Chari A, et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. *Leukemia.* 2025;39(4):942-50.
19. Durie BGM, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J.* 2020;10(5):53.
20. O'Donnell EK, Laubach JP, Yee AJ, Chen T, Huff CA, Basile FG, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol.* 2018;182(2):222-30.
21. Manier S, Lambert J, Hulin C, Macro M, Laribi K, Araujo C, et al. Safety and efficacy of a dexamethasone-sparing regimen with daratumumab and lenalidomide in patients with frailty and newly diagnosed multiple myeloma (IFM2017-03): a phase 3, open-label, multicentre, randomised, controlled trial. *Lancet Oncol.* 2025;26(10):1323-33.
22. Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood.* 2018;131(3):301-10.
23. Dimopoulos MA, Merlini G, Bridoux F, Leung N, Mikhael J, Harrison SJ, et al. Management of multiple myeloma-related renal impairment: recommendations from the International Myeloma Working Group. *Lancet Oncol.* 2023;24(7):e293-e311.

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
Amplify¹³	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
ALLIANCE³	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/GAIA¹⁰	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
CLL14⁹	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
CLL17¹⁷	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-TN⁵	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
GLOW¹¹	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-2²	Ibrutinib or Clb-O	Continuous	≥65 yr	No	9.6 yr	Est. 8.9 yr for ibrutinib vs. 1.3 yr for Clb-O
SEQUIOA⁶	Zanubrutinib vs. BR	Continuous	≥65 yr 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:** chemimmunotherapy; **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 BR¹⁹ 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 <i>TP53</i> /del(17p) aberrations; concerns about durability of finite therapy	Mutated <i>IGHV</i> ; 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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References

1. Kang S, Ahn IE. Prognostic markers in the era of targeted therapies. *Acta Haematol.* 2024;147(1):33-46.
2. Burger JA, Barr PM, Robak T, Owen C, Tedeschi A, Sarma A, et al. Final analysis of the RESONATE-2 study: up to 10 years of follow-up of first-line ibrutinib treatment for CLL/SLL. *Blood.* 2025;146:2168-76.
3. Woyach JA, Perez BG, Ruppert AS, Miller C, Heerema NA, Zhao W, et al. Follow-up from the A041202 study shows continued efficacy of ibrutinib regimens for older adults with CLL. *Blood.* 2024;143:1616-27.
4. Robak T, Witkowska M, Smolewski P. The role of Bruton's kinase inhibitors in chronic lymphocytic leukemia: current status and future directions. *Cancers (Basel).* 2022;14(3):771.
5. Sharman JP, Egyed M, Jurczak W, Skarbnik AP, Patel K, Flinn IW, et al. Acalabrutinib-obinutuzumab improves survival vs chemoimmunotherapy in treatment-naïve CLL in the 6-year follow-up of ELEVATE-TN. *Blood.* 2025;146:1276-85.
6. Shadman M, Munir T, Robak T, Brown JR, Kahl BS, Ghia P, et al. Zanubrutinib versus bendamustine and rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma: median 5-year follow-up of SEQUOIA. *J Clin Oncol.* 2024;43:780-7.
7. Brown JR, Eichhorst B, Lamanna N, O'Brien SM, Tam CS, Qiu L, et al. Sustained benefit of zanubrutinib vs ibrutinib in patients with R/R CLL/ SLL: final comparative analysis of ALPINE. *Blood.* 2024;144:2706-17.
8. Brown JR, Eichhorst B, Hillmen P, Jurczak W, Kaźmierczak M, Lamanna N, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2023;388:319-32.
9. Al-Sawaf O, Robrecht S, Zhang C, Olivieri S, Chang YM, Fink AM, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. *Blood.* 2024;144(18):1924-1935.
10. Fürstenau M, Kater AP, Robrecht S, von Tresckow J, Zhang C, Gregor M, et al. First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/ CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2024;25(6):744-759.
11. Niemann CU, Munir T, Moreno C, Owen C, Follows GA, Benjamini O, et al. Fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in previously untreated chronic lymphocytic leukaemia (GLOW): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2023;24(12):1423-1433.
12. Ghia P, Barr PM, Allan JN, Siddiqi T, Tedeschi A, Kipps TJ, et al. Final analysis of fixed-duration ibrutinib + venetoclax for chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) in the phase 2 CAPTIVATE study. *J Clin Oncol.* 2025;43:7036.
13. Brown JR, Seymour JF, Jurczak W, Aw A, Wach M, Illes A, et al. Fixed-duration acalabrutinib combinations in untreated chronic lymphocytic leukemia. *N Engl J Med.* 2025;392(8):748-62.
14. Davids MS, Stilgenbauer S, Tam CS. First-line treatment for CLL in the era of targeted therapy. *Blood Cancer J.* 2026;16:19.
15. Shanafelt TD, Wang XV, Kay NE, Hanson CA, O'Brien S, Barrientos J, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med.* 2019;381:432-443.
16. Munir T, Cairns DA, Bloor A, Allsup D, Cwynarski K, Pettitt A, et al. Chronic lymphocytic leukemia therapy guided by measurable residual disease. *N Engl J Med.* 2024;390:326-337.
17. Al-Sawaf O, Stumpf J, Zhang C, Simon F, Bosch F, Feyzi E, et al. Fixed-duration versus continuous treatment for chronic lymphocytic leukemia. *N Engl J Med.* 2025;394:1084-1096.
18. Lachaine J, Guinan K, Aw A, Banerji V, Fleury I, Owen C. Impact of fixed-duration oral targeted therapies on the economic burden of chronic lymphocytic leukemia in Canada. *Curr Oncol.* 2023;30(5):4483-4498.
19. Jurczak W, Kwiatak M, Czyz J, de Mattos ER, Eom K, Egle A, et al. BRUIN CLL-313: randomized phase iii trial of pirtobrutinib versus bendamustine plus rituximab in untreated patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol.* 2025;44(6):466-475.
20. Woyach J, Qiu L, Grosicki S, Wrobel T, Capra M, Czyz J, et al. Pirtobrutinib versus ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol.* 2026;44(6):476-485.

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.

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 <i>TP53</i>: chromosome 17	Deletion 17p: Deletion of the long arm of chromosome 17, resulting in loss of <i>TP53</i> ³⁴ <i>TP53</i> mutations: mutations causing deactivation of the <i>TP53</i> gene ³⁴ *Must be present in ≥20% of nucleated cells to be significant, as per recent IMWG/IMS guidelines ⁸
<i>IGH</i> translocations: chromosome 14, immunoglobulin heavy-chain locus at 14q32	t(4;14): <i>FGFR3-IGH</i> translocation – deregulation of fibroblast growth factor ³⁵ t(14;16): <i>MAF-IGH</i> translocation – deregulation of <i>c-MAF</i> proto-oncogene ³⁶ t(14;20): <i>MAFB-IGH</i> translocation – deregulation of <i>MAFB</i> oncogene ³⁷ t(8;14): <i>MYC-MAF</i> translocation – uncommon, results in rearrangement of <i>MYC</i> oncogene ³⁸
Chromosome 1 abnormalities	1q+: Gain (2 copies) vs. amplification (>3 copies); <i>CKS1B</i> – 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 cytogenetic 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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References

- Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: A review. *JAMA*. 2022;327(5):464-77.
- Hicks LK, Messersmith HJ, Al Hadidi S, Banerjee R, Derman BA, Kumar S, et al. Treatment of multiple myeloma: ASCO-Ontario Health (Cancer Care Ontario) Living Guideline. *J Clin Oncol*. 2026;44(10):914-41.
- Bobin A, Macro M, Touzeau C, Mariette C, Manier S, Brechignac S, et al. A dexamethasone-free daratumumab-ixazomib regimen in frail elderly patients with relapsed or refractory multiple myeloma: Results of the IFM 2018-02 phase II study. *Br J Haematol*. 2026; epub ahead of print.
- Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;390(4):301-13.
- Côté J, LeBlanc R, Mian H, Chu MP, McCurdy A, Masih-Khan E, et al. Real-world results of autologous stem cell transplantation in newly diagnosed multiple myeloma: a report from the Canadian Myeloma Research Group database. *Blood Cancer J*. 2023;13(1):137.
- Joseph NS, Kaufman JL, Dhodapkar MV, Hofmeister CC, Almaula DK, Heffner LT, et al. Long-term follow-up results of lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance approach in newly diagnosed multiple myeloma. *J Clin Oncol*. 2020;38(17):1928-37.
- Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2024;99(9):1802-24.
- Avet-Loiseau H, Davies FE, Samur MK, Corre J, D'Agostino M, Kaiser MF, et al. International Myeloma Society/International Myeloma Working Group Consensus Recommendations on the definition of high-risk multiple myeloma. *J Clin Oncol*. 2025;43(24):2739-51.
- Gay F, Bertuglia G, Mina R. A rational approach to functional high-risk myeloma. *Hematology Am Soc Hematol Educ Program*. 2023;2023(1):433-42.
- Banerjee R, Cicero KI, Lee SS, Cowan AJ. Definers and drivers of functional high-risk multiple myeloma: insights from genomic, transcriptomic, and immune profiling. *Front Oncol*. 2023;13:1240966.
- Beer SA, Cairns DA, Pawlyn C, Holroyd A, Ferris E, Cook G, et al. Challenging the concept of functional high-risk myeloma through transcriptional and genetic profiling. *Blood*. 2025;146(22):2670-80.
- Walker BA, Mavrommatis K, Wardell CP, Ashby TC, Bauer M, Davies F, et al. A high-risk, double-hit, group of newly diagnosed myeloma identified by genomic analysis. *Leukemia*. 2019;33(1):159-70.
- Dimopoulos MA, Sonneveld P, Rodriguez-Otero P, Quach H, Ho PJ, Beksac M, et al. MM-329 daratumumab + bortezomib/lenalidomide/dexamethasone (D-VRd) in transplant-eligible (TE) patients with newly diagnosed myeloma (NDMM): Analysis of the Phase 3 PERSEUS study based on high-risk cytogenetic abnormalities (HRCAs). *Clinical Lymphoma, Myeloma and Leukemia*. 2024;24:S547-S8.
- Callander NS, Silbermann R, Kaufman JL, Godby KN, Laubach J, Schmidt TM, et al. Daratumumab-based quadruplet therapy for transplant-eligible newly diagnosed multiple myeloma with high cytogenetic risk. *Blood Cancer J*. 2024;14(1):69.
- Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst HM, Goldschmidt H, Rosinol L, et al. revised international staging system for multiple myeloma: A report from International Myeloma Working Group. *J Clin Oncol*. 2015;33(26):2863-9.
- Wu J, Chu E, Chase CC, Choi T, Gasparetto C, Young K, et al. Anaplastic Multiple myeloma: case series and literature review. *Asploro J Biomed Clin Case Rep*. 2022;5(1):1-11.
- Fernández de Larrea C, Kyle R, Rosiñol L, Paiva B, Engelhardt M, Usmani S, et al. Primary plasma cell leukemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage. *Blood Cancer J*. 2021;11(12):192.
- Cazaubiel T, Leleu X, Perrot A, Manier S, Buisson L, Maheo S, et al. Primary plasma cell leukemias displaying t(11;14) have specific genomic, transcriptional, and clinical features. *Blood*. 2022;139(17):2666-72.
- Charalampous C, Goel U, Kapoor P, Binder M, Buadi FK, Cook J, et al. Outcomes of patients with primary refractory multiple myeloma in the era of triplet and quadruplet induction therapy. *Blood Adv*. 2023;7(16):4371-80.
- Lim SL, Engelhardt M, Terpos E, Gay F, Van de Donk N, Einsele H, et al. European Myeloma Network Consensus Statement on functional high-risk multiple myeloma. *Am J Hematol*. 2025;100(12):2320-32.
- Spencer A, Mollee P, Blacklock HA, Harrison S, Quach H, Ho PJ, et al. Real-world outcome for newly diagnosed patients with functional high-risk myeloma - a myeloma and related diseases registry analysis. *Blood*. 2019;134(Supplement_1):269.
- Bygrave CA, Pawlyn C, Davies FE, Cairns D, Striha A, Hockaday A, et al. Progression free survival below 12 months following stem cell transplant is a hallmark of high-risk myeloma which is associated with inferior overall survival — Data from the Ukmrc Myeloma XI Trial. *Blood*. 2018;132:122.
- Corre J, Montes L, Martin E, Perrot A, Caillot D, Leleu X, et al. Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk. *Haematologica*. 2020;105(9):e480-3.
- Costa L, Bal S, Godby K, Ravi G, Medvedova E, Callander N, et al. Redefining function high-risk (FHR) multiple myeloma (MM) in the context of upfront quadruplet (QUAD) therapy and autologous stem cell transplantation (ASCT). *Blood*. 2025;146(Supplement 1):1037.
- Cerchione C, Usmani SZ, Stewart AK, Kaiser M, Rasche L, Kortüm M, et al. Gene expression profiling in multiple myeloma: redefining the paradigm of risk-adapted treatment. *Front Oncol*. 2022;12:820768.
- Manasanch EE, Berrios D, Fountain E, Claussen CM, Chuang T, Kaufman G, et al. Gene expression profiling predicts relapse-free and overall survival in newly diagnosed myeloma patients treated with novel therapies. *Br J Haematol*. 2021;192(4):e115-e20.

27. Grasedieck S, Panahi A, Jarvis MC, Borzooee F, Harris RS, Larijani M, et al. Redefining high risk multiple myeloma with an APOBEC/Inflammation-based classifier. *Leukemia*. 2024;38(5):1172-7.
28. Papadimitriou M, Tauro M, Panahi A, Ziccheddu B, Poos AM, Alaoui AY, et al. Replication stress induces hyperapobec mutagenesis in multiple myeloma. *Blood*. 2024;144(Supplement 1):3276.
29. Goldschmidt H, Lokhorst HM, Mai EK, van der Holt B, Blau IW, Zweegman S, et al. Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial. *Leukemia*. 2018;32(2):383-90.
30. Facon T, Dimopoulos MA, Leleu XP, Beksac M, Pour L, Hájek R, et al. Isatuximab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2024;391(17):1597-609.
31. Mai EK, Bertsch U, Pozek E, Fenk R, Besemer B, Hanoun C, et al. Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy for transplant-eligible newly diagnosed multiple myeloma: final part 1 analysis of the GMMG-HD7 trial. *J Clin Oncol*. 2025;43(11):1279-88.
32. Usmani SZ, Facon T, Hungria V, Bahlis NJ, Venner CP, Braunstein M, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. *Nat Med*. 2025;31(4):1195-202.
33. Costa LJ, Bahlis NJ, Perrot A, Nooka AK, Lu J, Pawlyn C, et al. Teclistamab plus daratumumab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2026;394(8):739-52.
34. Flynt E, Bisht K, Sridharan V, Ortiz M, Towfic F, Thakurta A. Prognosis, Biology, and targeting of TP53 dysregulation in multiple myeloma. *Cells*. 2020;9(2).
35. Mirabella F, Wu P, Wardell CP, Kaiser MF, Walker BA, Johnson DC, et al. MMSET is the key molecular target in t(4;14) myeloma. *Blood Cancer J*. 2013;3(5):e114.
36. Schavgoulidze A, Perrot A, Cazaubiel T, Leleu X, Montes L, Jacquet C, et al. Prognostic impact of translocation t(14;16) in multiple myeloma according to the presence of additional genetic lesions. *Blood Cancer J*. 2023;13(1):160.
37. Ross FM, Chiecchio L, Dagrada G, Protheroe RK, Stockley DM, Harrison CJ, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. *Haematologica*. 2010;95(7):1221-5.
38. Walker BA, Wardell CP, Brioli A, Boyle E, Kaiser MF, Begum DB, et al. Translocations at 8q24 juxtapose MYC with genes that harbor superenhancers resulting in overexpression and poor prognosis in myeloma patients. *Blood Cancer J*. 2014;4(3):e191.
39. McAuley N, Cymer I, McAvera R, Hopkins AM, Glavey SV. Chromosome 1 alterations in multiple myeloma: considerations for precision therapy. *Eur J Haematol*. 2025;114(3):400-10.
40. Obiekwe D, Joseph N, Hofmeister CC, Almaula D, Heffner LT, Gupta VA, et al. The impact of complex karyotype identified by conventional cytogenetics on survival outcomes of 1,000 patients with newly diagnosed myeloma (NDMM). *J Clin Oncol*. 2022;40(16_suppl):8063.
41. Podvin B, Paiva B, Ghobrial IM, Manier S. Circulating tumor cells in multiple myeloma: from peripheral clues to central insights. *Am J Hematol*. 2026; epub ahead of print.
42. Usmani SZ, Heuck C, Mitchell A, Szymonifka J, Nair B, Hoering A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. *Haematologica*. 2012;97(11):1761-7.



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