ABOUT THE AUTHORS

Christopher Venner, MD

Dr. Venner is hematologist with the BC Cancer - Vancouver Centre to advance the Plasma Cell Dyscrasias Program. In addition to being actively involved in clinical trials, his current academic interest involves clinical outcomes research in plasma cell dyscrasias, examining the evolution of therapy in these diseases and the impact novel combinations have on survival. Much of this work is done through the Canadian Myeloma Research Group through activities in the CMRG Canadian Multiple Myeloma Database initiative which he led as Chair, and the CMRG clinical trials group. He is also the Co-Chair of the Myeloma Sub-Committee with the Canadian Cancer Trials Group.

Affiliations:
University of British Columbia
British Columbia Cancer Agency

Julia Varghese, MD

Julia Varghese is a hematologist in Vancouver, BC. She obtained her MD through the University of British Columbia's Northern Medical Program and completed both her Internal Medicine and Hematology training at UBC. She is currently completing a Myeloma fellowship at the British Columbia Cancer Agency (Vancouver site) under the mentorship of Dr. Christopher Venner.

Affiliations:
University of British Columbia
British Columbia Cancer Agency

FRONTLINE MANAGEMENT OF TRANSPLANT INELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA (TINDMM) IN CANADA

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow leading to end organ dysfunction including hypercalcemia, anemia, renal dysfunction, and/or bony lytic lesions.[1] The median age of diagnosis is 69 years of age with approximately one-third of newly diagnosed patients presenting over age 75.[2] Therefore, a significant portion of patients presenting with newly diagnosed MM are considered ineligible for transplant due to chronological age, comorbidities or frailty. This category represents a largely heterogeneous group of patients. With options for frontline management rapidly changing, practitioners must consider the optimal treatment modality.

Patient Eligibility for Autologous Stem Cell Transplant

In younger, fit populations, autologous stem cell transplant (ASCT) remains the standard of care and multiple trials have demonstrated a consistent progression-free survival (PFS) benefit.[3,4] However, most of these studies excluded patients who were >65 years of age. The Myeloma XI trial attempted to address this gap with a subgroup analysis of patients up to age 75. In this trial, the transplant decision was left to the discretion of the clinician. Older patients who underwent ASCT were found to have an improvement in PFS (HR=0.41, P<0.0001), as well as OS (HR=0.51, P<0.0001) compared to their age-matched cohort that did not.[5] Patients age 65-69 had a PFS of 40 months, and a PFS of 34.4 was seen in those aged 70-75.[5] These results are similar to those of newer non-ASCT based therapies, thus calling into question the role of ASCT in these age groups.[6,7]

There is no universally accepted age cut-off for transplant eligibility. The European guidelines recommend an age cut-off of 70 years of age for transplant eligibility,[8] whereas there is no formal age cut-off in the National Comprehensive Cancer Network guidelines.[9] Knowing this, the majority of Canadian clinicians will assess therapeutic options based on performance status. Several tools have been validated for use in stratifying patients into "fit" and "frail" categories, including the International Myeloma Working Group (IMWG) frailty assessment and the Revised Myeloma comorbidity index.[10,11] These tools are helpful in assessing transplant eligibility as well as how patients may tolerate chemotherapy in general. Regardless of transplant status, the objective of therapy is to achieve the best possible response with minimal toxicities and to maximize disease control in the long term.

Treatment modalities for transplant ineligible newly diagnosed multiple myeloma

As per the most recent Canadian Agency for Drugs and Technologies in Health (CADTH) review, the six regimens that are currently approved and funded for front-line treatment for transplant ineligible newly diagnosed multiple myeloma (TINDMM) patients in Canada appear below and are further described in **Table 1**.[12]

- Daratumumab, lenalidomide, dexamethasone (DRd)
- Bortezomib, lenalidomide, dexamethasone (VRd)
- Lenalidomide, dexamethasone (Rd)
- Daratumumab, cyclophosphamide, bortezomib, dexamethasone (Dara+CyBorD)
- Daratumumab, bortezomib, melphalan, prednisone (Dara+VMP)
- Cyclophosphamide, bortezomib, dexamethasone (CyBorD)

Trial	Therapy	Number of patients	mPFS	mOS
MAIA[13] (DRd)	DRd vs Rd	737	61.9 months vs 34.4 months with Rd	66.7% at 60 months vs 53.7%
ALCYONE[14] (Dara+VMP)	DVMP vs VMP	706	36.4 months vs 19.3 months with VMP	78% at 36 months vs 67.9%
SWOG-S0777[6] (VRd)	VRd vs Rd	525	43 months vs 30 months with Rd	75 months vs 64 months
FIRST[15] (Rd)	Rd vs MPT	1623	25.5 months vs 21.2 months with MPT	70% at 3 years vs 62% with MPT
VISTA[16] (VMP)	VMP vs MP	682	19.9 months (time to progression) vs 13.1 months with MP	Not reported

Table 1. *Comparison of PFS and OS of the current CADTH-approved frontline regimens for transplant ineligible patients based on Phase III trial data. mPFS= median Progression Free Survival; mOS= median Overall Survival*

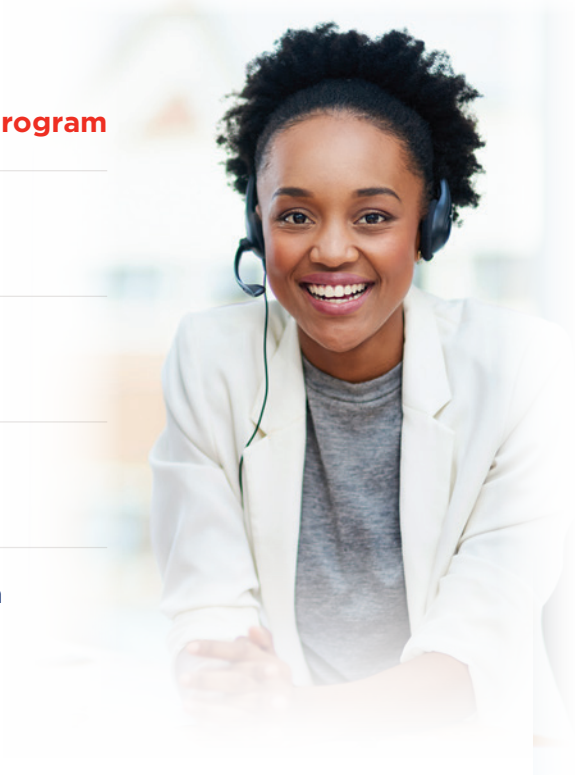
TWO EASY WAYS TO ACCESS BRUKINSA

Enroll your BRUKINSA patients

myBeiGene® Patient Support Program

- Reimbursement/Payment support
- BRUKINSA education and support
- Connections to third-party advocacy organizations

Enroll by visiting the Patient Support section on **brukinsa.ca** or calling **1-833-234-4366**.



Order a BRUKINSA sample*

Order by visiting the Sample Program section on **brukinsa.ca** For more information, please contact **samples@beigene.com**.

* These are prescription drug samples provided in accordance with the Food and Drug Regulations. It is unlawful to sell, trade, barter, return for credit, utilize to seek reimbursement or bill patients for samples.

0223-BRU-PRC-086

Pr Brukinsa® zanubrutinib 80 mg capsules

BeiGene

Although CyBorD has never been studied in a phase III clinical trial, it is a widely used regimen in Canada. It was adopted following a phase II trial in transplant eligible patients which demonstrated its efficacy as an induction regimen.[17] Given the efficacy and tolerability, this regimen was moved into the transplant ineligible population with similar outcomes compared with VMP.[18,19]

When reviewing the real-world Canadian data from the Canadian Myeloma Research Group (CMRG) of various frontline regimens there appears to be an increased PFS benefit with lenalidomide-containing regimens, particularly the triplet regimen VRD.[19] Data from the CMRG database examining patients from 2007-2021 demonstrated a median PFS for VMP of 23.5 months (n=460); 22.9 months for CyBorD (n=932); 34 months for RD (n=472); and a median PFS not yet reached for VRD (n=115) at the time of analysis.[19]

These results are comparable to the recent trial data that led to their respective approvals, such as data from the FIRST trial which compared continuous Rd to MPT and demonstrated improved PFS (25.5 months vs 21 months) as well as OS.[15] It is also comparable to the control arms of other recent trials where Rd was the backbone.[6,13,20] This benefit was further improved with the addition of bortezomib to Rd in the SWOG S0777 trial which demonstrated a further increase in PFS (43 vs 30 months) and median OS (75 vs 64 months) in the study arm.[6] Due to tolerability concerns of lenalidomide, as well as twice weekly bortezomib, a phase II trial reviewing the efficacy of "RVD-lite" in 53 transplant ineligible patients (median age 73) was conducted. This regimen examined a lower dose of lenalidomide (15 mg) and weekly bortezomib. The median PFS with this regimen was 35.1 months; the median OS was not reached after a median follow-up of 30 months. The regimen was well tolerated.[21] The rates of peripheral neuropathy were 62%; however only one patient (2%) had peripheral neuropathy recorded as grade 3 or higher. The treatment discontinuation rate due to side effects was low, at 4%.[22] This clinical trial demonstrated the efficacy and tolerability of the modified RVd regimen in the elderly non-transplant population, even at reduced doses.

More recent clinical studies have evaluated anti-CD38 monoclonal antibodies in combination with gold standard therapies. The ALCYONE trial reported a benefit for Dara + VMP compared to VMP in both PFS and OS (**Table 1**).[14] The most promising data, however, has been demonstrated with DRd from the MAIA study.[13] This phase 3 trial comparing DRd to Rd demonstrated superior PFS (mPFS 61.9 vs 31.9 months). Recent follow-up data of the MAIA study has shown a higher proportion of patients achieving minimal residual disease (MRD) negativity status (32.1% vs 11.1%; P<0.0001), with a significant portion of patients achieving sustained MRD negativity for >18 months at a median follow-up of 64.5 months (16.8% vs 3.3 %; P<0.0001).[13] This is notable as numerous clinical studies have demonstrated improved outcomes for patients who achieve a sustained MRD status.[22] In the MAIA trial, OS was improved overall but also specifically for patients who achieved an MRD negative status compared to those who were MRD positive regardless of the arm. An increased number of DRd patients achieving MRD negativity may explain the improved survival endpoints with the monoclonal antibody (mAb)- containing triplet.

The benefit of DRd over Rd was demonstrated throughout the subgroup analysis.[7,23] This included patients with one high-risk cytogenetic abnormality (HRCA) (PFS 61.4 vs 31.2 months); age >75 years (54.3 vs 31.4 months); International Staging System (ISS) Stage III disease (42.4 vs 24.2 months); renal insufficiency (56.7 vs 29.7 months); and extramedullary plasmacytomas (57.5 vs 19.4 months). No significant difference was reported between patients with two or more HRCA (24.9 vs 24 months) although there were small numbers in each group making it difficult to draw conclusions from this data.[23] Interestingly, for patients aged 70-75 and 65-70, the median PFS was 61.9 months and not yet reached, respectively.[7] This is similar, if not longer, than what can be achieved with non-mAb transplant regimens used in Canada based on both prospective and real-world data.[5,24]

In the frailty subgroup analysis of MAIA, 341 patients were deemed frail (172 in the DRd arm vs 169 in the Rd arm). After a median follow-up of 36.4 months, the non-frail patients (n=396) had longer PFS vs the frail patients (n=341).[25] However, regardless of frailty, the PFS benefit of DRd persisted compared to that of Rd (mPFS not reached vs 30.4 months; P=0.003). Not surprisingly, the rates of treatment emergent adverse events (TEAE) were higher in the frail population vs that of the fit. The primary grade 3/4 TEAE for frail patients in the DRd arm was neutropenia ([DRd] 57.7% vs [Rd] 33.1%). The most serious non-hematologic TEAE was infections (primarily pneumonia/ upper respiratory tract infection [URTIs]) and was higher for the DRd arm (41.7% vs 27.7%). However, DRd was better tolerated overall and fewer of the frail patients discontinued DRd in comparison to Rd (45.3% vs 67.5%).[25]

Dexamethasone toxicity can be a limiting factor for many patients, and the efficacy of a dexamethasone sparing regimen was recently evaluated. In this clinical trial, 295 elderly patients (median age of 81 years) were randomized to daratumumab, lenalidomide and dexamethasone (administered weekly for 8 weeks, then discontinued) or lenalidomide and weekly dexamethasone 20 mg.[26] The overall response rates were higher for DR vs Rd (89% vs 77%; P=0.025). Patients in the DR arm had higher rates of neutropenia (44% vs 15%; P<0.001) but similar rates of grade 3 infections (13% vs 17%; P=0.38) and similar rates of discontinuation due to adverse events (AEs) (13% vs 16%; P=0.64).[26]

While frontline DRd is already improving patient outcomes, several new treatment approaches currently being evaluated in clinical trials may result in further future improvement. Anti-CD38 monoclonal antibody-containing quadruplet regimens are currently being evaluated in TINDMM, with the objective of improving the depth and duration of response. T-cell redirecting therapies such as B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR-T) and bispecific T-cell engagers (BiTEs) are also being evaluated in this population in the frontline setting.

Summary

When reviewing the status of TINDMM patients in Canada treated between 2007 and 2018, prior to the availability of daratumumab, the median OS was 54 months.[27] Incremental gains have been achieved with novel regimens such as RVd; however, the most significant advances have been reported with the anti-CD38 mAbs. In particular, the promising data with DRd demonstrates a median PFS of 61.9 months[13] exceeding the median OS with regimens from the previous era. Furthermore, DRd is well-tolerated and provides benefit regardless of age, cytogenetic risk, frailty or renal function.

Although there are several options approved for use by CADTH in the frontline setting for transplant ineligible patients, DRd remains the most broadly applicable regimen for frontline therapy in TINDMM and will serve as the backbone upon which future advances will be built.

Correspondence:

Dr. Christopher Venner
Email: christopher.venner@bccancer.bc.ca

Financial Disclosures:

C.V. : **Honoraria:** Janssen, Sanofi, Pfizer, Abbvie, BMS, Forus Therapeutics, GSK

J.V. has no disclosures to report

References

1. *Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, Kumar S, Hillengass J, Kastritis E, Richardson P, Landgren O. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The lancet oncology. 2014 Nov 1;15(12):e538-48.*
2. *Myeloma - Cancer Stat Facts [Internet]. SEER. [cited 2023 Jan 31]. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html*
3. *Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, Arnulf B, Macro M, Belhadj K, Garderet L, Roussel M. IFM 2009 Study. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med. 2017 Apr 6;376(14):1311-20.*
4. *Richardson PG, Jacobus SJ, Weller EA, Hassoun H, Lonial S, Raje NS, Medvedova E, McCarthy PL, Libby EN, Voorhees PM, Orlowski RZ. Triplet therapy, transplantation, and maintenance until progression in myeloma. New England Journal of Medicine. 2022 Jul 14;387(2):132-47.*
5. *Pawlyn C, Cairns DA, Menzies T, Jones JR, Jenner MW, Cook G, Boyd KD, Drayson MT, Kaiser MF, Owen RG, Gregory W. Autologous stem cell transplantation is safe and effective for fit, older myeloma patients: exploratory results from the Myeloma XI trial. haematologica. 2022 Jan 1;107(1):231.*
6. *Durie BG, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, Dispenzieri A, Kahanic SP, Thakuri MC, Reu FJ, Reynolds CM. 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 journal. 2020 May 11;10(5):53.*
7. *Facon T, Kumar SK, Weisel K, Usmani S, Moreau P, Plesner T, Orlowski RZ, Bahlis NJ, Basu S, Nahi H, Hulin C. Daratumumab Plus Lenalidomide and Dexamethasone in Patients with Transplant-ineligible Newly Diagnosed Multiple Myeloma: MAIA Age Subgroup Analysis. Blood. 2022 Nov 15;140(Supplement 1):10133-6.*
8. *Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, Delforge M, Hájek R, Schjesvold F, Cavo M, Goldschmidt H. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2021 Mar 1;32(3):309-22.*
9. *Kumar SK, Callander NS, Hillengass J, Liedtke M, Baljevic M, Campagnaro E, Castillo JJ, Chandler JC, Cornell RF, Costello C, Efebera Y. NCCN guidelines insights: Multiple myeloma, version 1.2020: Featured updates to the NCCN guidelines. Journal of the National Comprehensive Cancer Network. 2019 Oct 1;17(10):1154-65.*
10. *Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, Offidani M, McCarthy P, Evangelista A, Lonial S, Zweegman S. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood, The Journal of the American Society of Hematology. 2015 Mar 26;125(13):2068-74.*
11. *Engelhardt M, Domm AS, Dold SM, Ihorst G, Reinhardt H, Zober A, Hieke S, Baayen C, Müller SJ, Einsele H, Sonneveld P. A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. Haematologica. 2017 May;102(5):910.*
12. *Provisional Funding Algorithm on Multiple Myeloma.*
13. *Kumar SK, Moreau P, Bahlis NJ, Facon T, Plesner T, Orlowski RZ, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): Updated Analysis of the Phase 3 Maia Study. Blood. 2022 Nov 15;140(Supplement 1):10150-3.*
14. *Mateos MV, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, Knop S, Doyen C, Lucio P, Nagy Z, Pour L. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. The Lancet. 2020 Jan 11;395(10218):132-41.*
15. *Dimopoulos MA, Cheung MC, Roussel M, Liu T, Gamberi B, Kolb B, Derigs HG, Eom H, Belhadj K, Lenain P, Van der Jagt R. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica. 2016 Mar;101(3):363.*
16. *Miguel JFS, Khuageva NK, Shpilberg O, Petrucci MT, Dmoszynska A, Schots R, et al. Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma. N Engl J Med. 2008.*
17. *Reeder CB, Reece DE, Kukreti V, Chen C, Trudel S, Hentz J, Noble B, Pirooz NA, Spong JE, Piza JG, Zepeda VH. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia. 2009 Jul;23(7):1337-41.*
18. *Jimenez-Zepeda VH, Duggan P, Neri P, Tay J, Bahlis NJ. Bortezomib-containing regimens (BCR) for the treatment of non-transplant eligible multiple myeloma. Ann Hematol. 2017 Mar;96(3):431-9.*
19. *Kaedbey R, Venner C, McCurdy A, Masih-Khan E, Kardjadj M, Chu M, et al. P-201: Outcomes of transplant-ineligible myeloma patients using bortezomib/lenalidomidecontaining regimens in the real world: a report from the Canadian Myeloma Research Group Database. Clin Lymphoma Myeloma Leuk. 2022 Aug;22:S145--6.*
20. *Dimopoulos MA, Richardson PG, Bahlis NJ, Grosicki S, Cavo M, Beksaç M, Legieć W, Liberati AM, Goldschmidt H, Belch A, Magen H. Addition of elotuzumab to lenalidomide and dexamethasone for patients with newly diagnosed, transplantation ineligible multiple myeloma (ELOQUENT-1): An open-label, multicentre, randomised, phase 3 trial. The Lancet Haematology. 2022 Jun 1;9(6):e403-14.*
21. *O'Donnell EK, Laubach JP, Yee AJ, Chen T, Huff CA, Basile FG, Wade PM, Paba-Prada CE, Ghobrial IM, Schlossman RL, Burke JN. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. British journal of haematology. 2018 Jul;182(2):222-30.*
22. *San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, Mateos MV, Touzeau C, Jakubowiak A, Usmani SZ, Cook G. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood. 2022 Jan 27;139(4):492-501.*
23. *Moreau P, Facon T, Usmani SZ, Bahlis N, Raje N, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): Clinical Assessment of Key Subgroups of the Phase 3 MAIA Study.*
24. *Cherniawsky HM, Kukreti V, Reece D, Masih-Khan E, McCurdy A, Jimenez-Zepeda VH, Sebag M, Song K, White D, Stakiw J, LeBlanc R. The survival impact of maintenance lenalidomide: an analysis of real-world data from the Canadian Myeloma Research Group national database. haematologica. 2021 Jun 6;106(6):1733.*
25. *Facon T, Cook G, Usmani SZ, Hulin C, Kumar S, Plesner T, Touzeau C, Bahlis NJ, Basu S, Nahi H, Goldschmidt H. Daratumumab plus lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. Leukemia. 2022 Apr;36(4):1066-77.*
26. *Manier S, Corre J, Hulin C, Laribi K, Araujo C, Pica GM, Touzeau C, Godmer P, Slama B, Karlin L, Orsini-Piocelle F. A Dexamethasone Sparing-Regimen with Daratumumab and Lenalidomide in Frail Patients with Newly-Diagnosed Multiple Myeloma: Efficacy and Safety Analysis of the Phase 3 IFM2017-03 Trial. Blood. 2022 Nov 15;140(Supplement 1):1369-70.*
27. *Jimenez-Zepeda V, Reece DE, Arleigh MR, Masih-Khan E, Atenafu EG, Sebag M, Stakiw J, Song K, Leblanc R, Reiman T, Louzada ML. Real-World outcomes with bortezomib-containing regimens and lenalidomide plus dexamethasone for the treatment of transplant ineligible MM patients: a multi-institutional report from the National Myeloma Canada Research Network (MCRN) database. Blood. 2018 Nov 29;132:2008.*