

# ABOUT THE AUTHORS



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# 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.<sup>1</sup> The median age of diagnosis is 69 years of age with approximately one-third of newly diagnosed patients presenting over age 75.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>5</sup> Patients age 65-69 had a PFS of 40 months, and a PFS of 34.4 was seen in those aged 70-75.<sup>5</sup> These results are similar to those of newer non-ASCT based therapies, thus calling into question the role of ASCT in these age groups.<sup>6,7</sup>

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,<sup>8</sup>

whereas there is no formal age cut-off in the National Comprehensive Cancer Network guidelines.<sup>9</sup> 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.<sup>10,11</sup> 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**.<sup>12</sup>

- 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 <sup>13</sup> (DRd)	DRd vs Rd	737	61.9 months vs 34.4 months with Rd	66.7% at 60 months vs 53.7%
ALCYONE <sup>14</sup> (Dara+VMP)	DVMP vs VMP	706	36.4 months vs 19.3 months with VMP	78% at 36 months vs 67.9%
SWOG-S0777 <sup>6</sup> (VRd)	VRd vs Rd	525	43 months vs 30 months with Rd	75 months vs 64 months
FIRST <sup>15</sup> (Rd)	Rd vs MPT	1623	25.5 months vs 21.2 months with MPT	70% at 3 years vs 62% with MPT
VISTA <sup>16</sup> (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

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.<sup>17</sup> Given the efficacy and tolerability, this regimen was moved into the transplant ineligible population with similar outcomes compared with VMP.<sup>18,19</sup>

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.<sup>19</sup> 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.<sup>19</sup>

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.<sup>15</sup> It is also comparable to the control arms of other recent trials where Rd was the backbone.<sup>6,13,20</sup> 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.<sup>6</sup> 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.<sup>21</sup> 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%.<sup>22</sup> 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**).<sup>14</sup> The most promising data, however, has been demonstrated with DRd from the MAIA study.<sup>13</sup> 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 %;  $P < 0.0001$ ).<sup>13</sup> This is notable as numerous clinical studies have demonstrated improved outcomes for patients who achieve a sustained MRD status.<sup>22</sup> 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.<sup>7,23</sup> 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.<sup>23</sup> Interestingly, for patients aged 70-75 and 65-70, the median PFS was 61.9 months and not yet reached, respectively.<sup>7</sup> 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.<sup>5,24</sup>

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).<sup>25</sup> 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%).<sup>25</sup>

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.<sup>26</sup> 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%;  $P = 0.64$ ).<sup>26</sup>

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.<sup>27</sup> 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<sup>13</sup> 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.

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