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# Current Frontline Treatment of Multiple Myeloma

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## ABSTRACT

Treatment paradigms for management of newly diagnosed (ND) multiple myeloma have been evolving over the past 20 years as a consequence of the development of immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. While recent studies have continued to confirm the progression-free survival benefit of consolidation with upfront autologous stem cell transplant in those considered transplant eligible (TE), the line between induction strategies for TE and transplant-ineligible (TI) patients has blurred, based on studies evaluating both populations. Here, we present an overview of the data guiding current treatment approaches in the ND setting and discuss areas of ongoing investigation, including the role of quadruplet combination therapies in TE patients, the optimal strategies for frail TI patients, and management of high-risk disease.

## Introduction

The past 20 years have seen the development of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs), which have dramatically reshaped the treatment paradigms for newly diagnosed (ND) multiple myeloma (MM). While consolidation with high-dose melphalan and autologous stem cell transplant (ASCT) remains a standard of care (SOC) for patients who are considered to be transplant eligible (TE), the use of alkylating agents and other traditional cytotoxic agents has decreased dramatically. Effective triplet

and even quadruplet combination therapies consisting of IMiDs, PIs, and/or mAbs can induce very deep responses, including achievement of minimal residual disease (MRD) negativity. These advances in therapies have led to considerable prolongation of survival times, although frail transplant-ineligible (TI) patients or patients with high-risk disease features continue to represent populations with inferior survival outcomes. In this review, we present an overview of the data that guide current treatment approaches for NDMM as well as the evolving strategies that may lead to future standards of care.

## PERSPECTIVE

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## Current Standards for Diagnosis

Diagnostic evaluation for a patient suspected to have MM includes laboratory evaluation, a bone marrow aspirate/biopsy, and whole-body imaging. Laboratory evaluation should include a complete blood count with differential, comprehensive metabolic panel (including creatinine, calcium, and albumin), lactate dehydrogenase (LDH),  $\beta_2$ -microglobulin, and testing for monoclonal proteins (including quantitative immunoglobulins, serum free light chains, serum and urine protein electrophoresis, and immunofixation). In addition to bone marrow aspirate and biopsy specimens sent for histopathological review, aspirate samples should also be sent for flow cytometric analysis to evaluate for the presence of clonal plasma cells as well as fluorescence in situ hybridization (FISH) on CD138-selected cells and cytogenetic testing. The Revised International Staging System (R-ISS) includes testing of albumin,

$\beta_2$ -microglobulin, and LDH, as well as evaluation of key high-risk cytogenetic abnormalities observed from the FISH analysis of the bone marrow aspirate (including del[17p], t[4;14], and t[14;16]).<sup>1</sup> Several options for whole-body imaging exist, including low-dose whole-body CT (LDWBCT), whole-body PET/CT, and whole-body MRI imaging.<sup>2</sup> In both the International Myeloma Working Group and the National Comprehensive Cancer Network guidelines, the initial choices for imaging modality in the setting of suspected MM include either LDWBCT or PET/CT, with axial or whole-body MRI performed in the setting of negative or inconclusive testing.<sup>2,3</sup> In the setting of known or suspected extramedullary involvement, PET/CT is the preferred imaging modality. These imaging modalities have replaced conventional skeletal surveys; the latter, while widely available, offer comparatively poor sensitivity. For example, in one head-to-head comparison between skeletal survey and LDWBCT, 25% of patients with negative skeletal surveys had lytic lesions on LDWBCT.<sup>4</sup>

**Molecular Testing**

Current staging and risk stratification systems primarily rely on information obtained from the CD138-selected FISH panel, which, at minimum, should evaluate for the presence of del(13), del(17p), t(4;14), t(11;14), t(14;16), and t(14;20), and for gain/amplification of 1q21 and del(1p). The frequency of these cytogenetic abnormalities is shown in **Table 1**. Within this panel, the “traditional” high-risk abnormalities have included del(17p), t(4;14), t(14;16), and t(14;20). Increasing evidence supports that 1q abnormalities, particularly amplification (>4 copies) or in combination with other high-risk abnormalities, should also be considered a high-risk abnormality.<sup>5</sup> “Double-hit” biallelic inactivation of TP53 (eg, del[17p] in one allele plus mutation in the other allele) appears

**TABLE 1. Frequencies of Cytogenetic Abnormalities in Multiple Myeloma<sup>78</sup>**

Abnormality	Frequency (%)
<b>Hyperdiploidy</b>	50
<b>Gain 1q</b>	40
<b>IGH translocation</b>	
t(11;14)	17
t(4;14)	15
t(14;16)	5
t(6;14)	2
t(14;20)	1
<b>Deletions</b>	
13q	45
1p	30
6q	33
8p	25
14q	38
16q	35
17p	10

to be associated with the highest risk, although a recent publication demonstrated that del(17p) by itself is also associated with poor outcomes.<sup>6,7</sup>

A number of gene signatures associated with standard- or high-risk disease have been reported over the years, and while the different panels have been demonstrated to identify different risk groups, these panels generally do not share any overlapping genes across the signatures.<sup>8</sup> Thus, consensus has not been reached in the field regarding the optimal gene expression profiling (GEP) panel to utilize, and therefore this testing is not considered SOC.

**Stratification for Treatment Selection**

**TRANSPLANT ELIGIBILITY.** For many patients, recommendations for initial treatment still hinge on whether the patient is considered to be eligible for high-dose therapy and ASCT. However, there is increasing overlap in the

induction strategies used in the transplant-eligible (TE) and transplant-ineligible (TI) groups, and multiple studies have demonstrated the feasibility and efficacy of ASCT in older adults.<sup>9-11</sup> While ASCT candidacy is still sometimes in the eye of the beholder (namely, the transplant physician), several key factors that lead to ineligibility include poor performance status, liver cirrhosis, and heart failure (New York Heart Association functional status Class III/IV). Unfortunately, many patients who are potentially TE are never referred to an ASCT center for evaluation.<sup>12-15</sup>

The line between TI and TE has also been blurred by the study design of several recent cooperative group phase 3 studies. In these, ND patients could either be TE who chose not to go through an upfront ASCT or TI (**Table 2**). As previously discussed,<sup>16</sup> it can be difficult to apply the results of these studies (eg, SWOG S0777, ECOG E1A11) to the more typical TI patient seen in practice, one who is often older with more comorbidities. For instance, in the SWOG S0777 study (NCT00644228), 68% of the enrolled population were noted to have intent to pursue ASCT. Thus, while this trial is often used to support the assertion that lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone (RVd) is an SOC in the TI population, in actuality this study primarily enrolled a TE population who chose not to undergo upfront ASCT. In addition, the region of the world in which a trial was conducted is important, because age cutoffs for transplant eligibility may differ by nation. For example, in the MAIA study (NCT02252172; discussed further below), which helped establish the combination of daratumumab, (Dara; Darzalex), lenalidomide, and dexamethasone (Dara-Rd) as an SOC for TI patients, more than half of the enrolled subjects were aged less than 75 years<sup>17</sup> and thus may have been considered TE in the United States.

**TABLE 2. Summary of Recent Randomized Phase 2 or 3 Studies in Patients With Newly Diagnosed Multiple Myeloma**

Study	Eligible age (yrs)	TE or TI	Treatment
SWOG S0777 <sup>61,62</sup>	≥18	TE (without plan for upfront) and TI	RVd × 8 → Rd vs Rd
ECOG E1A11 <sup>35</sup>	≥18	TE (without plan for upfront) and TI	KRd × 9 vs RVd × 12 (R maintenance for both groups)
SWOG-1211	≥18	TE (without plan for upfront) and TI	RVd × 8 → RVd maintenance vs Elo-RVd × 8 → Elo-RVd maintenance
MAIA <sup>17,64</sup>	≥18	TI	Dara-Rd vs Rd
TOURMALINE-MM2 <sup>65</sup>	≥65 (or TI due to comorbidities)	TI	IRd × 18 → IR vs Rd × 18 → R
ALCYONE <sup>68,69</sup>	≥65 (or TI due to comorbidities)	TI	Dara-VMP × 9 → Dara vs VMP × 9
CLARION <sup>67</sup>	≥18	TI	KMP × 9 vs VMP × 9
KEYNOTE-185 <sup>66</sup>	≥18	TI	Pembro-Rd vs Rd
GRIFFIN <sup>46,47</sup>	≤70	TE	Dara-RVd × 4 → ASCT → Dara-RVd × 2 → Dara-R vs RVd × 4 → ASCT → RVd × 2 → R
CASSIOPEIA <sup>45</sup>	≤70	TE	Dara-VTd × 4 → ASCT → Dara-VTd × 2 vs VTd × 4 → ASCT → VTd × 2 (Second randomization to Dara maintenance vs observation)
GMMG-HD6 <sup>79</sup>	≤70	TE	RVd × 4 → ASCT → RVd × 2 → R vs RVd × 4 → ASCT → Elo-RVd × 2 → Elo-R vs Elo-RVd × 4 → ASCT → RVd × 2 → R vs Elo-RVd × 4 → ASCT → Elo-RVd × 2 → Elo-R
FORTE <sup>38</sup>	≤65	TE	KRd × 4 → ASCT → KRd × 4 vs KRd × 12 vs KCd × 4 → ASCT → KCd × 4 (Second randomization to R vs KR maintenance)
IFM 2009 <sup>40</sup>	≤65	TE	RVd × 3 → ASCT → RVd × 2 vs RVd × 8 (Both arms include R maintenance × 1 yr)
DFCI 2009 <sup>41</sup>	≤65	TE	RVd × 8 vs RVd × 3 → ASCT → RVd × (Both arms include R maintenance × until progression)

ASCT, autologous stem cell transplant; C, cyclophosphamide; Dara, daratumumab; d, dexamethasone; Elo, elotuzumab; I, ixazomib; K, carfilzomib; M, melphalan; mo, month; NR, not reached; OS, overall survival; P, prednisone; pembro, pembrolizumab; PFS, progression-free survival; R, lenalidomide; T, thalidomide; TE, transplant eligible; TI, transplant ineligible; upfront, upfront ASCT; V, bortezomib; yr, year.

	Median age (yrs)	PFS	OS
	63 (43% ≥65 yrs)	Median: 41 vs 29 mos (HR, 0.742; 96% CI, 0.594-0.928; <i>P</i> = .003)	Median: NR vs 69 mos (HR, 0.709; 96% CI, 0.543-0.926; <i>P</i> = .0114)
	65 (32% ≥70 yrs)	34.6 vs 34.4 mos (HR, 1.04; 95% CI, 0.83-1.3; <i>P</i> = .74)	Median: NR in either arm (HR, 0.98; 95% CI, 0.71-1.36; <i>P</i> = .92)
	66 (24% ≥70 yrs)	33.6 vs 31.5 mos (HR, 0.968; 80% CI, 0.697-1.344; <i>P</i> = .90)	Median: NR vs 68 mos (HR, 1.279; 80% CI, 0.819-2.000; <i>P</i> = .48)
	73 (44% ≥75 yrs)	Median: NR vs 34.4 mos (HR, 0.53; 95% CI, 0.43-0.66; <i>P</i> < .0001)	Median: NR in either arm (HR, 0.68; 95% CI, 0.53-0.86; <i>P</i> = .0013)
	73-74 (43%-44% ≥75yrs)	Median: 35.3 vs 21.8 mos (HR, 0.83; 95% CI, 0.676-1.018; <i>P</i> = .073)	Median: NR in either arm (HR, 0.998; 95% CI, 0.790-1.261; <i>P</i> = .988)
	71 (30% ≥75 yrs)	Median: 36.4 vs 19.3 mos (HR, 0.42; 95% CI, 0.34-0.41; <i>P</i> < .0001)	Median: NR in either arm (HR, 0.60; 95% CI, 0.46-0.80; <i>P</i> = .0003)
	72 (31% ≥75 yrs)	Median: 22.3 vs 22.1 mos (HR, 0.906; 95% CI, 0.746-1.101; <i>P</i> = .159)	Median: NR in either arm (HR, 1.08; 95% CI, 0.82-1.43)
	74 (31%-32% ≥80 yrs)	6-mo: 82% vs 85% (HR, 1.22; 95% CI, 0.67-2.22; <i>P</i> = .75)	Median NR in either arm (HR, 2.06; 95% CI, 0.93-4.55; <i>P</i> = .97)
	60 (27% ≥65 yrs)	3-yr: 88.9% vs 81.2% (HR, 0.46; 95% CI, 0.21-1.01)	3 yr: 92.6% vs 92.2% (HR, 0.90; 95% CI, 0.32-2.57)
	58	Median: NR in either arm (HR, 0.47; 95% CI, 0.33-0.67; <i>P</i> < .0001)	Median: NR in either arm (HR, 0.43; 95% CI, 0.23-0.80)
	59	3-yr: 68.8% vs 68.5% vs 66.2% vs 67.2% ( <i>P</i> = .86)	3-yr: 89.4% vs 89.1% vs 92.5% vs 89.7% ( <i>P</i> = .43)
	57 (39% ≥60 yrs)	3-yr: 68.8% vs 68.5% vs 66.2% vs 67.2% ( <i>P</i> = .86) 4-yr: 69% (KRd-ASCT) vs 56% (KRd-12) vs 51% (KCd-ASCT) (HR for KRd-ASCT vs KCd-ASCT, 0.54; 95% CI, 0.38-0.78; <i>P</i> = .0008) (HR for KRd-ASCT vs KRd x 12, 0.61; 95% CI, 0.43-0.88; <i>P</i> = .0084)	4-yr: 86% (KRd-ASCT) vs 85% (KRd-12) vs 76% (KCd-ASCT)
	59-60	Median: 50 vs 36 mos (HR, 0.65; 95% CI, 0.53-0.80; <i>P</i> < .001)	4-yr: 81% vs 82% (HR, 1.16; 95% CI, 0.80-1.68; <i>P</i> = .87)
	55-57	Median: 46.2 vs 67.5 mos (HR, 1.53; 95% CI, 1.23-1.91; <i>P</i> < .001)	5-yr: 79% vs 81% (HR, 1.10; 95% CI, 0.73-1.65; <i>P</i> > .99)

**FRAILTY-BASED ASSESSMENT.** A growing body of literature supports the use of geriatric and frailty assessment in determining treatment strategies for older adults who are being considered for ASCT as well as those who are considered TI.<sup>18-21</sup> Frailty status has been shown to be a predictor of mortality in patients with MM.<sup>22,23</sup> Multiple different frailty indices have been developed, including the International Myeloma Working Group (IMWG) Frailty Index, the Revised Myeloma Comorbidity Index, the Simplified Frailty Scale, and the UK Myeloma Research Alliance (UKMRA) Myeloma Risk Profile. The IMWG Frailty Index encompasses patient age, the Katz Activity of Daily Living scale, the Lawton Instrumental Activity of Daily Living scale, and the Charlson Comorbidity Index (CCI) score.<sup>24,25</sup> The Revised Myeloma Comorbidity Index incorporates age, renal function, lung function, Karnofsky performance status, frailty (as determined by the Fried definition<sup>26</sup>), and disease cytogenetics.<sup>27</sup> The Simplified Frailty Scale includes age, ECOG status, and CCI<sup>28</sup> score; the UKMRA Myeloma Risk Profile includes age, World Health Organization performance status, ISS, and C-reactive protein.<sup>29</sup>

To date, the majority of the literature derives from post hoc analysis of clinical trials or large database reviews, and there is no consensus about the best available instrument to assess frailty.<sup>22,23,30-32</sup> The Hovon 143 phase 2 study, which evaluated an induction strategy of daratumumab, ixazomib (Ninlaro), and dexamethasone, was of interest as it was specifically designed for frail TI patients.<sup>33</sup> To be eligible for this study, patients had to be deemed frail by the IMWG frailty index. The median age of the enrolled subjects was 81 years (range, 70-92).<sup>33</sup> While the reported overall response rate (ORR) was high (78%), the median progression-free survival (PFS) was only 13.8 months and 30% of patients died within the

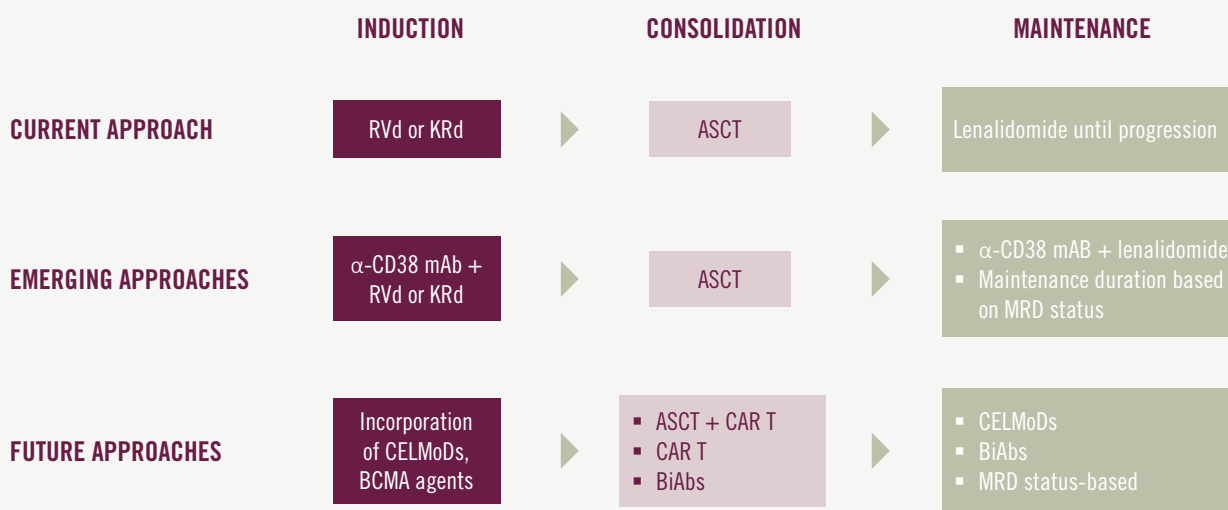
first year, highlighting the difficulty of treating this population. The ongoing FiTNEss (Frailty-adjusted therapy in Transplant Non-Eligible patients with newly diagnosed Multiple Myeloma) study (NCT03720041; Myeloma XIV) is a randomized phase 3 trial evaluating ixazomib/lenalidomide/dexamethasone (IRd) induction therapy in TE patients. The first randomization is to non-frailty-adjusted IRd induction vs frailty index-adjusted induction where different dose levels of lenalidomide and dexamethasone are used based on fit vs intermediate vs frail status.<sup>34</sup> A second randomization involves maintenance with lenalidomide/placebo vs lenalidomide/ixazomib. The primary objectives are to compare early treatment cessation (<60 days from randomization) between standard and frailty-adjusted induction and PFS for the maintenance component. A report of the first 180 of a planned 740 subjects noted the feasibility of recruiting older patients (median age thus far 77 years, with 26% aged more than 80 years).<sup>34</sup> Additional studies focused on these frail patients—who more accurately represent the real-world population of patients seen in practice—are needed.

**CYTOGENETIC RISK.** Another potential stratification for treatment selection involves standard-risk vs high-risk disease. However, in the era of triplet/quadruplet induction regimens, few data suggest that one specific induction strategy has superior outcomes over others for patients with high-risk disease. This is primarily because the majority of randomized phase 2/3 studies have relied on underpowered subgroup analyses to compare standard- vs high-risk groups, and typically, patients with high-risk disease are underrepresented. This problem has been further exacerbated by differing definitions of high-risk disease (eg, whether 1q abnormalities are included, differing cut-offs for positivity,

or exclusion of primary plasma cell leukemia) across studies.

The ENDURANCE trial (NCT01863550; ECOG E1A11) randomized patients to RvD vs carfilzomib (Kyprolis), lenalidomide, and dexamethasone (KRd) induction (without upfront ASCT) (Table 2).<sup>35</sup> This study excluded patients with del(17p), t(14;16), t(14;20), LDH greater than 2 times the upper limit of normal (ULN), or greater than 20% circulating plasma cells. There was no difference in the primary end point (PFS) between the 2 treatment arms. Furthermore, subgroup analysis of the patients with t(4;14) did not reveal benefit for KRd over RvD (HR, 1.16; 95% CI, 0.54-2.47).<sup>35</sup> In contrast, the SWOG-1211 study (NCT01668719) enrolled all of the high-risk patients who had been excluded from the ENDURANCE trial (high-risk GEP, t[14;16], t[14;20], del[17p], amp[1q], primary plasma cell leukemia, or LDH >2x ULN). In this study, which again did not include upfront ASCT, patients were randomized to elotuzumab (Emluciti) plus RvD vs RvD induction.<sup>36</sup> This study failed to demonstrate benefit of adding elotuzumab to the backbone of RvD induction in patients with high-risk MM. The UK OPTIMUM/MUKnine trial (NCT03188172) exclusively enrolled patients considered to have ultra-high-risk disease, defined as having 2 or more high-risk features (t[4;14], t[14;16], t[14;20], gain[1q], del[1p], del[17p], gene expression SKY92 profiling, or >20% circulating plasma cells). This study was designed as a digital comparator-arm trial in which enrolled subjects were compared with molecularly matched patients from the National Cancer Research Institute Myeloma XI/XI+ trial (NCT01554852). A superior 18-month PFS rate (the primary end point) was observed with the UK OPTIMUM/MUKnine treatment strategy (involving a 5-drug induction regimen, transplant, and intensive

**FIGURE. Current, Emerging, and Future Treatment Strategies for Newly Diagnosed Transplant-Eligible Multiple Myeloma**



The current treatment paradigm includes induction with a triplet combination, consolidation with ASCT, and posttransplant lenalidomide maintenance. Based on recent and ongoing studies, standards of care are evolving to include anti-CD38 mAb therapy in the induction and maintenance settings as well as potentially utilizing MRD status to determine treatment duration. Looking further ahead, it is predicted that other classes of drugs will be incorporated into the induction setting and that ASCT may be used in conjunction with CAR T-cell therapy or be replaced entirely by CAR T-cell therapy or BiAb therapies. Maintenance therapy may include novel agents and may be based on MRD status.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; BiAb, bispecific antibody; CAR T, chimeric antigen receptor T-cell therapy; CELMoD, cereblon E3 ligase modulator; KRd, carfilzomib/lenalidomide/dexamethasone; mAb, monoclonal antibody; MRD, minimal residual disease; RVd, lenalidomide/bortezomib/dexamethasone.

consolidation/maintenance strategies) compared with that achieved by the molecularly matched participants from the previous Myeloma XI trial: 81.7% vs 65.9%, respectively.<sup>37</sup> It is hoped that ongoing phase 3 studies comparing quadruplets vs triplets (eg, PERSEUS [NCT03710603], GMMG HD7 [NCT03617731]) will provide more information regarding the potential benefit of quadruplets in patients with high-risk disease.

**Therapy Selection**

**TRANSPLANT ELIGIBLE.** In the TE setting, induction therapy consisting of lenalidomide, a PI (either bortezomib or carfilzomib), and dexamethasone is established as SOC (Figure). A direct

comparison of RVd and KRd induction followed by ASCT has not been conducted. As noted above, no difference in PFS (comparing RVd vs KRd) was observed in the ENDURANCE study; however, this study did not include consolidation with ASCT or most categories of high-risk disease.<sup>35</sup> While prospective randomized data are lacking for the comparison of RVd vs the combination of bortezomib, cyclophosphamide, and dexamethasone (VCd), some trial results have demonstrated the superiority of bortezomib, thalidomide, and dexamethasone (VTd) over VCd (IFM2013-04; NCT01971658) as well as KRd over carfilzomib, cyclophosphamide, and dexamethasone (FORTE; NCT02203643).<sup>38,39</sup>

The IFM/DFCI2009 (NCT01191060) and FORTE trials demonstrated superior PFS rates for the inclusion of upfront ASCT as consolidation following RVd (IFM/DFCI2009) or KRd (FORTE) induction.<sup>38,40,41</sup> None of these studies have demonstrated superior overall survival (OS) outcomes with inclusion of upfront ASCT, but given the increasing number of salvage therapies available and the overall trend for longer duration of survival in this patient population, it is becoming increasingly difficult to demonstrate OS benefit in the upfront setting.

As shown in Table 2 and Table 3, many recent and/or ongoing randomized studies have included post-ASCT consolidation with multiagent therapy prior to transitioning to maintenance



therapy. Whether these cycles of post-ASCT consolidation contribute significantly to the long-term outcomes of these treatment strategies is not clear. The BMT CTN 0702 trial (NCT01109004) randomized patients who had completed induction therapy to 1 of 3 arms: single ASCT, tandem ASCT, or single ASCT followed by 4 cycles of RVd consolidation.<sup>42</sup> All 3 arms then went on to receive lenalidomide maintenance. No differences in either PFS or OS outcomes were observed across the 3 arms, suggesting that single ASCT followed by lenalidomide maintenance was an SOC.<sup>42</sup> The EMN02/HOVON 95 MM trial (NCT01208766) compared post-VCd induction therapy of the combination of bortezomib, melphalan, and prednisone (VMP) vs ASCT (1 or 2 transplants).<sup>43</sup> A second randomization involved additional consolidation with either 2 cycles of RVd or nothing, followed by lenalidomide maintenance in both arms. As a whole, a superior PFS rate was observed for those receiving RVd consolidation (59.3 vs 42.9 months; HR, 0.81; 95% CI, 0.68-0.96;  $P = .016$ ).<sup>44</sup> However, upon closer examination of the subset of patients who received ASCT, one observes that the trend toward superior PFS with RVd consolidation did not quite reach statistical significance (HR, 0.83; 95% CI, 0.66-1.03).<sup>44</sup> Of note, no patients in the EMN02/HOVON 95 MM trial received lenalidomide with induction, whereas 56% of patients in the BMT CTN 0702 trial received RVd induction and 10% received lenalidomide and dexamethasone (Rd) induction. Overall, outside the context of a clinical trial, patients commonly proceed directly from ASCT to maintenance therapy, bypassing multiagent consolidation.

A major unanswered question in the TE setting is the potential role of mAb therapy as an addition to the backbone of IMiD/PI/dexamethasone induction; many recent and ongoing studies are addressing this knowledge gap (Tables

2 and 3). For instance, the CASSIOPEIA trial (NCT02541383), a randomized phase 3 study, evaluated the addition of daratumumab to the backbone of VTd induction/consolidation (Table 2). While the study met its primary end point (median PFS not reached in either arm; HR, 0.47; 95% CI, 0.33-0.67;  $P < .0001$ ),<sup>45</sup> resulting in the FDA approval of Dara-VTd, it has not been practice-changing in the United States given the use of thalidomide. Of more interest have been the studies evaluating the addition of mAb therapy to RVd or KRd backbones. GRIFFIN (NCT02874742), a randomized phase 2 trial, compared RVd induction, ASCT, RVd consolidation, and R maintenance with Dara-RVd induction, ASCT, Dara-RVd consolidation, and Dara-R maintenance. The study met its primary end point of stringent complete response (sCR) rate post consolidation (42.4% vs 32.0%; odds ratio [OR], 1.57; 95% CI, 0.87-2.82; 1-sided  $P = .068$  with a prespecified 1-sided  $\alpha$  of 0.10).<sup>46</sup> However, the 24-month PFS rates were similar (95.8% vs 89.8%). With longer follow-up, the PFS curves have had more separation, not yet meeting statistical significance (3-year PFS rate, 88.9% vs 81.2%; HR, 0.46; 95% CI, 0.21-1.01).<sup>47</sup> Higher rates of grade 3/4 neutropenia, thrombocytopenia, and upper respiratory tract infections were observed in the daratumumab-containing group.<sup>47</sup> The ongoing phase 3 PERSEUS study (Table 3), which has a similar design (with the exception of the maintenance portion), is powered to evaluate PFS as the primary end point and should therefore provide more substantive evidence for the use of Dara-RVd as an induction strategy. The phase 3 GMMG-HD7 trial evaluated isatuximab (Isa; Sarclisa), another anti-CD38 mAb, in the context of RVd induction. This study was designed to evaluate the achievement of MRD negativity (at  $10^{-5}$  sensitivity using flow cytometry) post induction therapy as the primary end point. A statistically

significant improvement in rates of MRD negativity post induction was observed for the Isa-RVd arm (50.1%) vs the RVd arm (35.6%) (OR, 1.83; 95% CI, 1.34-2.51;  $P < .001$ ).<sup>48</sup> No data regarding PFS outcomes have been reported thus far. Several single-arm studies have evaluated Dara-KRd induction (with or without ASCT) and reported high rates of MRD negativity.<sup>49,50</sup> As neither sCR nor rates of MRD negativity have been confirmed as surrogate end points for PFS or OS, further follow-up is required from ongoing studies to determine whether initial achievement of deeper response rates in the setting of quadruplet therapies translate to superior long-term outcomes.

An in-depth discussion of maintenance is outside the scope of this review and is discussed more extensively elsewhere.<sup>51-53</sup> However, the current SOC, established through four randomized phase 3 studies, is the use of single-agent lenalidomide maintenance therapy. These studies demonstrated significant PFS benefit with lenalidomide maintenance (compared with placebo or observation) and in aggregate also showed superior OS outcomes.<sup>54-59</sup> Current unanswered questions include whether addition of mAb therapy to the backbone of lenalidomide maintenance improves outcomes, whether maintenance must be continued indefinitely to achieve optimal long-term outcomes, and whether a response-adapted approach using MRD negativity can be utilized to determine maintenance intensity and duration.

**TRANSPLANT INELIGIBLE.** Many of the randomized studies conducted over the past decade have built upon the backbone of continuous Rd induction, which had previously been established as an SOC by the FIRST trial (NCT00689936).<sup>60</sup> As noted above, SWOG S0777 randomized patients to RVd vs Rd induction in the absence of ASCT, but the minority of enrolled subjects were considered TI.<sup>61</sup> This study demonstrated superior PFS

**TABLE 3. Ongoing Randomized Phase 3 Studies in NDMM**

Study	ASCT candidacy requirement at entry	Induction regimens	Primary end point	Study scheme details
<b>NCT03742297</b>	TI	VMP→ Rd vs KRd +/- Dara → Dara-R	CR rate	Induction therapy followed by maintenance (Rd or Dara-R)
<b>NCT03993912 (IFM2017-03)</b>	TI (frail)	Dara-R vs Rd	PFS	Continuous treatment until progression
<b>NCT04751877 (IFM2020-05)</b>	TI (nonfrail)	Isa-RVd vs Isa-Rd	Rate of MRD negativity rate at 18 mos (10 <sup>-5</sup> )	
<b>NCT04096066</b>	TI	KRd vs Rd	MRD negativity and PFS	In the KRd arm, if ≥VGPR within first year and in sustained MRD-negativity (10 <sup>-5</sup> ) after 1 and 2 years, then K is stopped and Rd is continued
<b>NCT03720041 (Myeloma XIV, FiTNEss)</b>	TI	IRd (reactive vs adaptive dosing)	Early treatment cessation rate	First randomization based on frailty scoring. Second randomization to R/placebo vs R/I maintenance
<b>NCT03652064 (CEPHEUS)</b>	TE (without plan for upfront) and TI	Dara-RVd vs RVd	MRD negativity	Induction (8 cycles), maintenance (Rd vs Dara-Rd) until disease progression or unacceptable toxicity
<b>NCT04566328 (EQUATE)</b>	TE (without plan for upfront) and TI	Dara-Rd vs Dara-RVd	OS	Dara-Rd induction, MRD testing, randomization to DRd vs Dara-RVd × 9, followed by Dara-R until progression
<b>NCT03710603 (PERSEUS)</b>	TE	Dara-RVd vs RVd	PFS	Induction (4 cycles), ASCT, consolidation (2 cycles), maintenance (R or Dara-R) until disease progression or unacceptable toxicity. Duration of Dara based on MRD.
<b>NCT03617731 (GMMG-HD7)</b>	TE	Isa-RVd vs RVd	MRD negativity after induction; PFS from second randomization	Induction (three 42-day cycles), ASCT (× 2 if not in CR after first), 2nd randomization to Isa-R vs R maintenance
<b>NCT04483739 (IsKia)</b>	TE	Isa-KRd vs KRd	MRD negativity post ASCT	Induction (4 cycles), ASCT, consolidation (4 cycles plus 12 “light” cycles), R maintenance
<b>NCT03948035</b>	TE	Elo-KRd vs KRd	Induction: MRD negativity Maintenance: PFS	Induction/consolidation Elo-KRd vs KRd, ASCT, maintenance (Elo-R or R)
<b>NCT04923893 (CARTITUDE-5)</b>	TE (without plan for upfront) and TI	RVd→Rd vs RVd→ciltacabtagene autoleucl	PFS	8 cycles of RVd prior to Rd vs CAR T-cell therapy
<b>NCT05257083 (CARTITUDE-6)</b>	TE	Dara-RVd/ASCT/ Dara-RVd vs Dara-RVd/ciltacabtagene autoleucl	PFS and sustained MRD negativity (10 <sup>-5</sup> for at least 12 mos)	Both arms receive R maintenance for up to 2 years

ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CR, complete response; Dara, daratumumab; d, dexamethasone, Elo, elotuzumab; I, ixazomib; Isa, isatuximab; K, carfilzomib; mos, months; M, melphalan; MRD, minimal residual disease; OS, overall survival; P, prednisone; PFS, progression-free survival; R, lenalidomide; TE, transplant eligible; TI, transplant ineligible; V, bortezomib; VGPR, very good partial response.



and OS outcomes with the triplet vs the doublet (Table 2).<sup>61,62</sup> However, it is again worth noting that the majority of patients enrolled in this study were TE. As real-world experience has highlighted the difficulties of utilizing full-dose lenalidomide, twice-weekly bortezomib, and/or

prolonged dexamethasone in more frail patients, a single-arm phase 2 study was conducted to evaluate the “RVd lite” regimen.<sup>63</sup> In this study, lenalidomide was decreased to 15 mg, bortezomib was administered once weekly (subcutaneously), and dexamethasone was administered only during

the induction phase. The trial consisted of 9 cycles of triplet therapy followed by 6 cycles of consolidation with lenalidomide and bortezomib.<sup>63</sup> Maintenance was not dictated by the trial, but lenalidomide maintenance could be utilized per investigator discretion. Consistent

#### PERSPECTIVE BY

**Kimberley R. Doucette, MD, MSC; and David H. Vesole, MD, PhD**

## Recent Advancements and Future Directions in Frontline Treatment of Multiple Myeloma

**T**he author of “Current Frontline Treatment of Multiple Myeloma,” provides a thorough review of the current standard of care for multiple myeloma in the frontline setting. It is becoming more apparent that multiple myeloma is a heterogenous disease that requires individually tailored treatment, dependent on patient factors and biologic characteristics, including disease stage and molecular features. We have traditionally divided patients into transplant eligible vs transplant ineligible, but there are important nuances in making these determinations. The literature has varying definitions of transplant eligibility. In addition, there are restrictions on medical financial resources in some countries outside the United States, sometimes limiting accessibility to transplant options. Supportive care for autologous stem cell transplants is continuously improving, allowing us to perform successful transplants in a greater number of patients.<sup>1</sup> As the FORTE trial (NCT02203643) highlights,<sup>2</sup> autologous stem cell transplant remains a standard of care in multiple myeloma even in the era of novel therapies. The experience at our center, and in numerous centers across the United States, is that successful transplants can be done in fit patients aged up to 80 years or a little older, without significant morbidity and mortality.<sup>3</sup> The challenge has been to increase the number of patients referred to transplant centers to optimize this treatment strategy. According to statistics compiled by the Center for International Blood and Marrow

Transplant Research, less than 50% of individuals who are transplant eligible actually receive a transplant, and for members of US minority populations, this percentage is substantially lower.<sup>4</sup>

Aside from chronologic age, many other factors can affect treatment options and outcomes. The authors successfully point out that geriatric and frailty assessments are becoming increasingly important in identifying optimal treatment strategies for each individual patient. Clinical trials are addressing these assessments as a more objective measure of morbidity and mortality. For non-transplant-eligible patients, equally important therapeutic advancements have been made with the triplet regimen daratumumab (Darzalex), lenalidomide (Revlimid), and dexamethasone, which was studied in the MAIA trial (NCT02252172).<sup>5</sup> This trial has provided a new standard of care for frail older adults. This regimen is both tolerable and has good long-term outcomes (the most recent update shows a 53% progression-free survival [PFS] rate at 5 years). Unfortunately, despite the PFS advantage, many practitioners in the community have not yet adopted this as first-line therapy and are most commonly utilizing RVd-lite (lenalidomide, bortezomib [Velcade], and dexamethasone),<sup>6</sup> a regimen with a less favorable administration schedule, increased risk of toxicity (eg, peripheral neuropathy), and shorter PFS.

A critical goal for the multiple myeloma community is to identify treatment strategies that benefit patients

with a TI population, the median age was 73 years (range, 65-91). The reported median PFS was 35.1 months (95% CI, 30.9 to not reached).<sup>63</sup> The overall feasibility of this approach was demonstrated by 64% of the patients completing the 15 cycles of induction/consolidation

(with only 4% discontinuing due to toxicity) and patient-reported quality-of-life outcomes showing statistically significant improvements in physical function, future perspective, and disease symptom scores at the end of treatment compared with baseline.<sup>63</sup>

MAIA, a phase 3 study comparing Dara-Rd with Rd in the ND TI setting, has established Dara-Rd as an SOC in that setting. With a median follow-up of 56.2 months, the median PFS was not reached in the Dara-Rd group, compared with 34.4 months in the Rd

with high-risk disease, because their outcomes remain poor, despite recent advances in therapy. Most outcomes for high-risk disease are focused on subgroup analyses, and they therefore lack statistical strength. As pointed out by the authors, an increasing number of trials are focusing on high-risk groups to help identify successful treatment strategies. Thus far, we have had conflicting results regarding the benefit of quadruplet therapies on outcomes in patients with high-risk disease. Additionally, this is a heterogeneous group of patients with varying definitions of high-risk disease. For example, the revised International Staging System,<sup>7</sup> the International Myeloma Work Group,<sup>8</sup> and the Mayo Clinic's mSmart<sup>9</sup> all have different definitions of high risk. Regardless of which definition is utilized, optimal management of high-risk disease is a focus of active research as the field attempts to identify strategies to overcome its aggressive nature in these individuals.

As more knowledge emerges about patient outcomes with newer targeted therapies, clinicians are also learning about the importance of incorporating agents with different mechanisms of action and the role of minimal residual disease (MRD). MRD negativity, a surrogate marker of depth of response, is being incorporated as a biological end point in virtually all ongoing clinical trials. As the number of trials utilizing MRD negativity as a surrogate end point increases, we will hopefully gain deeper understanding into how to incorporate MRD data into our clinical decision making. Quadruplet therapies are likely going to become standards of care as they produce deep responses with high rates of MRD negativity and prolonged PFS. These include daratumumab + RVd as examined in the GRIFFIN trial (NCT02874742),<sup>10</sup> daratumumab + VTd (bortezomib, thalidomide, and dexamethasone) in the CASSIOPEIA trial (NCT02541383),<sup>11,12</sup> and daratumumab + KRd (carfilzomib, lenalidomide, and dexamethasone) in the MANHATTAN<sup>13</sup> and MASTER (NCT03224507)<sup>14</sup> trials.

The current dogma in multiple myeloma is to continue treatment until treatment intolerance or disease progression. In contrast, the MASTER trial is utilizing an MRD-adapted treatment approach, whereby after confirmation of MRD negativity, patients will enter a treatment-free phase. This would markedly change the current treatment paradigm of continuous therapy.

Lastly, the future of upfront therapy is likely to change as more targeted therapies and novel agents are being investigated in combinations with current standard of care. These therapies and agents include antibody-drug conjugates, cereblon E3 ligase modulating drugs, and T-cell engagers such as bispecific antibodies, chimeric antigen receptor T cells, and natural killer cells. These agents are revolutionizing the relapsed/refractory therapeutic landscape and are likely to make significant impact in the upfront setting as well. The advantage of many of these agents is their safety profile; their tolerability allows more patients to be successfully treated with fewer serious adverse effects. Studying these new agents and combinations in high-risk groups will be important.

We anticipate many ongoing changes in the frontline treatment setting over the next few years, with the goals of further increasing overall survival, PFS, and, importantly, quality of life.

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group (HR, 0.53; 95% CI, 0.43-0.66;  $P < .0001$ ).<sup>64</sup> Furthermore, an OS benefit was observed (HR, 0.68; 95% CI, 0.53-0.86;  $P = .0013$ ).<sup>64</sup> Median duration of response, overall response rate, and rate of MRD negativity were all superior in the Dara-Rd arm.<sup>64</sup>

The addition of a third drug to the Rd backbone has not always resulted in superior outcomes. In the phase 3 TOURMALINE-MM2 study (NCT01850524), patients were randomized to the combination of ixazomib, lenalidomide, and dexamethasone (IRd) vs Rd.<sup>65</sup> While the median PFS of the IRd group improved numerically relative to the Rd group (35.3 vs 21.8 months), this did not meet statistical significance (HR, 0.83; 95% CI, 0.676-1.018;  $P = .073$ ). No difference in OS was observed, although the median time to progression was superior in the IRd arm (45.8 vs 26.8 months; HR, 0.738; 95% CI, 0.589-0.925;  $P = .008$ ).<sup>65</sup> The phase 3 KEYNOTE-185 trial (NCT02579863) evaluated the addition of the immune checkpoint inhibitor pembrolizumab (Pembro; Keytruda) to the Rd backbone.<sup>61</sup> Notably, this study, as well as several others involving combination therapy with checkpoint inhibitors and IMiDs, were halted by the FDA due to imbalances in the proportion of deaths. With short follow-up (median, 6.6 months), the 6-mos PFS rate estimates were 82.0% (Pembro-Rd) vs 85.0% (Rd; HR, 1.22; 95% CI, 0.67-2.22;  $P = .75$ ). Overall response rates did not differ between the 2 treatment groups (64% vs 62%). Higher rates of serious adverse events (AEs) were observed in the Pembro-Rd arm (54%) compared with the Rd arm (39%) as were more treatment-related deaths (6 vs 1).<sup>66</sup>

VMP was historically an SOC induction regimen, particularly in Europe. The phase 3 CLARION study (NCT01818752) compared fixed-duration VMP induction therapy with

carfilzomib, melphalan, and prednisone (KMP). No differences in PFS (the primary end point), OS, complete response, or rate of MRD negativity were observed.<sup>67</sup> Consistent with the known AE profiles of the 2 PIs, the VMP arm was associated with higher rates of peripheral neuropathy while the KMP arm was associated with higher rates of acute renal failure and cardiac failure.<sup>67</sup> The results of this study, as well as those of ENDURANCE,<sup>35</sup> failed to demonstrate superiority of carfilzomib over bortezomib in the ND setting.

The phase 3 ALCYONE trial (NCT02195479) built upon the VMP backbone by adding daratumumab.<sup>68,69</sup> Fixed-duration VMP induction followed by observation was compared with Dara-VMP induction followed by daratumumab maintenance until progression. Here, the daratumumab-containing arm had significantly improved PFS (median, 36.4 vs 19.3 months; HR, 0.42; 95% CI, 0.34-0.41;  $P < .0001$ ).<sup>68</sup> Not surprisingly, there was more marked separation of the curves following the induction period, as the control arm was simply being observed off therapy (vs continued daratumumab therapy in the experimental arm). While neither the CLARION nor ALCYONE studies are particularly relevant to US ND TI treatment practices, given the backbones of melphalan plus prednisone, they do provide insight into the toxicity profile of upfront carfilzomib and the potential role for single-agent daratumumab maintenance, respectively.

### Emerging and Novel Therapies

As noted above, the incorporation of anti-CD38 mAb therapy is now well established in the TI setting and likely represents a future SOC in the TE setting as well. However, there is also interest in the incorporation of other novel agents into the newly diagnosed setting, such as anti-B-cell maturation antigen (BCMA) agents, chimeric antigen receptor (CAR)

T-cell therapy, the XPO1 inhibitor selinexor (Seli; Xpovio), and cereblon E3 ligase modulators (CELMoDs). The first-in-class anti-BCMA antibody-drug conjugate (ADC) belantamab mafodotin (Bela; Blenrep) is currently approved as a single agent in the heavily relapsed/refractory setting. Several ongoing studies are evaluating Bela in combination with other MM therapies in earlier lines of therapy, including in the ND setting. A phase 2 study (NCT04802356) is evaluating the combination of Bela-RVd induction followed by ASCT, Bela-RVd consolidation, and then maintenance with Bela-R (up to 2 years of Bela; lenalidomide until progression). The Bela-RVd combination is also being studied in the ND TI setting (DREAMM-9, NCT04091126) in which patients receive 8 cycles of Bela-RVd followed by Bela-Rd until progression.<sup>70</sup> During the phase 1 portion, the optimal dosing/schedule of Bela will be determined, followed by a phase 3 portion in which patients will be randomized 1:1 to Bela-RVd vs RVd. Determining a dose/schedule that minimizes the corneal toxicity associated with Bela, and thus allows long-term administration of this agent, will be critical. Also, some studies under development will incorporate novel bispecific antibody (BiAb) therapies such as teclistamab (an anti-BCMA/anti-CD3 agent) into the ND setting.

Several ongoing studies are evaluating the incorporation of BCMA-directed CART-cell therapy in the ND setting. The phase 1 KarMMa-4 (NCT04196491) study involves consolidation with idecabtagene vicleucel following induction (RVd, Dara-RVd, KRd, Dara-KRd, or CyBorD allowed) in patients with high-risk disease. Maintenance therapy with lenalidomide is allowed. The phase 3 CARTITUDE-5 (NCT04923893) trial randomizes patients who are not planning upfront ASCT to either RVd induction followed by ciltacabtagene autoleucel CAR T-cell therapy or RVd induction followed by Rd. In CARTITUDE-6

(NCT05257083), ND patients are randomized to treatment with Dara-RVd, ASCT, Dara-RVd, and R maintenance vs treatment with Dara-RVd, ciltacabtagene autoleucel (Carvykti), and R maintenance. The phase 2 BMTCTN1902 trial (NCT05032820) involves patients who have achieved less than a VGPR on lenalidomide maintenance within 12 months of ASCT; they will receive idecabtagene vicleucel (Abecma) CAR T-cell therapy followed by lenalidomide maintenance. Setting aside potential differences in cost, it remains to be seen whether CAR T-cell therapy will eventually replace ASCT because of its ability to induce longer-lasting disease-free intervals.

Several studies are exploring the incorporation of selinexor into the ND setting. The preliminary reported results of patients enrolled in the Seli-Rd arm of the STOMP study (NCT02343042) include an ORR of 100% in 8 patients.<sup>71</sup> An ongoing phase 2 study (NCT04782687) is exploring the combination of Seli-Dara-Rd in TI patients. Establishing a dose of Seli that has long-term tolerability will be critical, as use of this drug is often limited by its AE profile, which includes asthenia, weight loss, nausea, vomiting, and other gastrointestinal toxicity.<sup>72</sup>

Finally, the next-generation IMiD agents such as iberdomide and mezigdomide (CC-92480)—the CELMoDs—have shown promising activity in relapsed/refractory disease, including IMiD-refractory disease.<sup>73,74</sup> Multiple ongoing studies are evaluating CELMoDs in combination with other anti-MM agents, such as proteasome inhibitors and alkylators. Several studies are incorporating iberdomide into the TI and TE ND settings (eg, NCT05272826, NCT05199311) and post-ASCT maintenance setting (eg, NCT05177536). If these agents, with their increased potency, are determined to have superior toxicity profiles, then they could take the place of currently used IMiDs (Figure).

## Conclusions

Remarkable strides have been made in the treatment of NDMM in large part due to the development of IMiDs, PIs, and mAbs. Incorporation of anti-CD38 mAb therapy into the ND setting has been a significant advance for the TI population and appears poised to become an SOC in the TE setting as well (Figure). Looking ahead to the next 15 years, the hope is that incorporation of other strategies, including CAR T-cell therapy and BiAbs, will shift the treatment paradigms, potentially eradicating the disease with frontline therapy. Even if a cure remains out of reach during that timeframe, it is anticipated that incorporating novel therapies into the frontline setting will significantly improve survival outcomes. Whether these new therapies could be accompanied by prolonged treatment-free intervals, which would represent a notable shift from current treatment strategies, remains to be determined. Integral in the development of these emerging treatment paradigms will be incorporation of novel surrogate end points, such as MRD negativity, into trial design; this will not only allow earlier readouts of trials, but also help guide decision making regarding treatment de-escalation, intensification, or cessation.<sup>49,75-77</sup> ■

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