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Opinion

The Role of Autologous Stem Cell Transplantation in the Treatment of Newly Diagnosed Multiple Myeloma: Is It Time to Rethink the Paradigm in the Era of Targeted Therapy?

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Abstract: High-dose melphalan (HDM) plus autologous stem cell transplant (ASCT) remains a standard-of-care treatment approach for eligible patients with newly diagnosed multiple myeloma (NDMM) based on demonstrated superiority in terms of progression-free survival (PFS) versus nontransplant approaches. Very high rates of minimal residual disease (MRD)-negative responses are also being seen with novel triplet and quadruplet induction regimens plus HDM-ASCT. However, recent clinical trials have shown no overall survival benefit with transplant versus nontransplant approaches. Furthermore, HDM is associated with several important downsides, including acute and long-term toxicities, transient decreases in quality of life, the need for hospitalization, an increased mutational burden at relapse, and an elevated risk of second primary malignancies. In this context, given the highly heterogeneous nature of MM in the NDMM patient population, as well as the continued emergence of novel agents and treatment approaches, there is an increasing rationale for considering deferred HDM-ASCT approaches in selected patients. Approaches under investigation include MRD-adapted therapy and the use of novel immune-based therapies as alternatives to HDM-ASCT. Ongoing developments in understanding the pathobiology and prognostic factors in NDMM, plus immune profiling and routine MRD evaluation, will result in novel, HDM-sparing treatment paradigms, enabling further improvement in patient outcomes.

Keywords: bispecific antibody; CAR T cell therapy; high-dose melphalan; minimal residual disease; monoclonal antibody; personalized therapy; quadruplet; quality of life; second primary malignancies; toxicity

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1. Introduction

It has now been over 40 years since the first publication by Tim McElwain and Ray Powles on their pioneering work with high-dose melphalan (HDM) for patients with multiple myeloma (MM) [1]. The past four decades have witnessed an explosion of new treatments, such that the modern therapeutic armamentarium is barely recognizable from that of the 1980s. And yet, HDM not only endures but also retains its position as a standard-of-care approach, together with autologous stem cell transplantation (ASCT), for eligible patients with newly diagnosed MM (NDMM) [2–5]. Clearly, melphalan matters in MM. However, as the late, great Tim McElwain himself remarked to me when I was fortunate enough to be working for him at the Royal Marsden in Sutton, UK in 1990, "We will be doing our patients a real service if we can do better than melphalan in the years ahead". So, the question now is can we do better? Can we build on the positive aspects of HDM while leaving behind the undesirable features that can be a burden—or potentially worse—for our patients? In the emerging era of highly efficacious immune-based therapies and minimal residual disease (MRD)-guided therapy, I believe that, in an increasing number of selected patients, we can.

2. The Benefits of HDM

Large, randomized trials have unequivocally demonstrated the superiority of HDM-ASCT-based versus non-HDM-ASCT-based approaches for NDMM in terms of progression-free survival (PFS), both prior to [6,7] and in the era of novel agents [3,8,9]. In the DETERMINATION phase 3 trial of lenalidomide–bortezomib–dexamethasone (RVd) ± HDM-ASCT, followed by lenalidomide maintenance to progression, median PFS with RVd + ASCT versus RVd-alone was 67.5 versus 46.2 months, a benefit of 21.3 months, and the risk of progression/death was 35% lower with RVd + ASCT [3].

Furthermore, modern triplet and quadruplet induction regimens coupled with ASCT and maintenance therapy are demonstrating ever higher rates of deep and durable responses, including MRD-negative rates of up to 94% [3,8–31]. Importantly, in the MANHATTAN study, MRD negativity was seen in 71% of patients without ASCT as part of a prespecified analysis, using daratumumab–carfilzomib–lenalidomide–dexamethasone as induction remission therapy, supporting the efficacy of the quadruplet alone [31]. MRD negativity represents an increasingly important goal of MM therapy [32] given the high rates now achievable and the strong prognostic value of MRD elimination for improved outcomes [11,13,14,33,34]. Of note, the proportion of patients achieving MRD-negative status was higher in the RVd + ASCT versus RVd-alone arm in both DETERMINATION (54% vs. 40% at the start of maintenance) [3] and the IFM 2009 trial (29.8% vs. 20.4%, $p = 0.01$) [11], although the PFS benefit in those patients in DETERMINATION who achieved MRD-negative status was similar irrespective of treatment arm [11].

These deep responses may be associated, in part, with the profound effects of HDM on both tumor cells and the immunosuppressive tumor microenvironment [35,36]; not only is the "stemness" of the disease targeted but also cytokine secretion and other signaling processes in MM cells that result in the stimulation of immunosuppressive cells and the inhibition of cytotoxic effector T cells and others, contributing to the depth of responses seen. Myeloablative conditioning with HDM-ASCT "resets" elements of the tumor microenvironment, thereby engendering an improved antitumor immune microenvironment and tumor-specific immunity following cellular reconstitution [37,38]. The continued success of HDM may be due to these beneficial immune effects, as well as their potential impacts on MM stem-like cells in the bone marrow milieu [39].

3. The Downsides of HDM

Although some early trials demonstrated an overall survival (OS) benefit with the use of ASCT-based versus non-ASCT-based approaches for NDMM [6,7], more recent evidence indicates no OS benefit from upfront transplant approaches with the use of novel combination therapy as induction and maintenance treatment [3,8,9,11,40,41]. Both the DETERMINATION and IFM 2009 trials demonstrated highly significant improvements in PFS with RVd + ASCT but no OS improvement after a median follow-up of >6 and almost 7.5 years, respectively [3,11]. While this may have reflected the use of salvage transplant in 77% of RVd-alone patients in IFM 2009 [11], only 28% of RVd-alone patients in the DETERMINATION trial had received subsequent HDM-ASCT [3]. In the modern era, with numerous, highly active salvage options available, early PFS benefit may no longer translate into OS benefit, especially if there are competing risks [3,40,42].

It is therefore important to consider the disadvantages of HDM-ASCT. These include both acute toxicities and long-term adverse effects. There are significantly higher rates of grade ≥ 3 hematologic toxicities associated with myeloablative HDM compared with nontransplant approaches [3,8,11], plus increased risks of infections and gastrointestinal disorders [3,8]. While the rate of acute treatment-related mortality is now gratifyingly low at 2% or less [3,8,40], elevated rates of acute toxicities, coupled with the need for hospitalization and the burden associated with treatment, also result in a transient but clinically meaningful decrease in patients' quality of life while undergoing transplant [3,8,43]. Patients may therefore prefer more convenient and tolerable treatment, based on these and other real-world factors [44].

The long-term effects of HDM are also important. In DETERMINATION, elevated rates of grade $\geq$ 3 hematologic toxicities and infections were seen during lenalidomide maintenance following RVd + ASCT versus RVd-alone, which impacted lenalidomide tolerability and dosing [3]. DETERMINATION also exemplified the well-known mutagenic effect of HDM [3,45], with a significantly higher rate of acute myeloid leukemia (AML) and/or myelodysplastic syndrome (MDS) seen with RVd + ASCT versus RVd alone (n = 10 vs. 0, p = 0.002), events that had resulted in death in four out of ten patients at data cut-off [46]. Additionally, an increasing risk of AML/MDS over time has been demonstrated in an analysis of the Center for International Blood and Marrow Transplant Research registry [47]. More broadly, and importantly, HDM has been shown to increase the mutational burden at relapse [48] compared with non-transplant-based therapy [49], with a four-fold increase observed in the IFM/DFCI 2019 trial, which may adversely impact not only the risk of secondary hematologic malignancies but also increase resistance and growth advantages and decrease disease sensitivity to subsequent treatment over time.

4. One Size Does Not Fit All—Personalized Treatment Decision Making

4.1. Patient and Disease Heterogeneity

Patients with NDMM are typically a diverse population, with differing preferences and needs [44,50]. Transplant-eligible patients' ages can range from ~30 years to >70 years [3,8,17], and they may have a wide variety of real-world considerations in their treatment decision making. Real-world effectiveness depends not only on demonstrated clinical trial efficacy but also on factors including work requirements, disruption to activities of daily living, impact on quality of life, management of comorbidities, symptom burden, and treatment-related toxicity [44,50]. Strategic considerations and a long-term perspective are thus critical, as transplant-eligible patients can expect to survive for a median of ~10 years [51], warranting evaluation of potential long-term toxicities and sequelae [47,52]. Furthermore, our understanding of specific patient-related factors is evolving and may in turn help guide HDM use. In this context, data from DETERMINATION indicated possible differential PFS benefit from transplant-based versus non-transplant-based approaches according to factors such as race, performance status, and body mass index, warranting further exploration [3,53,54]. Also of interest is the potential impact of clonal hematopoiesis of indeterminate potential (CHIP) on patients' susceptibility to developing therapy-related myeloid neoplasms post transplant [55]; the presence of CHIP is an adverse prognostic factor in MM [55] and may facilitate the evolution of myeloid neoplasms following ASCT [56–58], suggesting its role as a biomarker of increased genotoxic risk [59].

MM is intrinsically a highly heterogeneous disease, with multiple prognostic clinical features. Immune dysfunction is fundamental to disease pathobiology [37], and MM is also genetically unstable and carries a high mutational burden [60,61]. Specific disease-related factors such as disease stage, isotype, and cytogenetic abnormalities are associated with long-term outcomes as well as with sensitivity to specific treatment approaches, including HDM [61]. Ongoing studies will help confirm characteristics indicating the potential need for transplant-based therapy, such as specific high-risk cytogenetic abnormalities, as well as characteristics that could inform deferring HDM-ASCT for selected patients, and so avoid both toxicity and worse long-term outcomes.

4.2. MRD Evaluation for Adaptive Therapy

The utility of MRD assessment for guiding treatment decision making is increasing given the high rates of MRD-negative responses being achieved with novel therapeutic approaches [3,8–15,17]. MRD negativity is not only strongly associated with better long-term outcomes [33] but also a direct surrogate for PFS, independent of the treatment approach [34]. Preliminary data from DETERMINATION showed similar PFS from the start of lenalidomide maintenance among MRD-negative patients on the RVd + ASCT and RVd-alone arms [3]. MRD-adapted therapeutic approaches are now being investigated

with the aim of using risk-adapted consolidation treatment and reserving ASCT in select patients, such as in the ongoing MIDAS and ADVANCE trials (Figure 1).

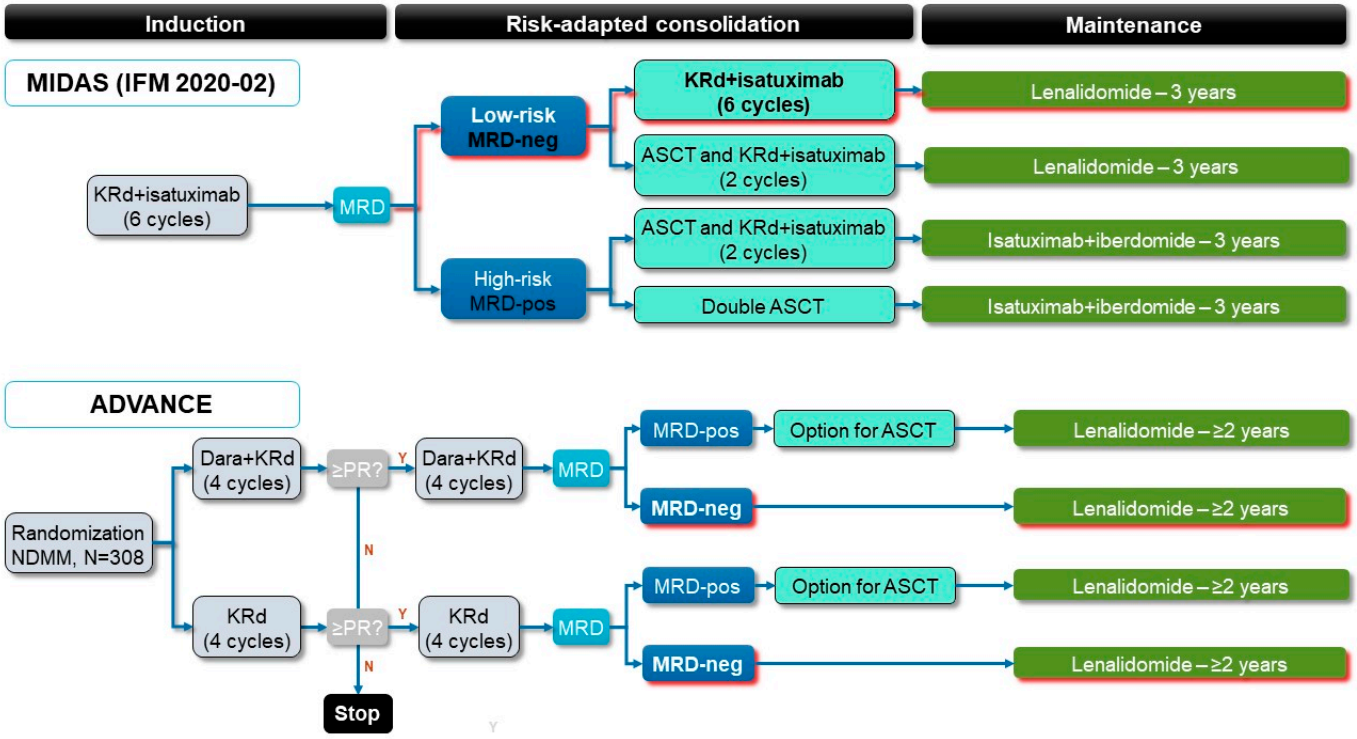

Figure 1. Examples of MRD-adapted therapeutic approach—**top**, the MIDAS trial (IFM 2020-02; NCT04934475); **bottom**, the ADVANCE trial (NCT04268498) [62]. Red shadow indicates the HDM-ASCT-sparing treatment pathway for patients achieving MRD-negative status. ASCT, autologous stem cell transplantation; Dara, daratumumab; HDM, high-dose melphalan; IFM, Intergroupe Francophone du Myelome; KRd, carfilzomib, lenalidomide, dexamethasone; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; neg, negative; pos, positive.

Additional studies will also inform the optimal duration of maintenance in patients achieving and sustaining MRD-negative status; indeed, it is sustained MRD negativity (two assessments $\geq$ 1 year apart) rather than simply achieving MRD-negative status that is more highly prognostic for PFS and OS [25,63] and a prerequisite for a functional "cure". Continuous induction/maintenance until disease progression is the standard of care in some geographies [4,5]; however, for those achieving MRD negativity, with or without ASCT, it will be important to understand "how much is enough"—i.e., after what duration of sustained MRD negativity can treatment be stopped without adversely affecting outcome—in order to avoid toxicities from unnecessarily prolonged therapy. Furthermore, the threshold for MRD-negative status in treatment decision making—i.e., 10^{-5} or 10^{-6}—is an area of ongoing study, with the more sensitive threshold offering greater prognostic value [33,64] and emerging as the gold standard in research and clinical trials.

5. Alternatives to HDM-ASCT and the Emerging Role of Quadruplet Therapy

The evolving therapeutic armamentarium for NDMM includes multiple active, immune-based agents and triplet/quadruplet combination regimens, such as those utilizing immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies, which provide very high rates of MRD negativity both in conjunction with HDM-ASCT as well as in ASCT-sparing approaches (Table 1), leading to very promising outcomes [3,8–31]. Thus, an increasing proportion of transplant-eligible NDMM patients could potentially defer transplant based on achieving MRD negativity; however, for patients with high-risk and ultra-high-risk cytogenetics, ongoing studies are primarily investigating quadruplet

therapies as induction and consolidation with HDM-ASCT and doublet or triplet maintenance [18,23,25,26,28]. Furthermore, the small percentage of patients who have primary refractory disease to triplet or quadruplet induction may achieve improved second-line outcomes by utilizing HDM-ASCT in this setting [65,66], although optimal therapy for this population remains an area of ongoing study and unmet need for innovative therapies.

In addition to quadruplet regimens, there are multiple novel immune therapy approaches approved or being studied, including cereblon E3 ligase modulators (CELMoDs®) [67,68], antibody–drug conjugates [69], bispecific antibodies/T cell engagers [69], and chimeric antigen receptor (CAR) T cell therapies [69]. Through the immune mechanisms of these agents, substantial levels of antimyeloma immune effects that may complement or obviate the need for those arising from HDM are being described, with these agents being studied in early-phase and phase 3 trials in NDMM (Table 2) and additional studies planned, including a next-generation trial following on from DETERMINATION, called DETERMINATION 2. The future treatment landscape will likely contain an increased number of immune-based options, challenging the standard use of HDM-ASCT for eligible patients. Furthermore, other novel agents have been developed, including melphalan flufenamide (melflufen), which is fully approved for relapsed/refractory MM in Europe and elsewhere, although its US approval was recently withdrawn by the Food and Drug Administration for complex and controversial regulatory reasons. This notwithstanding, melflufen is a novel targeted cytotoxic drug–peptide conjugate that delivers the alkylator warhead directly to plasma cells and may thereby retain melphalan's cytotoxic activity, including against "stemness", while potentially resulting in less toxicity and an improved therapeutic index [70,71]. Moreover, current data support the use of this novel, first-in-class, peptide–drug conjugate in the management of relapsed and refractory MM in additional combination approaches, such as those recently reported in the ANCHOR study [72] and LIGHTHOUSE trial [73], with promising results seen using either bortezomib or daratumumab in combination with melflufen and dexamethasone.

Table 1. MRD negativity rates with modern triplet and quadruplet induction therapies, with or without high-dose melphalan plus ASCT, followed by immune-therapy-based maintenance.

Study	Induction Therapy	ASCT	Consolidation Therapy	Maintenance Therapy	MRD-Negativity Rate
IFM 2009 [8,11]	RVd × 3 3-week cycles	No	RVd × 5 3-week cycles	R, 1 year	20%
IFM 2009 [8,11]	RVd × 3 3-week cycles	Yes	RVd × 2 3-week cycles	R, 1 year	30%
GRIFFIN [12,29]	RVd × 4 3-week cycles	Yes	RVd × 2 3-week cycles	R	30%
DSMM XVII [24]	KRd × 6 4-week cycles	Yes	KRd × 4 4-week cycles	R	35% post induction
GMMG-HD7 [22]	RVd × 3 6-week cycles	No	–	R + Isa vs. R	36% post induction
DETERMINATION [3]	RVd × 3 3-week cycles	No	RVd × 5 3-week cycles	R until progression	40% *
FORTE [9]	KCd × 4 4-week cycles	Yes	KCd × 4 4-week cycles	KR vs. R	43%
CASSIOPEIA [10]	VTd × 4 4-week cycles	Yes	VTd × 2 4-week cycles	Dara vs. observation	44%
PERSEUS [27]	RVd × 4 4-week cycles	Yes	RVd × 2 4-week cycles	R until progression	48%
GEM2012MENOS65 [14]	RVd × 6 3-week cycles	Yes	RVd × 2 3-week cycles	IRd or Rd	49% (SR); 37% (HR)
DETERMINATION [3]	RVd × 3 3-week cycles	Yes	RVd × 2 3-week cycles	R until progression	54% *
FORTE [9]	KRd × 12 4-week cycles	No	–	KR vs. R	56%
FORTE [9]	KRd × 4 4-week cycles	Yes	KRd × 4 4-week cycles	KR vs. R	62%
Myeloma XI [13]	CTD/CRD/KCRD × 4 cycles	Yes	–	R vs. none	63% (3 months post-ASCT)
IsKia [21]	KRd × 4 4-week cycles	Yes	KRd × 4, KRd-light × 12	R	67% post consolidation
CASSIOPEIA [10]	Dara-VTd × 4 4-week cycles	Yes	VTd × 2 4-week cycles	Dara vs. observation	44%
DSMM XVII [24]	Elo-KRd × 6 4-week cycles	Yes	Elo-KRd × 4 4-week cycles	Elo-R	50% post induction
GMMG-HD7 [22]	Isa-RVd × 3 6-week cycles	No	–	R + Isa vs. R	50% post induction
IFM 2018-01 [30]	Dara-IRd × 6 3-week cycles	Yes	Dara-IRd × 4 4-week cycles	R, 2 years	51% (SR, after 1 year of maintenance)

Table 1. *Cont.*

Study	Induction Therapy	ASCT	Consolidation Therapy	Maintenance Therapy	MRD-Negativity Rate
NCT04113018 [16]	Dara-KRd × 8 4-week cycles	No/Yes/No	–/Dara-KRd × 12 4-week cycles/Dara-KRd × 12 4-week cycles	R	62% post induction
Derman et al. [19]	Dara-KRd × 24 4-week cycles	No	–	–	63% (post 8 cycles)
GRIFFIN [12,29]	Dara-RVd × 4 3-week cycles	Yes	Dara-RVd × 2 3-week cycles	Dara-R	64%
SKylaRk [26]	Isa-KRd × 4 4-week cycles	Yes/No	Isa-KRd × 2/4 4-week cycles	Isa-KR (HR), R (SR)	66% (post 6 cycles)
GMMG-CONCEPT [25]	Isa-KRd × 6 4-week cycles	Yes/No	Isa-KRd × 4 4-week cycles	Isa-KR, 26 cycles	68%/54%
IRB16-1138 [20]	Elo-KRd × 12 4-week cycles	No	Elo-KRd × 0–12 4-week cycles	Elo-Rd	70%
MANHATTAN [31]	Dara-KRd × 8 4-week cycles	No	–	–	71%
PERSEUS [27]	Dara-RVd × 4 4-week cycles	Yes	Dara-RVd × 2 4-week cycles	Dara-R/R until progression	75%
IsKia [21]	Isa-KRd × 4 4-week cycles	Yes	Isa-KRd × 4, Isa-KRd-light × 12	R	77% post consolidation
MASTER [17,18]	Dara-KRd × 4 4-week cycles	Yes	Dara-KRd × 0–8 4-week cycles	R	38% (post induction) 81% (post MRD-directed consolidation)
IFM2018-04 [28]	Dara-KRd × 6 4-week cycles	Yes	Dara-KRd × 4 4-week cycles	Dara-R, 2 years	94%
OPTIMUM/MUKnine (UHR NDMM) [23]	Dara-CRVd × 6 cycles	Yes	Dara-RVd × 6 cycles, Dara-RV × 12 cycles	Dara-R until progression	64% post ASCT

* Subset of patients at start of maintenance therapy. ASCT, autologous stem cell transplantation; CRD, cyclophosphamide, lenalidomide, dexamethasone; CTD, cyclophosphamide, thalidomide, dexamethasone; Dara, daratumumab; DSMM, Deutsche Studiengruppe Multiples Myelom; Elo, elotuzumab; GEM, Grupo Español de Mieloma; GMMG, German-Speaking Myeloma Multicenter Group; HR, high-risk cytogenetics; IFM, Intergroupe Francophone du Myelome; IRd, ixazomib, lenalidomide, dexamethasone; Isa, isatuximab; KCd, carfilzomib, cyclophosphamide, dexamethasone; KCRD, carfilzomib, cyclophosphamide, lenalidomide, dexamethasone; KR(d), carfilzomib, lenalidomide, (dexamethasone); MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; R(d), lenalidomide (plus dexamethasone); RVd, lenalidomide, bortezomib, dexamethasone; SR, standard-risk cytogenetics; UHR, ultra high-risk; VTd, bortezomib, thalidomide, dexamethasone.

Table 2. Novel immune-based therapies under investigation in the setting of NDMM (ongoing trials per ClinicalTrials.gov, accessed on 20 March 2024).

Agent	Study	Phase	ClinicalTrials.gov ID	Setting	Primary Endpoint	Initial Completion Date
CAR T cell therapies						
Ide-cel	KarMMa-2 [74]	2	NCT03601078	Inadequate response to ASCT in 1st line	ORR CR rate	July 2025
	KarMMa-9	3	NCT06045806	Ide-cel + R vs. R maintenance for sub-optimal response post ASCT	PFS	March 2031
	BMTCTN1902	2	NCT05032820	Sub-optimal response post ASCT and R maintenance	sCR/CR rate at 6 months	January 2025
Cilta-cel	CARTITUDE-6 [75]	3	NCT05257083	- NDMM - Dara-RVd, cilta-cel, R maintenance; vs. Dara-RVd, ASCT, Dara-RVd, R maintenance	PFS Sustained MRD-neg CR	June 2033
	CARTITUDE-2	2	NCT04133636	- Cohort D: <CR post ASCT for NDMM - Cohort E: High-risk NDMM; Dara-RVd, cilta-cel, R maintenance - Cohort F: Standard-risk NDMM	MRD-neg	May 2025
	CARTITUDE-5	3	NCT04923893	- Non-transplant NDMM - RVd–cilta-cel vs. RVd-Rd	PFS	June 2026
Antibody–drug conjugates						
Belantamab mafodotin	GEM-BELA-RVd	2	NCT04802356	- Belantamab mafodotin + RVd induction/consolidation - ASCT - Belantamab mafodotin + R maintenance	Safety, AEs	July 2025

Table 2. *Cont.*

Agent	Study	Phase	ClinicalTrials.gov ID	Setting	Primary Endpoint	Initial Completion Date
	LCI-HEM-NDMYE-KRDB-001	1/2	NCT04822337	- Belantamab mafodotin + KRd - High-risk NDMM	CR rate	October 2024
	Winship5382-21	2	NCT05208307	Belantamab mafodotin plus Pom-dex as post-ASCT maintenance in high-risk patients	CR rate	October 2024
	I 797720	2	NCT04876248	Belantamab mafodotin plus R as post-ASCT maintenance in MRD-pos patients	MRD-neg rate	September 2026
	MDACC 2021-0201	2	NCT05091372	Belantamab mafodotin plus R as MRD-guided post-ASCT maintenance	MRD-pos to MRD-neg rate	March 2025
	UPCC 37420	2	NCT04680468	Belantamab mafodotin prior to ASCT and with R as maintenance	MRD-neg rate	July 2026
	DREAMM-9	1	NCT04091126	Belantamab mafodotin + RVd or Rd, nontransplant setting	Safety, AEs	April 2025
	MC1989	1/2	NCT04892264	Belantamab mafodotin + Dara-Rd, nontransplant setting	CR rate	March 2025
	EAE120	1/2	NCT05280275	Belantamab mafodotin + Dara-Rd, nontransplant setting	Safety, AEs ORR	March 2026
	EAE128	1/2	NCT05573802	Belantamab mafodotin + Rd + nirogacestat, nontransplant setting	Safety, DLTs, AEs ORR	October 2026
	EAE-2020	1/2	NCT04808037	Belantamab mafodotin + Rd, nontransplant setting	Safety, AEs ORR	September 2028
Bispecific antibodies/T cell engagers						
Teclistamab (BCMA × CD3)	MASTER-2	2	NCT05231629	- MRD-pos post ASCT - Dara-R vs. Dara-teclistamab as consolidation and maintenance	Sustained MRD-neg rate	December 2026
	IFM 2021-01	2	NCT05572229	- Elderly NDMM - Teclistamab + Dara-R	VGPR rate	May 2025
	MajesTEC-2	1	NCT04722146	- Teclistamab + Dara-RV - Teclistamab + Dara-R	Safety, DLTs	October 2024
	MajesTEC-4 [76]	3	NCT05243797	Teclistamab-R vs. R as post-ASCT maintenance	PFS	April 2028
	MajesTEC-5/GMMG-HD10	2	NCT05695508	- Teclistamab-Dara-R(V)d + ASCT - Teclistamab-Dara-R maintenance	Safety	October 2026
	MajesTEC-7 [77]	3	NCT05552222	- Nontransplant NDMM - Teclistamab-Dara-R vs. Dara-Rd	PFS MRD-neg CR	May 2029
	GEM-TECTAL	2	NCT05849610	- High-risk NDMM - Dara-RVd → Teclistamab-Dara → Teclistamab-Dara or Talquetamab-Dara	MRD-neg CR	January 2025
Elranatamab (BCMA × CD3)	MagnetisMM-7 [78]	3	NCT05317416	- MRD-positive post ASCT - Elranatamab vs. R	PFS	August 2027
	MagnetisMM-6 [79]	3	NCT05623020	- Nontransplant NDMM - Elranatamab + Dara-R vs. Dara-Rd	PFS MRD-neg rate	March 2028
	NCI-2024-00110	2	NCT06207799	Pre-ASCT purging/post-ASCT maintenance	Safety	December 2029
Talquetamab (GPRC5D × CD3)	MonumenTAL-2	1	NCT05050097	- MM—setting not specified - Talquetamab plus Dara-K/K/Dara-R/R/Pom	Safety DLTs	December 2024
Cevostamab (FcRH5 × CD3)	PLYCOM	1/2	NCT05583617	- Post-transplant maintenance in high-risk cytogenetics NDMM - Cevostamab + R + tocilizumab	Safety, Response rates PFS, OS	March 2026
CELMoDs						
Iberdomide	MIDAS IFM 2020-02	3	NCT04934475	Iberdomide + Isa vs. R + Isa as post-ASCT maintenance	MRD-neg rate	December 2024
	EXCALIBER-Maintenance	3	NCT05827016	Iberdomide vs. R maintenance post ASCT	PFS	March 2029
	GMMG-HD9/DSMM XVIII	3	NCT06216158	Iberdomide + Isa vs. iberdomide maintenance post ASCT	2-year MRD-neg rate	December 2028
	GEM21menos65	3	NCT05558319	Iberdomide + Isa-Vd vs. RVd vs. Isa-RVd	MRD-neg rate	April 2027

Table 2. *Cont.*

Agent	Study	Phase	ClinicalTrials.gov ID	Setting	Primary Endpoint	Initial Completion Date
	CC-220-MM-001	1/2	NCT02773030	- Iberdomide + Vd in NDMM - Iberdomide + Dara-dex in transplant-ineligible NDMM	Safety ORR	July 2026
	BOREALIS	2	NCT05272826	- Iberdomide +Vd in transplant-ineligible NDMM	sCR rate	March 2028
	EMN26 [80]	2	NCT04564703	- Single-agent iberdomide maintenance post ASCT	Improved efficacy Tolerability	December 2027
	IBEX	2	NCT06107738	Iberdomide + SC Dara as post-ASCT maintenance	12-month MRD-neg rate	December 2025
	KID	1/2	NCT05199311	- Transplant-eligible NDMM - Iberdomide + Kd	AEs CR/sCR rate	November 2025
	MSKCC 22-040	2	NCT05354557	- Single-agent iberdomide maintenance after suboptimal post-ASCT response	CR rate	April 2025
	University of Nebraska 852-21	2	NCT05177536	- Single-agent iberdomide maintenance post ASCT	1-year tolerability	March 2025
	IDEAL	1/2	NCT05392946	- Iberdomide + Dara-Vd in NDMM	MTD CR rate	May 2027
	COMMANDER	1b/2	NCT05434689	- Iberdomide + Dara-dex - Iberdomide + Dara-Kd - MRD-pos patients post-ASCT	DLT MRD conversion rate	December 2025
	GEM-IBERDARAX	2	NCT05527340	- Iberdomide + Dex - Iberdomide + Dara-dex	ORR CR rate	December 2029

AE, adverse event; ASCT, autologous stem cell transplantation; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CELMoD, cereblon E3 ligase modulator; cilta-cel, ciltacabtagene autoleucel; (s)CR, (stringent) complete response; Dara, daratumumab; dex, dexamethasone; DLT, dose-limiting toxicity; FcRH5, Fc receptor homolog 5; G protein–coupled receptor, class C, group 5, member D; GMMG, German-Speaking Myeloma Multicenter Group; Ide-cel, idecabtagene vicleucel; IFM, Intergroupe Francophone du Myelome; Isa, isatuximab; K(d), carfilzomib, (dexamethasone); KRd, carfilzomib, lenalidomide, dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; MTD, maximum tolerated dose; NDMM, newly diagnosed multiple myeloma; neg, negative; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Pom-(dex), pomalidomide, (dexamethasone); pos, positive; R(d), lenalidomide, (dexamethasone); RV(d), lenalidomide, bortezomib, (dexamethasone); SC, subcutaneous; Vd, bortezomib, dexamethasone.

6. Conclusions

Therapeutic innovations for transplant-eligible NDMM have resulted in significant improvements in PFS and OS, and ongoing approvals will further augment this, with potent quadruplet regimens emerging as new standards of care. The role of HDM-ASCT has already evolved, through MRD-adapted approaches, and the next wave of immune therapies will further expand alternative combination therapy options. Ongoing refinement and understanding of prognostic factors, characteristics, and biomarkers for treatment decision making, coupled with immune profiling and routine MRD evaluation, will provide the necessary tools to "do better" than HDM for select subgroups, further improving outcomes for our patients.

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