

# Daratumumab in untreated newly diagnosed multiple myeloma

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**Abstract:** The treatment of multiple myeloma has evolved markedly in the last decade, but mortality remains high, emphasizing the need for more effective therapies. Daratumumab, a fully human monoclonal antibody targeting CD38, has shown clinical efficacy in relapsed/refractory multiple myeloma both as monotherapy and in combination with other drugs, including novel agents. More recently, promising results have been reported in patients with untreated newly diagnosed multiple myeloma (NDMM). Clinical trials thus far have shown enhanced efficacy and tolerability of several daratumumab-based combinations in both transplant ineligible and eligible patients, without compromising transplant ability. However, benefit in high-risk subpopulations is still unclear. A subcutaneous formulation of daratumumab has been introduced to decrease the risk of infusion reactions, with preliminary results showing non-inferior efficacy. The antimyeloma activity of daratumumab is achieved through multiple mechanisms including direct, Fc-dependent, and immunomodulatory mechanisms. Enhanced efficacy of daratumumab in combination with immunomodulatory drugs and proteasome inhibitors is supported by preclinical data showing synergism. This review will focus on the role of daratumumab in untreated NDMM patients, highlighting the results of major clinical trials, and listing ongoing trials that are evaluating various daratumumab-based combinations in this setting.

**Keywords:** daratumumab, newly diagnosed multiple myeloma, untreated multiple myeloma

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## Introduction

Multiple myeloma (MM) is a neoplastic clonal plasma cell disorder characterized by secretion of a monoclonal protein in the blood or urine and organ dysfunction manifesting as anemia, hypercalcemia, renal failure, and lytic bone lesions.<sup>1</sup> MM is more commonly diagnosed in men and older patients between the age of 65 and 74 years, and accounts for 1.8% of all new cancer cases in the US.<sup>2</sup> Treatment strategies in MM have evolved markedly in the past decade with the introduction of novel treatment agents.<sup>3–5</sup> This has expanded the treatment options for both newly diagnosed multiple myeloma (NDMM) and relapsed or refractory (R/R) disease. These include immunomodulatory drugs (IMiD) like thalidomide, lenalidomide, and pomalidomide; and proteasome inhibitors (PI) like bortezomib,

carfilzomib, and ixazomib. The heterogeneity of drug classes and nonoverlapping mechanisms of action has allowed their use in combination to achieve greater responses.<sup>3–5</sup> In the absence of direct comparisons among all available combinations, the choice of initial treatment is currently guided by physician and patient preference, taking into account disease stage, transplant eligibility, risk stratification based on cytogenetic abnormalities, comorbidities, frailty, and functional status.<sup>6</sup> Despite advances in treatment, MM mortality remains high, with 5-year overall survival estimated at 52.2%.<sup>2</sup> This highlights the need for more effective therapeutic options. The CD38 targeted monoclonal antibody (mAb) daratumumab has shown clinical efficacy in R/R MM both as monotherapy, and in combination with other drugs, including novel agents, leading

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to its approval for use in this setting. More recently, it has been explored in untreated NDMM patients, with promising results in both transplant eligible and ineligible patients. The role of daratumumab in untreated NDMM patients will be the primary focus of this review.

### Mechanisms of daratumumab activity

Daratumumab is an IgG1 $\kappa$  fully human mAb that targets CD38, a type II transmembrane glycoprotein composed of extracellular, transmembrane, and intracellular domains.<sup>7</sup> CD38 is widely expressed on nonhematopoietic and hematopoietic tissues, including plasma cells (PCs), natural killer (NK) cells, lymphoid cells, and myeloid cells. Its high expression in MM has made it an attractive target for treatment.<sup>8</sup> CD38 serves as a receptor for CD31. Upon ligand binding, CD38 interacts with other cell surface receptors, resulting in activation of intracellular signaling pathways, leading to cellular responses ranging from proliferation to apoptosis.<sup>7,9</sup> In addition, CD38 is considered an ectoenzyme using NAD<sup>+</sup> and NADP<sup>+</sup> as its main substrates.<sup>7,9</sup> The antimyeloma activity of daratumumab is exerted through several mechanisms: direct, Fc-dependent, and immunomodulatory mechanisms.<sup>9</sup> Direct effects are mediated by inhibition of intracellular signal transduction, and by inhibition of CD38 enzymatic activity, which leads to decreased levels of immunosuppressive adenosine. Fc-dependent mechanisms include complement-dependent cytotoxicity (CDC),<sup>8</sup> antibody-dependent cellular cytotoxicity (ADCC),<sup>8</sup> antibody-dependent cellular phagocytosis (ADCP),<sup>10</sup> and induction of apoptosis through cross-linking *via* the Fc $\gamma$  receptor.<sup>11</sup> In addition, daratumumab exerts immunomodulatory effects by increasing the production of helper and cytotoxic T cells and depleting CD38-expressing immunosuppressive cells like regulatory T (Tregs) and B cells, and myeloid-derived suppressor cells (MDSCs).<sup>12</sup>

### The rationale for daratumumab-based combinations

The benefit of adding daratumumab to other treatment regimens, particularly IMiD- and PI- based combinations, is supported by preclinical data. Daratumumab has exhibited synergistic effects in enhancing MM cell lysis *ex vivo* when combined with lenalidomide or bortezomib, particularly in the triplet combination. Interestingly, this effect

was more pronounced in myeloma cells of patients who had low response or refractoriness to treatment with lenalidomide or bortezomib.<sup>13</sup> This implies that daratumumab may have the potential to reinstate the host susceptibility to these agents through its immunomodulating effects.<sup>14</sup> The ability of IMiDs, including thalidomide, lenalidomide, and pomalidomide, to activate immune effector cells like NK cells or reduce inhibitory T cell populations *in vitro*, may be a potential explanation for this synergism.<sup>15</sup> Lenalidomide, in particular, has been shown to augment daratumumab-induced myeloma cell lysis by ADCC by inducing endogenous NK cells,<sup>14</sup> and to potentiate ADCP by inducing endogenous macrophages through vitamin D pathway activation.<sup>16</sup> Furthermore, lenalidomide has the potential to sensitize Tregs to the action of daratumumab by upregulating CD38 expression on Tregs, and by increasing the fraction of CD38-high Tregs.<sup>17</sup> Lenalidomide has not been shown to influence complement-mediated cytotoxicity.<sup>18</sup>

### Role of daratumumab in R/R MM

Since initial use in 2015,<sup>19</sup> there has been clear evidence for daratumumab efficacy in pretreated MM patients both as monotherapy and in combination with other agents. The GEN501 and SIRIUS trials provided the earliest reports on efficacy and safety of daratumumab as monotherapy in heavily pretreated R/R MM patients. A combined analysis showed durable responses after 36.6 months of median follow up, with an overall response rate (ORR) of 30.4%, median overall survival (OS) of 20.5 months (CI 16.6–28.1), and 3-year OS rate of 36.5% (28.4–44.6).<sup>19–21</sup> Results from these studies led to the approval of daratumumab monotherapy in patients with at least three lines of prior therapy including an IMiD and PI, or double refractory to an IMiD and PI. Evidence for clinical efficacy in combination with bortezomib and lenalidomide in R/R patients was provided by the CASTOR and POLLUX trials, respectively.<sup>22,23</sup> In the CASTOR trial, the combination of daratumumab with bortezomib and dexamethasone (DVd) was superior to bortezomib and dexamethasone (Vd) alone, achieving significantly longer progression-free survival (PFS) (median PFS: 16.7 *versus* 7.1 months at 31.3 months median follow up) and superior overall and deeper responses, including minimal residual disease (MRD) negativity.<sup>24</sup> After showing safety and efficacy in the phase I/II GEN503 trial,<sup>25,26</sup> the combination of daratumumab with

lenalidomide and dexamethasone (DRd) was found to be superior to lenalidomide and dexamethasone alone (Rd) in R/R MM in the phase III POLLUX trial.<sup>23</sup> The addition of daratumumab to Rd was associated with longer PFS; at a median follow up of 39.5 months, median PFS was NR *versus* 17.5 months with hazard ratio (HR) 0.44, 0.35–0.55  $p < 0.0001$ . Similarly, greater overall and deeper responses were achieved, including significantly improved and sustained MRD negativity rate.<sup>27</sup> Together, these results lead to the approval of daratumumab in combination with Vd or Rd in R/R MM patients.<sup>28</sup> The combination of daratumumab, pomalidomide, and dexamethasone (Dara-Pom-Dex) has also gained FDA approval for use in R/R patients based on results from the EQUULEUS trial, showing an ORR of 60% and MRD negativity of 29%.<sup>29</sup> Interestingly, retreatment with the Dara-Pom combination in patients who were previously refractory to Dara or Pom was associated with response in a retrospective study.<sup>30</sup> This regimen is not yet approved for use in Europe and other countries outside the US. Encouraging results have also been reported for daratumumab in combination with carfilzomib and dexamethasone in R/R patients following one to three lines of therapy.<sup>31</sup>

### Role of daratumumab in untreated MM

The efficacy of daratumumab observed in R/R MM, particularly among patients with fewer lines of prior therapy,<sup>24</sup> has been replicated in untreated MM, expanding its labeled use to include transplant-ineligible NDMM.<sup>32</sup> This was based on results from the ALCYONE and MAIA trials, showing improved responses when daratumumab is combined with Rd or melphalan-bortezomib-prednisone (MVP) respectively.<sup>33,34</sup> In addition, encouraging results are being reported in other combinations with standard-of-care regimens, and deeper responses are being achieved even in transplant-eligible patients, without compromising the ability to proceed to transplant. We discuss below the most important clinical trials evaluating daratumumab combinations in NDMM.

### Daratumumab in transplant-ineligible NDMM

The dosing and safety of daratumumab, in combination with standard regimens in NDMM patients, were established in a phase Ib trial

where four different daratumumab-based combinations were used, including melphalan, bortezomib, thalidomide, and pomalidomide.<sup>35</sup> Subsequently, the phase III ALCYONE trial evaluated the efficacy of daratumumab in combination with bortezomib-melphalan-dexamethasone (D-VMP), compared with bortezomib-melphalan-dexamethasone alone (VMP), among 706 transplant ineligible NDMM patients. After a median follow up of 16.5 months, the D-VMP group had significantly improved PFS compared with the VMP group with a median PFS NR *versus* 18.1 months, respectively and HR 0.5 (95% CI 0.38–0.65  $p < 0.001$ ). The superiority of the daratumumab combination was maintained in patients who were  $\geq 75$  years, had higher ISS stage, poor performance status, impaired hepatic or renal function. However, patients with high-risk cytogenetics (53 patients) appeared to have less benefit compared with the patients with standard-risk cytogenetics (261 patients) (HR: 0.78, 0.43–1.43 *versus* 0.39, 0.28–0.55, respectively). The overall response, very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) rates, were all significantly higher in the daratumumab group. The MRD rate was also increased significantly in the D-VMP group (22.3% *versus* 6.2%  $p < 0.001$ ).<sup>33</sup> An updated analysis was recently reported after a median follow up of 27.8 months, showing continued responses in the D-VMP group (Median PFS NR *versus* 19.1 months in the D-VMP and control groups, respectively and HR 0.43, 0.35–0.54  $p < 0.0001$ ). The rate of grade 3–4 infection was higher in the D-VMP group compared with the control group (25.1% *versus* 14.7%, respectively). In particular, pneumonia was higher in the D-VMP group (12.4% *versus* 4%). However, these caused treatment discontinuation in only a small number of patients.<sup>36</sup> The clinical efficacy of DRd, compared with Rd, was evaluated in the phase III MAIA trial among 737 transplant ineligible NDMM patients. Rd is one of the standard treatments used in this group of patients, particularly elderly patients unable to tolerate triplet regimens.<sup>37</sup> Results from a preplanned interim analysis of the MAIA trial were recently reported. At a median follow up of 28 months, PFS was longer in the DRd group compared with the Rd group, with median PFS NR *versus* 31.9 months, respectively and HR 0.56 (95% CI 0.43–0.73  $p < 0.001$ ). Superiority was maintained in

patients  $\geq 75$  years, but not in the subgroup of patients with high risk cytogenetics (HR: 0.85, 0.44–1.65).<sup>34</sup> This is in contrast to results from the POLLUX study, comparing DRd with Rd in R/R patients, where PFS was longer in the subgroup with high-risk cytogenetics, albeit to a lesser extent than standard-risk patients (HR: 0.53, 0.25–1.13 versus 0.30, 0.20–0.47, respectively).<sup>27,38</sup> Patients in the DRd group experienced a higher rate of deeper responses including  $\geq$ CR (47.6% versus 24.9%). Similarly, the rates of overall response,  $\geq$ VGPR and MRD negativity (24.2% versus 7.3%) were all higher in the DRd group. OS data is still immature. Overall, adverse events were manageable. The most common grade 3–4 adverse events in the DRd and Rd groups were neutropenia (50% versus 35.3% respectively) and infections (32.1% versus 23.3% respectively). Pneumonia was the most common infection, occurring in 13.7% versus 7.9%, and leading to death in 0.5% versus 0.8% of patients in the DRd and Rd groups, respectively.<sup>34</sup> Based on results from these two trials, D-VMP has been approved in the US and Europe, and DRd has been approved only in the US, for use as first line treatments in transplant ineligible MM patients.

Given the lack of direct head-to-head comparisons, there is little evidence to guide treatment choice between the various standard regimens at this time. A recently published meta-analysis by Cao and colleagues compared the efficacy of currently used treatment regimens in this group of patients using Rd as reference. In terms of PFS, three combinations showed superiority to Rd: DRd (HR: 0.57, 0.43–0.73), D-VMP (HR, 0.59, 0.36–0.91), and VRd (HR, 0.72, 0.56–0.90). VRd showed superior OS, but the analysis excluded daratumumab-based regimens given immaturity of OS data.<sup>39</sup> The efficacy of daratumumab is also being evaluated in other PI-based doublet regimens, specifically in frail patients with NDMM. The phase II HOVON 143 study is evaluating the efficacy of daratumumab in combination with ixazomib and low-dose dexamethasone in this subset of patients. In its first planned safety analysis, the combination was tolerated with manageable side effects. A preliminary ORR of 70% has been reported, including 20% VGPR. Updated efficacy results are awaited.<sup>40</sup> Ongoing trials of daratumumab-based combinations in transplant ineligible NDMM patients are listed in Table 1.<sup>41</sup>

#### *Daratumumab in transplant-eligible NDMM*

Favorable results, including deeper responses, observed in transplant ineligible patients have stimulated efforts to evaluate daratumumab in transplant eligible patients with NDMM. In the phase III CASSIOPEIA trial,<sup>42</sup> daratumumab was combined with bortezomib, thalidomide, and dexamethasone (DVTd) during induction and consolidation, showing increased rates of sCR at 100 days post-transplant; the sCR rate was 29% in the DVTd group compared with 20% in the bortezomib, thalidomide, and dexamethasone (VTd) group [odds ratio (OR): 1.60, 1.21–2.12  $p$ : 0.0010]. In addition, the DVTd group achieved higher rates of  $\geq$ CR,  $\geq$ VGPR, and MRD negativity (64% versus 44%  $p$  < 0.0001). Superiority, in terms of sCR rate, was maintained in patients  $\geq 50$  years, patients with poor performance status, baseline renal or hepatic dysfunction, but not in patients with ISS stage 3 MM. Patients with high-risk cytogenetics had lower odds for achieving sCR compared with standard risk MM (OR: 0.83, 0.42–1.66). However, both subgroups showed benefit with the daratumumab combination in terms of MRD negativity and PFS. The overall incidence of serious adverse events was similar in both groups (47% in both). There was a higher rate of grade 3–4 cytopenias in the DVTd group. Although infection rate was higher in the DVTd group, the rate of grade 3–4 infection was similar in both groups. The addition of daratumumab was associated with a lower yield of stem cells compared with VTd alone (median collected CD34+ cells  $6.3 \times 10^6/\text{kg}$  versus  $8.9 \times 10^6/\text{kg}$ ) and increase rate of plerixafor use during mobilization. However, the rates of transplant and hematopoietic reconstitution were similar. The impact of daratumumab maintenance in patients achieving  $\geq$ PR from both groups is currently being evaluated in another part of this study.<sup>42</sup> The results of the CASSIOPEIA trial led to the FDA approval of Daratumumab in combination with VTd in transplant eligible patients with MM. Initial safety and efficacy reports on the combination of DVRd in transplant eligible NDMM patients were provided by the phase II GRIFFIN study. Patients received DVRd induction and post-transplant consolidation, followed by maintenance with daratumumab and lenalidomide. All 16 included patients proceeded to transplant and achieved  $\geq$ VGPR, including 63% with  $\geq$ CR after consolidation. Of 16 patients, 15 had not progressed at the median follow up of 15.6 months.

**Table 1.** Trials evaluating daratumumab combinations in transplant ineligible patients with NDMM.

NCT number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT02252172	Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in participants with previously untreated multiple myeloma (MAIA) <sup>34</sup>	Transplant ineligible with untreated NDMM	Arm 1: DRd Arm 2 (control): Rd	28-day cycles: Len: 25mg PO D1-21 Dex: 40mg PO/IV D1,8,15,22 Dara (arm 1 only): 16 mg/kg IV Qw ×8w, then Q2w ×16w, then Q4w	PFS Time	III	Active, not recruiting
NCT02195479	A study of combination of daratumumab and velcade (bortezomib) melphalan-prednisone (DVMP) compared with velcade melphalan-prednisone (VMP) in participants with previously untreated multiple myeloma (ALCYONE) <sup>33</sup>	Transplant ineligible with untreated NDMM	Arm 1 (control): VMP Arm 2: D-VMP	Up to 9 cycles: 42 days each: Bort: 1.3mg/m <sup>2</sup> SC 2×/w in W1,2,4,5 of C1, then Qw in W1,2,4,5 of C2-9 Mel: 9 mg/m <sup>2</sup> PO QD D1-4 of C1-9 Pred: 60mg/m <sup>2</sup> PO QD D1-4 of C1-9 Dara (arm 2 only): 16 mg/kg IV Qw ×6w in C1, then Q3w in C2-9, then Q4w	PFS	III	Active, not recruiting
NCT03993912	Compare lenalidomide and subcutaneous daratumumab versus lenalidomide and dexamethasone in frail subjects with previously untreated multiple myeloma who are ineligible for high dose therapy (IFM2017_03)	Transplant ineligible, elderly (≥65) frail, with untreated NDMM	Arm 1: Dara SC + Len + Dex Arm 2 (control): Len + Dex	28-day cycles: Arm 1: Len: 25mg PO D1-21 Dex: 20mg PO D1, 8,15,22 ×2 cycles only Dara: 1800mg SC Qw ×8w, then Q2w ×16w, then Q4w Arm 2: Len: 25mg PO D1-21 Dex: 20mg PO D1, 8,15,22	PFS	III	Not yet recruiting
NCT03742297	Treatment for elderly fit newly diagnosed multiple myeloma patients aged between 65 and 80 years	Elderly (65-80), fit transplant ineligible with untreated NDMM	Arm 1 (control): induction with VMP×9 + Rd×9, consolidation with Rd + low dose-Dara ×4 Dara ×4 Arm 2b: induction with D-KRd×18 Part 2: randomization to: Arm 1: no maintenance Arm 2: Dara + Len	Induction: Arm 1: VMP: one 6-week cycle and eight 4-week cycles: Mel: 9 mg/m <sup>2</sup> PO D1-4 Pred: 60mg/m <sup>2</sup> PO D1-4 Bort: 1.3 mg/m <sup>2</sup> D1,4,8,11,22,25,29,32 of C1, then D1,8,15,22 of C2-9 Rd: Len: 25mg PO D1-21 Dex: 40 mg D1,8,15,22 Arm 2a (28-day cycles): Car: C1: 20 mg/m <sup>2</sup> D1 and 36 mg/m <sup>2</sup> D2,8,9,15,16. C2: 36 mg/m <sup>2</sup> D1,2,8,9,15,16. C3-18: 56 mg/m <sup>2</sup> D1,8,15 Len: 25mg D1-21 Dex: 40 mg D1,8,15,22 Arm 2b (28-day cycles): Car: C1: 20 mg/m <sup>2</sup> D1 and 36 mg/m <sup>2</sup> D2,8,9,15,16. C2: 36 mg/m <sup>2</sup> D1,2,8,9,15,16. C3-18: 56 mg/m <sup>2</sup> D1,8,15	Immuno-phenotypic CR rate at 18 months	III	Recruiting

(Continued)

Table 1. (Continued)

NCT number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT03652064	A study comparing daratumumab, Velcade (Bortezomib), lenalidomide, and dexamethasone (D-VRd) with Velcade, lenalidomide, and dexamethasone (VRd) in participants with untreated multiple myeloma and for whom hematopoietic stem cell transplant is not planned as initial therapy (CEPHEUS)	Untreated NDMM and SCT not planned as Initial Therapy	Arm 1 (control): VRd, then Rd Arm 2: D-VRd then DRd	C1-8: 21-days each. C9+: 28 days each: Bort: 1.3 mg/m <sup>2</sup> SC 2x/w on D1, 4, 8, 11 of C1-8 Len: 25 mg PO D1-14 for C1-8 and D1-21 for C9+ Dex: 20 mg PO D1, 2, 4, 5, 8, 9, 11, 12 of C1-8 and 40 mg PO D1, 8, 15, 22 of C9+ Dara (arm 2 only): 1800 mg SC Qw for C1-2, then Q3w for C3-8, and Q4w for C9+	% with negative MRD status	III	Recruiting
NCT03217812	A study of Velcade (Bortezomib) melphalan-prednisone (VMP) compared with daratumumab in combination with VMP (D-VMP), in participants with previously untreated multiple myeloma who are ineligible for high-dose therapy (Asia Pacific region)	Transplant ineligible with untreated NDMM	Arm 1 (control): VMP Arm 2: D-VMP	Up to 9 cycles. 42 days each: Bort: 1.3 mg/m <sup>2</sup> SC 2x/w in W1, 2, 4, 5 of C1, then Qw in W1, 2, 4, 5 of C2-9 Mel: 9 mg/m <sup>2</sup> (4.5 if Cr >2) PO QD D1-4 of C1-9 Pred: 60 mg/m <sup>2</sup> PO QD D1-4 of C1-9 Dara (arm 2 only): 16 mg/kg IV Qw x 6w in C1, then Q3w in C2-9, then Q4w	≥VGPR rate at 6 months and 3 years after last participant 1st dose	III	Recruiting
NCT04052880	Study of subQ Dara with dose-attenuated bortezomib, lenalidomide, dexamethasone in elderly NDMM	Transplant ineligible elderly (age ≥70) with untreated NDMM	1 arm: SC Dara with dose-attenuated VRd x12. Maintenance with Dara with either Len or Ixa. Maintenance choice is based on cytogenetic risk at diagnosis: Dara-Ixa if high-risk, defined by FISH with t(4;14) only and Dara-Len in all others	Induction [28-day cycles]: Dara: 1800 mg SC Qw in C1-2, then Q2w in C3-6, then Q4w Bort: 1.3 mg/m <sup>2</sup> SC D1, 8, 15 Len 15 mg (10 if CrCl 30-60 ml/min, 5 if CrCl 15-30 ml/min) PO QD D1-21 Dex: A total of 20 mg PO Qw Maintenance [28-day cycles]: Dara: 1800 mg SC Q4w Len: 1 dose level below C1-12 dosing (10 mg QD if CrCl >60, 5 QD if CrCl 30-60 ml/min, 5 QOD if CrCl 15-30 ml/min) PO Ixa: 3 mg (2.3 Qw if CrCl 15-30 ml/min) PO QD D1, 8, 15	≥VGPR rate after 8 cycles	II	Not yet recruiting

(Continued)

Table 1. (Continued)

NCT number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT04009109	Study of lenalidomide/ixazomib/dexamethasone/daratumumab in transplant-ineligible patients with newly diagnosed MM	Transplant ineligible with untreated NDMM	Arm 1: induction with Len, Ixa, Dara and Dex ×12. Maintenance with Len Arm 2: induction with Len, Ixa, Dara and Dex ×12. Maintenance with Len, Ixa and Dara	Induction [28-day cycles]: Arm 1 and 2: Len: 15mg PO QD D1-21 Ixa: 4 mg PO D 1,8,15 Dara: 16 mg/kg IV Qw ×8w, then Q2w ×16w, then Q4w Dex: 20mg PO D1,2,8,9,15,16 Maintenance [28-day cycles, up to 2years]: Len: 10mg PO QD D1-21 Ixa (arm 2 only): 3 mg PO D1,8,15 Dara (arm 2 only): 16 mg/kg IV D1	PFS	II	Not yet recruiting
NCT03695744	Daratumumab in combination with bortezomib and dexamethasone in newly diagnosed transplant ineligible multiple myeloma (AMN006)	Transplant ineligible with untreated NDMM	1 arm: DVd ×9 months followed by Dara	Dara: 16 mg/kg IV Qw in W1-9, then Q3w in W10-24, then Q4w in W25+Bort: SC Qw Dex: 40 mg [20 mg if >75years] PO Qw	ORR	II	Not yet recruiting
NCT02918331	A study of JNJ-54767414 (daratumumab) in combination with lenalidomide and dexamethasone in Japanese participants with previously untreated multiple myeloma who are ineligible for high-dose therapy and autologous stem cell transplantation	Transplant ineligible with untreated NDMM	1 arm: DRd	28-day cycles: Dara: 16 mg/kg IV Qw ×8w, then Q2w ×16w, then Q4w Len: 25mg [10 if CrCl 30-60] PO D1-21 Dex: 40 mg D1,8,15,22	Safety: DLT	Ib	Active, not recruiting

Bort, bortezomib; Car, carfilzomib; CR, complete response; D-KRd, daratumumab, carfilzomib, lenalidomide, dexamethasone; D-VMP, daratumumab, bortezomib, melphalan, prednisone; D-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; Dara, daratumumab; Dex, dexamethasone; DLT, dose-limiting toxicity; DRd, daratumumab, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; IV, intravenous; Ixa, ixazomib; KRd, carfilzomib, lenalidomide, dexamethasone; Len, lenalidomide; Mel; melphalan; MRD, minimal residual disease; NCT, National Clinical Trial; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PFS, progression-free survival; PO, by mouth; Pred, prednisone; QD, daily; QOD, every other day; Qw, every week; Rd, lenalidomide; dexamethasone; SC, subcutaneous; SCT, stem cell transplant; dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, prednisone; VRd, bortezomib, lenalidomide.

Adverse events were manageable and did not lead to death or treatment discontinuation in any patient. The trial is ongoing to assess the impact of DVRd compared with VRd alone on sCR rate.<sup>43</sup> Based on these initial reports, the phase III PERSUES trial was designed to compare the efficacy of DVRd to VRd in terms of PFS in this group of patients, utilizing the subcutaneous formulation of daratumumab to minimize toxicity.<sup>44</sup> Ongoing trials of daratumumab-based combinations in transplant eligible NDMM patients are listed in Table 2.<sup>41</sup> The effect of daratumumab-based induction chemotherapy on bone marrow recovery was studied by a group at Mayo Clinic.<sup>45</sup> Neutrophil engraftment was found to be delayed among patients treated with daratumumab (12 patients) prior to stem cell mobilization, compared with patients who did not receive daratumumab (129 patients). Median time to engraftment was 19 and 16 days in the 2 groups, respectively ( $p$  value: 0.017).<sup>45</sup> As daratumumab use in the front-line setting increases, more data is needed to delineate its effect on stem cell mobilization and engraftment, and the clinical implications of these effects.

#### *Daratumumab in NDMM irrespective of transplant eligibility*

In addition to the aforementioned studies, other trials are investigating daratumumab combinations among NDMM patients, irrespective of transplant eligibility. A phase II clinical trial at Mayo Clinic was designed to evaluate the efficacy of the daratumumab in combination with ixazomib, lenalidomide and dexamethasone (D-IRd) as an induction regimen in this group of patients with a median age of 62 years (41–81). Early reports have shown encouraging results. Among 38 patients, 90% achieved  $\geq$ PR after only two cycles, and all patients (32 patients) who completed four cycles achieved  $\geq$ PR, including VGPR in 50%. Stem cell yield was not adversely influenced by treatment, and there were no reports of treatment discontinuation related to adverse events. Updated analysis including results on MRD is awaited.<sup>47</sup> The phase II Lyra trial studied the efficacy of daratumumab in combination with CYBORD in a heterogeneous group of MM patients including transplant eligible and ineligible NDMM patients and patients who relapsed after one line of therapy. Among patients with newly diagnosed MM

(87 patients), 44% achieved  $\geq$ VGPR after four induction cycles, including 5% with CR, with an ORR of 79%. Responses further improved by the end of induction with longer treatment; at a median of six induction cycles, ORR,  $\geq$ VGPR rate and CR rate increased to 81%, 56%, and 9% respectively. At 12 months, PFS was 87% and OS 99%. Adverse events, including infusion reactions, were consistent with previous studies.<sup>48</sup> Ongoing trials of daratumumab-based combinations in NDMM patients irrespective of transplant eligibility are listed in Table 3.<sup>41</sup>

#### **Daratumumab dosing and formulations**

The currently recommended dosing of intravenous (IV) daratumumab is 16 mg/kg administered on a weekly basis for 8 weeks, then biweekly for 16 weeks, and every 4 weeks thereafter, a schedule established based on efficacy and safety data from clinical trials.<sup>49</sup> The pharmacokinetic properties of daratumumab were found to be unchanged when used in combination with other regimens, compared with monotherapy and regardless of the backbone regimen and of baseline patient or disease characteristics.<sup>50</sup> Infusion reactions related to the IV formulation of daratumumab are very commonly encountered, especially with the first dose. They have been reported at a rate between 28% and 54% in major clinical trials, with the majority being grade 1–2.<sup>20,23,29,33,34,42,48</sup> Thus, a subcutaneous (SC) formulation of daratumumab with recombinant human hyaluronidase enzyme (DARA + rHuPH20) has been developed in attempts to mitigate this reaction. Indeed, significantly decreased rates of infusion reactions have been reported with this formulation at a daratumumab dose of 1800 mg in a phase Ib safety study.<sup>51</sup> Subsequently, the phase III COLUMBIA trial compared the DARA + rHuPH20 SC formulation (1800 mg) with the IV formulation (16 mg/kg) among 522 MM patients with at least 3 prior lines of therapy. The SC formulation was non-inferior to the IV formulation in terms of efficacy (ORR 41% versus 37% respectively) and pharmacokinetic properties, and exhibited a similar side effect profile. More importantly, it was associated with a significantly lower rate of infusion reactions (12.7% versus 34.5%  $p < 0.0001$ ), at a lower administration time.<sup>52</sup> As mentioned earlier, the phase III PERSUES trial is evaluating the efficacy of DVRd compared with VRd using SC daratumumab.<sup>44</sup>



**Table 2.** Trials evaluating daratumumab combinations in transplant eligible patients with NDMM.

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT02541383	A study to evaluate daratumumab in transplant eligible participants with previously untreated multiple myeloma (Cassiopeia) <sup>42</sup>	Transplant eligible with untreated NDMM	Part 1: Arm 1 (control): Vtd induction ×4, SCT, Vtd consolidation ×2 Arm 2: D-Vtd induction ×4, SCT, D-Vtd consolidation ×2 Part 2: maintenance (randomization of patients with ≥PR) Arm 1: observation Arm 2: Dara	Part1: Induction and consolidation (28-day cycles): Bort: 1.3 mg/m <sup>2</sup> D1,4 in W1, and D8,11 in W2 of each cycle Thal: 100 mg PO QD Dex: 40 mg PO/IV D1,2,8,9,15,16,22,23 of induction C1-2, D1-2 of induction C3-4, 20 mg D8,9,15,16 of induction C3-4, and D1,2,8,9,15,16 of consolidation cycles Dara (arm 2 only): 16 mg/kg IV Qw in induction C1-2, then Q2w in induction C3-4 and consolidation cycles Part 2: Maintenance (up to 2 years): Dara (arm 2 only): 16 mg/kg Q8w	sCR after consolidation PFS after maintenance	III	Active, not recruiting
NCT03710603	Daratumumab, velcade (bortezomib), lenalidomide and dexamethasone compared with velcade, lenalidomide and dexamethasone in subjects with previously untreated multiple myeloma (Perseus) <sup>44</sup>	Transplant eligible with untreated NDMM	Arm 1 (control): VRd induction ×4, SCT, VRd consolidation ×2. Len maintenance Arm 2: D-VRd induction, SCT, D-VRd consolidation ×2. Dara and Len maintenance	Induction and consolidation (28-day cycles): Bort: 1.3 mg/m <sup>2</sup> SC D1,4,8,11 in C1-6 Len: 25 mg PO D1-21 of C1-6 Dex: 40 mg PO QD D1-4 and D9-12 in C1-6 Dara (arm 2 only): 1800 mg SC Qw in C1-2, then Q2w in C3-6 Maintenance (28-day cycles): Len: 10 mg QD PO D1-28 Dara (arm 2 only): 1800 mg SC Q4w	PFS	III	Recruiting
NCT03792620	Daratumumab intensified treatment to eligible MM new patients CTD-Dara induction, follow by Dara consolidation (MAXDARA)	Transplant eligible with untreated NDMM	1 arm: induction with CTD-Dara ×4, SCT, consolidation with Dara + Thal, maintenance with Dara	Induction (28-day cycles): Cyclo: 500 mg D1,8,15 Dex: 40 mg Qw Thal: 100-200 mg D1-28 Dara: 16 mg/kg Qw of C1-2, then Q2w of C3-4 Consolidation: Thal: 100 mg D1-28 ×16w (full consolidation) Dara: 16 mg/kg Q2w after D+30 (pre consolidation) and Q2w D+90-120 (full consolidation) for 4 doses total Maintenance: Dara: 16 mg/kg Qm (28 doses)	Incidence of >VGPR after transplant	III	Recruiting

*(Continued)*

Table 2. (Continued)

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT03896737	Daratumumab-bortezomib-dexamethasone (Dara-VCd) versus bortezomib-thalidomide-dexamethasone (VTd), then maintenance with ixazomib (IXA) or IXA-Dara	Young ( $\leq 65$ ) transplant eligible with untreated NDMM	Part 1: Arm 1: D-VCd induction $\times 4$ , SCT, D-VCd consolidation $\times 2-4$ , Arm 2: VTd induction $\times 4$ , SCT, VTd consolidation $\times 2-4$ Part 2: maintenance (Randomization of patients with $\geq PR$ ) Arm 1: IXA Arm 2: IXA + Dara	Part 1: Induction and consolidation (28-day cycles): Arm 1: Bort: 1.3 mg/m <sup>2</sup> SC D1,8,15,22 Cyclo: 300 mg/m <sup>2</sup> PO/IV D1,8,15,22 Dex: 40 mg PO/IV D1,8,15,22 Dara: 16 mg/Kg IV D1,8,15,22 of C1-2, D1,15 of C3-4 and during consolidation Arm 2: Bort: 1.3 mg/m <sup>2</sup> SC D1,4,8,11 Thal: 100 mg PO D1-28 Dex: 20 mg PO/IV D1,2,3,4,8,9,10,11 Part 2: Maintenance (28-day cycles, up to 24 months): IXA: 3 mg D1,8,15 of C1-4, then 4 mg D1,8,15 of C5+Dara (arm 2 only): 16 mg/kg D1	PFS MRD negativity	II	Recruiting
NCT03669445	Study association of lenalidomide, ixazomib, dexamethasone and daratumumab in newly diagnosed standard risk multiple myeloma (IFM2018-01)	Transplant eligible with standard Risk NDMM	1 arm: Len, Ixa, Dex and Dara induction, SCT, consolidation (all 4 drugs) and Len maintenance	Treatment details not available	MRD-negativity rate	II	Recruiting
NCT03606577	An intensive program with quadruplet induction and consolidation plus tandem autologous stem cell transplantation in newly diagnosed high risk multiple myeloma patients (IFM 2018-04)	Transplant eligible with high risk untreated NDMM	1 arm: D-KRd induction $\times 6$ , tandem SCT and D-KRd consolidation $\times 4$ Maintenance with Len and Dara	Induction: Car: 20/36 mg/m <sup>2</sup> D1,2,8,9,15,16 (20 mg/m <sup>2</sup> D1,2 in C1) Dex: 20 mg QD D1,2,8,9,15,16,22,23 Dara: 8/16 mg/kg IV D1,8,15,22 in C1-2 and D1,15 in C3-6 (8 mg/kg D1,2 in C1) Len: 25 mg QD D1-21 Consolidation: Car: 20/36 mg/m <sup>2</sup> D1,2,8,9,15,16 (20 mg/m <sup>2</sup> D1,2 in C1) Dex: 40 mg QD D1,8,15,22 Dara: 16 mg/kg IV Day 1,15 Len: 15 mg QD D1-21 in C1 and 25 mg/day D1-21 in C2-4 Maintenance (up to 2 years) Dara: 16 mg/kg IV Q8w Len: 10 mg QD D1-21	% of patients receiving the second transplant	II	Recruiting

(Continued)

Table 2. (Continued)

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT03188172	MUK nine b: optimum treatment protocol (MUKnineb)	Transplant eligible with high risk untreated NDMM or plasma cell leukemia	1 arm: D-VRd + low-dose cyclo induction ×4-6, SCT, consolidation part 1 with D-VRd ×6, consolidation part 2 with Dara, Bort, Len ×12. Maintenance: Dara, Len	Induction: Cyclo: 500 mg D1,8 Dara: 16 mg/kg, D1,8,15 (C1,2) and D1 in C3+ Bort: 1.3 mg/m <sup>2</sup> D1,4,8,11 Len: 25 mg D1-14 Dex: 20-40 mg D1,4,8,11 Consolidation 1: Bort: 1.3 mg/m <sup>2</sup> D1,8,15,22 Len: 25 mg D1-21 Dex: 20-40 mg D1,8,15,22 Dara: 16 mg/kg D1 Consolidation 2: Dara: 16 mg/kg D1 Bort: 1.3 mg/m <sup>2</sup> D1,8,15 Len: 25 mg D1-21 Maintenance: Dara: 16 mg/kg D1 Len: 10 mg D1-21	PFS	II	Recruiting
NCT03004287	2015-12: A study exploring the use of early and late consolidation/maintenance therapy	Transplant eligible with untreated or ≤4 cycles of systemic therapy, high-risk MM	1 arm: KTd-Dara-PACE, SCT1, consolidation 1: Dara-Kd +/- SCT 2, consolidation 2: Dara. Maintenance: Dara-Kd alternating with Dara-Rd (alternating 3-month blocks)	Induction: Car: IV D1,2 Thal: PO D1-4 Dex: PO/IV D1-4 Dara: IV D1 Cisplatin: IV continuous infusion D1-4 Adriamycin: IV continuous infusion D1-4 Cyclo: IV continuous infusion D1-4 Etoposide: IV continuous infusion D1-4 Consolidation 1: Car: IV D1,8,15,22 Dara: IV D1,8 Dex: PO/IV D-4 and D-1 of SCT Consolidation 2: Dara: IV D1,8 Maintenance: Dara: IV D1 Car: IV D1,8,15,22 Len: PO D1-21 Dex: PO/IV D1,8,15,22	PFS	II	Recruiting

(Continued)

Table 2. (Continued)

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary outcome	Phase	Status
NCT02874742	Study comparing daratumumab, lenalidomide, bortezomib, and dexamethasone (D-RVd) versus lenalidomide, bortezomib, and dexamethasone (RVd) in subjects with newly diagnosed multiple myeloma	Transplant eligible with untreated NDMM	Arm 1: D-RVd induction ×4, SCT, consolidation ×2, then maintenance Arm 2: RVd induction ×4, SCT, consolidation ×2, maintenance	Induction and consolidation (21-day cycles): Len: 25 mg PO D1-14 Bort: 1.3 mg/m <sup>2</sup> SC D1,4,8,11 Dex: 20 mg PO D1,2,8,9,15,16 Dara (arm 1 only): 16 mg/kg IV Qw in induction, then Q3w in consolidation Maintenance [28-day cycles, up to 24 months]: Len: 10 mg PO D1-21 in C7-9 and 15 mg D1-21 in C10+ Dex: 20 mg PO D1,2,8,9,15,16 Dara (arm 1 only): 16 mg/kg IV Q4 or Q8w	sCR rate by the end of post-SCT consolidation	II	Active, not recruiting
NCT02955810	Cyclophosphamide-bortezomib-dexamethasone (CyBorD) with daratumumab (Dara) [CyBorD-Dara] <sup>4,6</sup>	Transplant eligible with untreated NDMM	1 arm: Dara-CyBorD induction ×4, SCT, Dara-CyBorD consolidation ×2, maintenance with Dara (and Bort if high-risk disease)	Induction and consolidation: Cyclo: PO D1,8,15,22 Bort: SC D1,8,15,22 Dex: 20 mg PO D1,2,8,9,15,16,22,23 Dara: 16 mg/kg IV D1,8,15,22 in C1,2 and D1,15 in C3,4 and consolidation cycles Cyclo and Bort dosing - 3 dose levels: L1: cyclo 150 mg/m <sup>2</sup> , bort 1.3 mg/m <sup>2</sup> L2: cyclo 300 mg/m <sup>2</sup> , bort 1.3 mg/m <sup>2</sup> L3: cyclo 300 mg/m <sup>2</sup> , bort 1.5 mg/m <sup>2</sup> -1L: cyclo 100 mg/m <sup>2</sup> , bor 1.3 mg/m <sup>2</sup> Maintenance (up to 2 years): Dara: 16 mg/kg IV D1 Q4w Bort (if high-risk disease): SC D1,15	MTD CR rate post SCT	Ib	Active, not recruiting

Bort, bortezomib; Car, carfilzomib; CR, complete response; CTD-Dara, cyclophosphamide, thalidomide, dexamethasone, daratumumab; Cyclo, cyclophosphamide; CYBORD, cyclophosphamide, bortezomib and dexamethasone; D-KRd, daratumumab, carfilzomib, lenalidomide, dexamethasone; D-RVd, daratumumab, lenalidomide, dexamethasone, bortezomib; D-Vcd, daratumumab, bortezomib, dexamethasone; D-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; D-VTd, daratumumab, bortezomib, thalidomide, dexamethasone; Dara, daratumumab; Dex, dexamethasone; IV, intravenous; Ixa, ixazomib; Kd, carfilzomib, dexamethasone; KTd, carfilzomib, thalidomide, dexamethasone; Len, lenalidomide; MRD, minimal residual disease; MTD, maximum tolerated dose; NCT, National Clinical Trial; NDMM, newly diagnosed multiple myeloma; PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide; PFS, progression-free survival; PO, by mouth; PR, partial response; QD, daily; Qw, every week; Rd, lenalidomide, dexamethasone; RVd, lenalidomide, dexamethasone, bortezomib; SC, subcutaneous; sCR, stringent complete response; SCT, stem cell transplant; Thal, thalidomide; VGPR, very good partial response; VRd, bortezomib, lenalidomide, dexamethasone; VTd, bortezomib, thalidomide, dexamethasone.

**Table 3.** Trials evaluating daratumumab combinations in NDMM irrespective of transplant eligibility.

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary Outcome	Phase	Status
NCT03942224	Daratumumab, ixazomib, and dexamethasone or daratumumab, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma (DeRIVE)	NDMM	Arm 1: induction with Did ×8 +/- SCT, maintenance with Did (up to 24 months) Arm 2: induction 1 with DVd ×3 + induction 2 with Did ×5 +/- SCT. Maintenance with Did	Induction: Arm 1 (28-day cycles): Dara: IV D1,8,15,22 of C1-2 and D1,15 of C3-8 Ixa: PO D1,8,15 Dex: IV/PO D1,8,15,22 Arm 2: Induction 1 (21-day cycles): Dara: IV D1,8,15 Bort: SC D1,4,8,11 Dex: IV/PO D1,8,15 Induction 2 (28-day cycles): Dara: IV D1,15 Ixa: PO D1,8,15 Dex: IV/PO D1,8,15,22 Maintenance (up to 24 months) Arm 1 (28-day cycles): Dara: IV D1 Ixa: PO D1,8,15 Dex: IV/PO D1,8,15,22 Arm 2 (28-day cycles): Dara: IV D1 Ixa: PO D1,8,15 Dex: IV D1	≥VGPR rate	II	Recruiting
NCT03500445	Daratumumab, carfilzomib, lenalidomide and low dose dexamethasone (DKRd) in newly diagnosed, multiple myeloma	Transplant eligible or ineligible untreated NDMM	1 arm: D-KRd ×24	Dara: 16 mg/kg IV, C1-2; Qw, C3-8; Q2w, C9-24; D1 Car: C1: 20 mg/m <sup>2</sup> IV D1,2 and 36 mg/m <sup>2</sup> D8,9,15,16, C2-9; 36 mg/m <sup>2</sup> D1,2,8,9,15,16, C9-24; 36 mg/m <sup>2</sup> D1,2,15,16 Len: 25 mg PO D1-21 in C1-24 Dex: 40 mg (20 if ≥75 years) PO Qw in C1-9 and 20 mg Qw in C9-24	sCR rate MRD negative rate by NGS	II	Recruiting
NCT03412565	A study to evaluate subcutaneous daratumumab in combination with standard multiple myeloma treatment regimens	NDMM (for D-VRd & D-VMP) or R/R MM (DRd & DKd)	Arm 1: D-VRd Arm 2: D-VMP Arm 3: DRd Arm 4: DKd	Dara: 1800 mg SC C1-4 in arm 1 and all cycles for arms 2-4 Bort: 1.3 mg/m <sup>2</sup> SC C1-4 in arm 1 and C1-9 in arm 2 Len: 25 mg PO C1-4 in arm 1 and all cycles in arm 3 Dex: 20 mg PO/IV C1-4 in arm 1 and 40 mg PO/IV in all cycles in arms 3&4 Mel (arm 2 only): 9 mg/m <sup>2</sup> PO C1-9 Pred (arm 2 only): 60 mg/m <sup>2</sup> PO C1-9 Car (arm 4 only): 20 mg/m <sup>2</sup> IV D1C1, then 70 mg/m <sup>2</sup> IV D8,15 of C1, and D1,8,15 of C2+	≥VGPR rate: For D-VRd Cohort ORR: For other cohorts	II	Recruiting

(Continued)

Table 3. (Continued)

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary Outcome	Phase	Status
NCT03290950	A study of daratumumab in patients with newly diagnosed multiple myeloma	Untreated NDMM	1 arm: D-KRd ×8 (2 cohorts)	28-day cycles: Dara: 16 mg/kg D1,8,15,22 in C1-2, D1,15 in C3-6 and D1 in C7-8 Car: C1: 20 mg/m <sup>2</sup> D2,3 and 36 mg/m <sup>2</sup> D8,9,15,16. C2-8: 36 mg/m <sup>2</sup> D1,2,8,9,15,16 Len: 25 mg PO QD D2-21 in C1 and D1-21 in C2-8 Dex (cohort 1): C1: 20mg PO D2,3,8,9,15,16. C2: 20mg D1,2,8,9,15,16,22. C3-4: 20mg D1,2,8,9,15,16. C5-8: 10mg PO D1,2,8,9,15,16 Dex (cohort 2): C1: 20mg PO D1,2,22 and 40mg D8,15. C2: 40mg D1,8,15 and 20mg D22. C3-4: 40mg D1,8,15. C5-8: 20mg PO D1,8,15	MRD negativity rate	II	Recruiting
NCT03224507	Monoclonal antibody-based sequential therapy for deep remission in multiple myeloma (MASTER)	Transplant eligible and ineligible with untreated NDMM	Arm 1: D-KRd induction ×4, SCT, D-KRd consolidation (up to 2 blocks, 4 cycles each) Arm 2: D-KRd induction ×4 and D-KRd consolidation (up to 3 blocks, 4 cycles each) Maintenance (Both): MRD+: Len MRD-: observation	Induction and consolidation: Arm 1: Dex: 40mg PO D1,8,15,22 Len: 25mg PO D1-21 Car: C1: 20mg/m <sup>2</sup> IV D8,9 and 36mg/m <sup>2</sup> IV D15,16. C2-4: 36mg/m <sup>2</sup> IV D1,2,8,9,15,16 Dara: 16mg/kg IV D1,8,15,22 in C1-2 and D1,15 in C3-4 Arm 2: Dex: 40mg PO D1,8,15,22 Len: 25mg PO D1-21 Car: C1: 20mg/m <sup>2</sup> IV D8,9 and 36mg/m <sup>2</sup> IV D15,16. C2-4: 36mg/m <sup>2</sup> IV D1,2,8,9,15,16 Dara: 16mg/kg IV D1,8,15,22 in C1-2 and D1,15 in C3-4 Maintenance: Len (MRD+ only)	% of MRD negative remissions post consolidation	II	Recruiting
NCT03012880	Ixazomib citrate, lenalidomide, dexamethasone, and daratumumab in treating patients with newly diagnosed multiple myeloma <sup>47</sup>	Untreated NDMM	1 arm: Ixa, Len, Dara, Dex induction ×12. Ixa and Dara maintenance (up to 36months)	Induction: Ixa: 4 mg D1,8,15 Len: 25 mg D1-21 Dara: 16 mg/kg IV D1,8,15,22 in C1-2, D1,15 in C3-6 and D1 (Q4w) thereafter Dex: 40mg D1,8,15,22 Maintenance: Ixa: D1,8,15 Dara: D1 Q4w	confirmed CR rate	II	Active, not recruiting

(Continued)

Table 3. (Continued)

NCT Number	Title	Conditions	Interventions	Dosing and schedule	Primary Outcome	Phase	Status
NCT02951819	A study to evaluate Dara-CyBorD in previously untreated and relapsed subjects with multiple myeloma (Lyra) <sup>48</sup>	Untreated MM or Relapsed with 1 prior line of therapy	1 arm: induction with Dara-CyBorD ×4–8, maintenance with Dara and Dex	Induction (28-day cycles): Cyclo: 300 mg/m <sup>2</sup> PO D1,8,15,22 Bort: 1.5 mg/m <sup>2</sup> SC D1,8,15 Dex: pre Dara infusion in all cycles. C1–8: pre + post-Dara infusion Dara: C1D1 and C1D2: 8 mg/kg. W2–8: 16 mg/kg IV Qw. W9–24: 16 mg/kg IV Q2w. W25+: Q4w Maintenance (12 28-day cycles): Dara: D1 Dex: D1	% with CR or VGPR	II	Active, not recruiting
NCT01998971	A study of JNJ-54767414 (HuMax CD38) (anti-CD38 monoclonal antibody) in combination with backbone treatments for the treatment of patients with multiple myeloma	Newly diagnosed (for KRd) or R/R (for CFZ-dex) MM	Arm 1: DVd Arm 2: D-VMP Arm 3: D-VTd Arm 4: Dara-Pom-Dex Arm 5: DKd Arm 6: D-KRd	Treatment details not available	Number affected by adverse events by MedDRA SOS and PT Number with DLT	Ib	Active, not recruiting

Bort, bortezomib; Car, carfilzomib; CR, complete response; CYBORD, cyclophosphamide, bortezomib and dexamethasone; D-KRd, daratumumab and dexamethasone; D-KRd, daratumumab, lenalidomide, dexamethasone; D-KRd, daratumumab, carfilzomib, lenalidomide, dexamethasone; D-VMP, daratumumab, bortezomib, melphalan, prednisone; D-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; D-VTd, daratumumab, bortezomib, thalidomide, dexamethasone; Dara, daratumumab; Dex, dexamethasone; Dld, daratumumab, ixazomib, dexamethasone; DKd, daratumumab, carfilzomib, dexamethasone; DLT, dose-limiting toxicity; DRd, daratumumab, lenalidomide, dexamethasone; DVd, daratumumab, bortezomib, dexamethasone; IV, intravenous; Ixa, ixazomib; Len, lenalidomide; Mel, melphalan; MRD, minimal residual disease; NCT, National Clinical Trial; NGS, next generation sequencing; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PO, by mouth; Pred, prednisone; Pom, pomalidomide; PT, preferred term; Qd, daily; Qw, every week; SC, subcutaneous; sCR, stringent complete response; SCT, stem cell transplant; SOS, system organ class; VGPR, very good partial response.

## Conclusion

Despite significant advances in MM treatment options, mortality remains high and more efficacious regimens are needed. Daratumumab has shown encouraging results both as monotherapy and in combination with other regimens in both R/R MM and untreated disease. Clinical trials so far have shown enhanced efficacy and tolerability of several daratumumab-based combinations in NDMM for both transplant ineligible and eligible patients, without hindering transplant. Although benefit in high-risk subpopulations is still unclear, data may be limited by the smaller number of participants in these subgroups, and thus more evidence is needed. Efforts are underway to explore other combinations with daratumumab, improve drug formulation, gain understanding of response predictors and mechanisms of resistance,<sup>53</sup> and identify patient subgroups more likely to respond to these treatments.

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