

Evaluating Daratumumab in the Treatment of Multiple Myeloma: Safety, Efficacy and Place in Therapy

This article was published in the following Dove Press journal:
Cancer Management and Research

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Abstract: Despite the tremendous advances in the treatment of multiple myeloma, mortality remains significant, highlighting the need for new effective strategies. In recent years, daratumumab, a novel human monoclonal antibody, binding CD38, has dramatically improved outcomes either as monotherapy or in combination with traditional regimens. Originally approved for relapsed/refractory multiple myeloma, this breakthrough medication is now being used as frontline therapy in patients with newly diagnosed multiple myeloma regardless of transplant eligibility, with trials showing promising results. Its tolerable side-effect profile and enhanced efficacy have led to its widespread incorporation into the management of multiple myeloma and further exploration about its use in other entities such as smoldering myeloma, MGUS, MGRS and amyloidosis. This comprehensive review will discuss daratumumab's mechanism of action and safety profile, as well as research which has defined its current approved indications, and ongoing clinical investigation that will define its future.

Keywords: daratumumab, newly diagnosed multiple myeloma, relapsed/refractory multiple myeloma

Introduction

Multiple myeloma (MM) is an incurable hematologic malignancy caused by the accelerated clonal proliferation of plasma cells. Generally, the abnormal plasma cell population is localized in the bone marrow with only 1–7% of patients having extramedullary disease at the time of initial diagnosis, and up to 8% of patients developing extramedullary disease at some point later in their course.^{1,2} The rapid growth of clonal plasma cells can lead to generalized organ dysfunction through various mechanisms. The most common presenting complications include renal failure, anemia, hypercalcemia and lytic bone lesions, the so-called “CRAB criteria.”³ MM accounts for 1.8% of all new cancer cases and approximately 10–18% of all hematologic neoplastic processes in the US. It is more common in males than females, and in African Americans compared to other ethnicities. It is most frequently diagnosed among older individuals aged 65–74 with a 5-year survival rate of only 52.2%, despite the tremendous advances and continuous evolving therapeutic strategies.⁴

Over the past decade, rigorous research has led to the discovery of new and innovative therapies that have been established as standard-of-care regimens in

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patients with both untreated and relapsed/resistant disease. These novel agents include proteasome inhibitors (PI; Bortezomib, Carfilzomib and Ixazomib) and immunomodulator IMiD (Thalidomide, Lenalidomide, Pomalidomide), which can be used as monotherapy or in various doublet and triplet combinations such as CyBORd and VRd.⁵⁻⁹ Despite the achievement of deeper remissions and improved survival with these breakthrough agents, the long-term outcomes for relapsed/refractory MM (RRMM) patients still remain poor, emphasizing the need for new effective therapies.

Monoclonal antibodies have proven to be exceptionally efficacious in several solid and hematologic malignancies.¹⁰ Development of monoclonal antibodies against promising molecular targets for MM began to take form in the 1990s. By 2008, daratumumab, a fully human monoclonal G1-k antibody against CD38 epitope on the surface of plasma cells was introduced into human studies as a Phase I clinical trial.¹¹ Its favorable effects quickly became evident, launching further clinical trials combining daratumumab with other existing antiplasma cell therapies in both the treatment-naïve and relapsed populations. In November 2015, daratumumab was approved for the treatment of RRMM patients by the US Food and Drug Administration (FDA), followed by the European Medicines Agency in May 2016. Its incorporation into clinical practice has radically shifted the treatment paradigm of MM and has dramatically improved outcomes by prolonging progression-free survival (PFS) and in some cases, overall survival (OS) with a relatively safe toxicity profile. In this review article, we will discuss how daratumumab has earned its rightful place in current MM therapy based on promising data from recent clinical trials and will explore its future role in the treatment of this complex disease.

Mechanism of Action

CD38 is a transmembrane glycoprotein with ectoenzymatic functions located predominately at the surface of plasma cells, making it a good target for novel therapeutic strategies.¹² CD38 is expressed on all clonal plasma cells regardless of the spectrum of disease (ex. MGUS, SMM, active MM). As a multifunctional ectoenzyme, CD38 modulates the NAD⁺ catabolism and plays an important role in the synthesis of cyclic-ADP-ribose, functions that contribute to cell survival via intracellular calcium mobilization and homeostasis. Recent studies suggest that CD38 may play a role in the synthesis of extracellular adenosine, which has been implicated in immune suppression.¹³

Daratumumab is a human monoclonal antibody that targets a unique epitope on the CD38 glycoprotein. Daratumumab induces cell death through various Fc-dependent immune effector mechanisms. These mechanisms include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis and apoptosis via crosslinking.¹⁴⁻¹⁶ Furthermore, inhibition of the CD38 ectoenzymatic function may lead to direct apoptosis induction of neoplastic cells. Another distinct mechanism is its immunomodulatory action. Specifically, daratumumab binds to the CD38 positioned on the surface of immune suppressor cells which play an important role in immune dysfunction observed in MM. These cells include regulatory T, regulatory B and myeloid-derived suppressor cells. Daratumumab effectively destroys these suppressive cell populations, resulting in marked increase of T (helper CD4⁺ and cytotoxic CD8⁺) cells in the blood and bone marrow. This increase in T cells leads to enhanced activity of the immune system against the tumor with subsequent elimination of MM cells^{17,18} (Figure 1).

Dosing, Administration and Safety Profile

Initial studies examining daratumumab's safety, dosing, and efficacy, as monotherapy or in combinations with other agents, only included individuals with RRMM.^{11,19-22} Over time, the favorable outcomes and well-manageable side effect profile of daratumumab led to further expansion of studies to include individuals with newly diagnosed MM (NDMM) irrespective of transplant eligibility.²³⁻²⁵ The safety and efficacy of daratumumab as monotherapy and in combination with other backbone regimens have been extensively described. The novel CD38 monoclonal antibody appears to be well tolerated without significant toxicities or reported deaths when given alone or in combination with proteasome inhibitors or immunomodulators.

The majority of clinical trials have utilized intravenous daratumumab, which is the initial formulation approved by the FDA. Recently, the subcutaneous formulation was also approved.²⁶⁻²⁹ The recommended dosing of the intravenous daratumumab formulation is 16 mg/kg once per week for the first 8 weeks, then biweekly for the next 16 weeks, and every four weeks thereafter. This dosing and schedule were meticulously established by pharmacokinetic analysis that was conducted in the context of pivotal phase I/II clinical trials and are fixed for all cases, whether

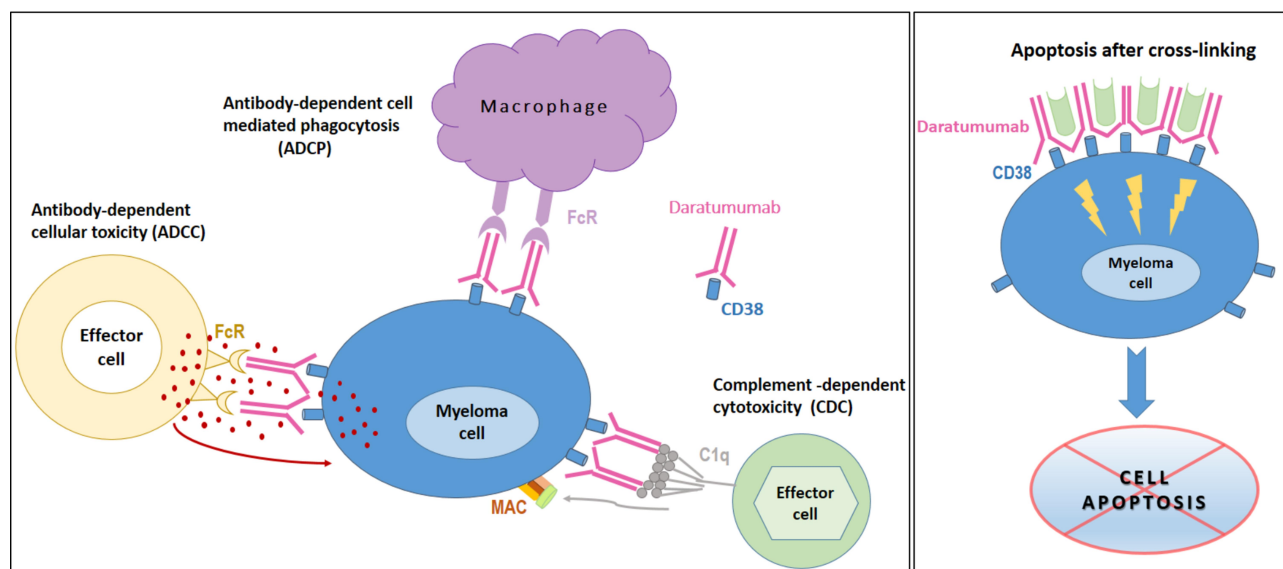


Figure 1 Daratumumab mechanism of action.

daratumumab is given as monotherapy or in combination with other agents and regardless of the patient or disease characteristics.^{30,31} Notably, no dosing adjustments are needed in case of mild-moderate renal or hepatic impairment, although there are no current data about the pharmacokinetic profile of daratumumab in patients who are on dialysis or have severe liver failure.

The most common side effect of daratumumab when given as monotherapy or combined with any backbone regimen is infusion reactions which include headache, nasal congestion, throat irritation, cough, chills, fevers, nausea and vomiting. Severe infusion-related reactions (IRRs) include bronchospasm, dyspnea, hypoxia and hypertension. Most IRRs are mild (grade 1–2 in severity), manageable and predominantly occur during the first administration.¹¹ Notably, the median duration of the first infusion is approximately 7 hours with subsequent infusions being shorter (approximately 1.5h). In an effort to limit the incidence and severity IRRs by reducing the infusion time, FDA approved the splitting of the first daratumumab dose over 2 consecutive days (8 mg/kg on days 1 and 2 of cycle 1), since this strategy was proven to not alter the weekly pharmacokinetic concentrations of the novel antibody.³²

The use of pre-medications approximately 1 hour prior to each daratumumab infusion also prevent the occurrence of IRRs. Pre-medications include: [1] methylprednisolone 100 mg IV or dexamethasone 20 mg IV for the first two infusions and methylprednisolone 60 mg IV or dexamethasone 12 mg (oral or IV) prior to following infusions, [2] oral

antipyretics (acetaminophen 650–1000 mg orally), and (iii) antihistamine (diphenhydramine 25 to 50 mg orally or IV). There is encouraging evidence about the use of Montelukast (leukotriene receptor antagonist) as a pre-medication agent. One study with 60 individuals concluded that the addition of Montelukast more than 30 min prior to the first daratumumab infusion reduced the rate of IRRs by one-third.³³

Nearly all reactions occur during daratumumab administration or within 4 hours of completing infusion; rarely reactions happen up to 48 hours after infusion. In order to avoid delayed reactions, the patients are post-medicated with oral corticosteroids for 2 days following daratumumab. For individuals with underlying lung pathology including asthma and/or chronic obstructive pulmonary disease, post-medications should also include diphenhydramine 25–50 mg oral or equivalent on the 2 days following daratumumab infusions and inhaled short-acting beta-2 adrenergic receptor agonist as well as, inhaled corticosteroids along with long-acting bronchodilators in more severe cases.³⁴

Other common side effects include infections with respiratory involvement being the most common (upper respiratory infections, pneumonia) as well as cytopenias (most commonly anemia, neutropenia thrombocytopenia) which are believed to be synergistic, due to the combination of daratumumab with traditional regimens.³⁵

Relapsed/Refractory MM

Historically, patients with MM who had been treated with prior lines of therapy had very limited options at disease

relapse.^{36–38} Daratumumab was initially studied for its role in managing these patients and the results were promising (Table 1). In a phase I trial (*GEN501*), there was no maximum tolerated dose (MTD) when using daratumumab as monotherapy in patients with RRMM despite having been heavily pretreated median of 4 prior therapies, 64% double refractory to PI and IMiD.¹¹ Additionally, patients who received 16 mg/kg achieved an overall response rate (ORR) of 36% compared to only 10% in the lower dose groups. *SIRIUS*, was a Phase II trial that reported an ORR of 29.2% after treating a RRMM population (median 5 prior lines of therapy) using 16mg/kg of daratumumab.¹⁹ The 1-year OS was 65%. In a two-part phase I trial (*GEN503*), daratumumab was combined with lenalidomide and dexamethasone. The findings were astounding with an ORR 81%.²⁰ These studies demonstrated that daratumumab was overall well tolerated and could be cleared for further studies.

Two landmark Phase III trials studied the synergism of daratumumab when combined with bortezomib and lenalidomide in RRMM. The *CASTOR* trial randomly assigned 499 patients with ≥ 1 prior treatment to receive bortezomib and dexamethasone (D-Vd) with or without daratumumab (Vd). Daratumumab significantly improved the ORR and PFS across all subgroups. The D-Vd arm had a 61% lower risk for death or disease progression compared to the Vd

arm.²⁵ Given daratumumab's unquestionable benefit the study was stopped early and patients in the Vd group had the option to receive daratumumab. After a median follow-up of 19.4 months, D-Vd arm continued to maintain significant benefit with respect to response rates and PFS.³⁹

Similarly, the *POLLUX* trial followed 569 patients with RRMM, this time assigned to receive either lenalidomide and dexamethasone alone (Rd) or with daratumumab (D-Rd) dosed at 16mg/kg. The 12-month PFS in the intervention arm was an amazing 83.2% compared to 60.1% in the control group, again a statistically significant difference. The ORR rate of the D-Rd group was 92.9% versus 76.4% in the Rd group, and the proportion of those achieving a CR or better was 43.1% vs 19.2%, respectively.²² After a median follow-up of 44.3 months, daratumumab continued to offer a PFS benefit, greater overall responses as well as sustained minimal residual disease (MRD) negativity.⁴⁰

In both trials, addition of daratumumab led to significantly prolonged PFS and improved responses in subgroups of patients with high and standard cytogenetic risk. Specifically, for the high-risk subgroup, *CASTOR* revealed that the median PFS with D-Vd was 11.2 months vs 7.2 months with Vd. The benefit of adding daratumumab although statistically significant was less pronounced

Table 1 Pilot Phase Clinical Trials Evaluating Daratumumab in Patients with RRMM

Study Name	Phase	N	Number of Prior Treatments	Regimen	Results
GEN501	I-II	104	4	Dara monotherapy Dose escalation: 0.005–24 mg/kg Expansion phase: 8 mg/kg and 16 mg/kg	No MTD At 16 mg/kg dose: • ORR 36% (\geq PR) • 12-month OS: 77% • mPFS 5.6 months • 65% no progression at 12 months
SIRIUS	II	106	5	Dara monotherapy (16 mg/kg)	• ORR 29.2% • 12-month OS: 64.8% • mPFS: 3.7 month
CASTOR	III	499	2	Arm 1: Dara-Vd Arm 2: Vd (control)	• \downarrow risk of progression by 61% • ORR (\geq VGPR) 83.8% vs 63.2% • MRD negativity: 11.6% vs 2.4% • mPFS 16.7 vs 7.1 months
POLLUX	III	569	1	Arm 1: Dara-Rd Arm 2: Rd (control)	• ORR (\geq VGPR) 92.9 vs 76.4% • MRD negativity 30.4% vs 5.3% • mPFS 44.5 vs 17.5 months OS: NR for either group

Abbreviations: ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; Vd, Velcade–dexamethasone, Rd, Revlimid–dexamethasone; MRD, minimal residual disease, mPFS, median progression-free survival; OS, overall survival; MTD, maximum tolerated dose.

compared to the benefit of the standard risk subgroup. ORR was higher with D-Vd by 81.8% versus 61.7%. Similarly, in POLLUX, PFS was significantly longer in high-risk patients receiving daratumumab versus Rd alone (median: 26.8 vs 8.3 months). D-Rd also prolonged PFS in first relapse and PFS2.⁴¹ Again, regardless of cytogenetic risk, the rates of ORR, VRPR and CR were higher with D-Rd than with Rd.

MRD was assessed in both studies. In CASTOR, addition of daratumumab increased MRD-negative rates at all sensitivity thresholds (10^{-4} , 10^{-5} , 10^{-6}), and evaluated subgroups (regardless of prior lines of therapy and cytogenetic risk) compare to Vd alone. Notably, only D-Vd but not Vd induced MRD negativity in high-risk patients. MRD-negative status was associated with prolonged PFS in both study arms. Among patients with MRD-positive status, D-Vd prolonged PFS versus Vd. Similarly, in POLLUX, MRD negativity (10^{-5}) in the D-Rd arm was significantly higher and has also continued to deepen over time compared to Rd alone. PFS was superior, but not significantly, with D-Rd versus Rd in patients who achieved MRD negativity and significantly prolonged with D-Rd versus Rd in patients with MRD-positive status.^{22,42}

A recent subgroup analysis of both trials revealed that patients who received daratumumab in the 65–74 and the ≥ 75 age categories had significantly prolonged PFS compared to the rest of the cohort who did not receive the novel antibody. However, in terms of ORR, the subgroup of individuals ≥ 75 years who received daratumumab did not have a statistically significant benefit, although they did have significantly higher rates of \geq CR and \geq VGPR.⁴³ Of note, there were limited number of patients ≥ 75 years of age in both trials.

Results from these studies led to the FDA approval of daratumumab in 2015 as monotherapy for RRMM patients who had received at least 3 lines of prior therapy (including PI and IMiD) or who were double refractory to an IMiD or PI. The following year, FDA approved daratumumab with Vd or Rd for RRMM patients who had received at least one prior line of therapy.

Daratumumab is also being studied in 103 individuals with RRMM in combination with pomalidomide-dexamethasone in a Phase 1b trial (*EQUULEUS*; NCT01998971). Results so far have shown an ORR of 52.2% with VGFR achieved in 28% and CR in 6% of the participants. Most of the patients were refractory to lenalidomide (89%), bortezomib (71%) or both (64%). This trial led to the 2017 FDA approval of daratumumab in combination

with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least 2 prior therapies including lenalidomide and a PI. In a retrospective study of 34 patients done by Emory, it was found that retreatment with daratumumab-pomalidomide-dexamethasone in patients who were previously refractory to pomalidomide and/or daratumumab resulted in response.⁴⁴

One arm of the innovative phase I/II STOMP trial (NCT02343042) combines daratumumab with selinexor and dexamethasone (SDd) in patients with RRMM who had received ≥ 3 prior line of therapy, in an effort to determine the maximum tolerated dose as well as the safety and efficacy of his combination. Selinexor is an oral 1st class selective inhibitor of exportin-1 (XPO1), which is the major nuclear export protein for tumor suppressor proteins and oncoprotein mRNAs. This protein is overexpressed in MM, has been associated with drug resistance and unfavorable prognosis. Gasparetto et al announced the preliminary efficacy data at the 2019 EHA meeting, then in ASCO 2020 reporting that SDd leads to deep and durable responses. ORR was 73% in patients who had not received prior daratumumab or selinexor with mPFS of 12.5 months, whereas ORR was 69% in the entire cohort. The safety profile of SDd was manageable, with the most common grade 3/4 side effects being pancytopenia. Further results are anxiously awaited.⁴⁵

Currently, daratumumab is being studied in several trials in combination with other novel agents including pomalidomide, carfilzomib (a 2nd generation PI) or ixazomib for the treatment of RRMM.^{32,44,46,47} Other trials are investigating combinations of daratumumab with all-trans retinoic acid (NCT02751255), venetoclax (a Bcl-2 inhibitor) (NCT03314181), or checkpoint inhibitors such as atezolizumab (NCT02431208), durvolumab (NCT02807454) and nivolumab (NCT03184194, NCT01592370). Johns Hopkins has recently developed a study combining daratumumab with CPI-444, an oral, small-molecule inhibitor targeting adenosine-2A receptors (NCT04280328). Other small molecules being paired with daratumumab include NKTR-255, an IL-15 receptor agonist (NCT04136756) and INCB001158 (NCT03837509), an investigational first-in-class, novel small molecule arginase inhibitor. These groundbreaking trials highlight the impressive anti-plasma cell activity of daratumumab and its widely positive impact on the outcomes of patients with refractory/relapse MM. These results led investigators to consider other applications for daratumumab, notably in newly diagnosed patients.

Newly Diagnosed MM

Now, a few years since its initial approval in 2015, daratumumab is being investigated for its utility in frontline therapy. Much of the data are encouraging, reaffirming daratumumab's favorable profile and unquestionable clinical benefit.

Transplant-Eligible Patients

The traditional induction/consolidation regimen for patients who are candidates for autologous stem cell transplantation (ASCT) in North America is VRd, a three-drug regimen of bortezomib, lenalidomide and dexamethasone, followed by lenalidomide maintenance therapy after ASCT.^{9,48-51} Numerous studies have shown the clinical efficacy of three drug regimens for the treatment of MM.^{7,52} Additionally, there is evidence to suggest superiority of triple therapy versus double.⁴⁸ However, with MM remaining a challenging disease with a high morbidity and mortality burden on patients, researchers are

continuously looking for clinical solutions to improve patient outcomes. Daratumumab, with its success amongst patients with relapsed/refractory MM, has emerged as a new frontier for patients in first-line therapy.

The 2019 CASSIOPEIA trial was the first major phase III trial that successfully showed daratumumab's benefit when combined with traditional frontline induction/consolidation therapy prior to ASCT (Table 2). The trial compared the combination of IV daratumumab with VTd (bortezomib-thalidomide-dexamethasone) versus VTd alone as induction regimen in preparation of ASCT and for consolidation therapy. The patients who achieved a PR or better were then further randomized to receive daratumumab maintenance versus observation until disease progression. Standard risk patients in the daratumumab group maintained a significantly better and deeper responses including stringent (sCR), improved MRD negativity and PFS. sCR was seen in all subgroups with the exception of

Table 2 Pilot Clinical Trials Evaluating Daratumumab in Transplant-Eligible Patients with NDMM

Study Name	Phase	N	Regimen	Results
CASSIOPEIA	III	1085	I/C: Dara-VTd vs VTd Patients achieving ≥ PR: Dara maintenance vs observation	<ul style="list-style-type: none"> • sCR 29% vs 20% • ≥CR 39% vs 26% • MRD negativity: 64% vs 44% • 18-mo PFS: 93% vs 85%, mPFS NR • ↓risk of progression/death by 53%
GRIFFIN	I [I] II [II]	I: 16 II: 224	Dara-VRd, single arm I/C: Dara-VRd vs VRd M: Lena/Dara vs Lenalidomide	<ul style="list-style-type: none"> • IRRs 31% • Grade ≥3: cytopenias, febrile neutropenia, pneumonias. All rare. • ≥VGPR 100%, ≥CR 63% • MDR negativity 50% <p><i>Preliminary data:</i></p> <ul style="list-style-type: none"> • sCR: 50% vs 37% • ≥VGPR: 91% vs 73% • MRD negativity: 59% vs 24% of those achieving ≥CR • PFS and OS immature
PERSEUS	III	690	I/C: SC Dara-VRd vs VRd M: Lena/SC Dara vs Lena	Data not yet mature
EMN 18 (NCT0389673)	II	400	I/C: Dara-VRd vs VRd Patients achieved ≥ PR: M: Ixazomib/Dara vs Ixazomib	Data not yet mature
MUKnineb ⁵⁷ (NCT03188172)	II	95 Single arm High-risk patients	I: Dara-VRd + low dose Cytosin C: Dara-VRd, Dara-VR M: Dara/Lena	Data not yet mature

Abbreviations: I/C, induction/consolidation; M, maintenance; NR, not reached; SC, subcutaneous; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; OS, overall survival; MRD, minimal residual disease; IRR, infusion-related reactions; VRd, Velcade–Revlimid–dexamethasone; VTd, Velcade–thalidomide–dexamethasone.

patients with high-risk cytogenetics and ISS stage III disease. The overall serious adverse events (AEs) were similar in both arms. This groundbreaking study led to FDA approval for daratumumab (9/2019) to be used as induction and consolidation for transplant-eligible NDMM patients.⁵³

Several other trials are currently ongoing to further investigate how daratumumab can be used in transplant-eligible candidates. The GRIFFIN phase I/II trial (NCT02874742) is examining the CR rates of 224 patients divided into two groups randomly assigned to receive either D-VRd or VRd as induction/consolidation, followed by lenalidomide/daratumumab vs lenalidomide maintenance, respectively. Preliminary results are reporting that daratumumab improved sCR rates except in patients with high-risk disease. Among patients who had achieved a CR, the daratumumab group reported higher MRD negativity⁵⁴ (Table 2). The PERSEUS (NCT03710603) phase III trial takes this further and will look at 690 patients in the same treatment arms, hoping to see an improved PFS rate of the daratumumab group vs the control group (Table 2).⁵⁵ Interestingly, this study used the subcutaneous formulation of daratumumab instead of the traditional IV, in an effort to limit side effects and infusion times. As outlined in Table 2, there are numerous other subsets of studies examining how daratumumab may play a role alone or in concert with other therapies prior to ASCT.

Daratumumab is also being also been studied as maintenance post ASCT. *DRAMMATIC* (NCT04071457) phase III study compares daratumumab and lenalidomide versus Lenalidomide alone as maintenance therapy post ASCT, followed by MRD assessment and continuation of therapy based on MRD status. Similarly, *AURIGA* (NCT03901963) phase III trial compares the combination of SC daratumumab + lenalidomide to lenalidomide maintenance in MRD-positive patients after ASCT. Another smaller phase II single-arm clinical trial in the City of Hope Medical Center studies the effectiveness of daratumumab monotherapy as consolidation/maintenance (NCT03346135), with primary outcome being the PFS.

Some of the data emerging from these studies are encouraging and suggest that adding daratumumab to traditional triplet regimens for pre-transplant induction, consolidation and subsequent maintenance therapy has favorable outcomes in achieving better, faster and deeper responses. So far, preliminary data from the above phase III studies suggest that standard risk patients are the ones who benefit the most from daratumumab therapy.

However, daratumumab's impact will not be completely understood until these studies are completed. Interestingly, a meta-analysis of the randomized major phase III clinical trials recently presented at ASCO 2020 suggests improved PFS among patients with high-risk cytogenetics, though final conclusions cannot be made until these studies are finalized.⁵⁶ For now, using Daratumumab as upfront induction and consolidation in ASCT eligible candidates with NDMM is considered by clinicians for select patients with a heavy burden of disease who have had suboptimal response to conventional induction treatments. This may change as more information becomes available.

ASCT Ineligible Patients

Patients with NDMM who are ineligible for ASCT carry their own challenges notably age and co-morbidities.⁵⁸ Rd (lenalidomide and dexamethasone), with other treatment regimens building upon this double as tolerated, is often strategy in fragile patients.^{59–61} Reduced-dose triplet regimens such as RVD-lite have been developed for transplant-ineligible patients.⁶² Just as with ASCT eligible candidates, there are several drug combinations using daratumumab which are currently being evaluated for use in transplant-ineligible patients. Results of these trials should have significant implications in the treatment of this subset of patients in the near future (Table 3).

The key phase III MAIA (NCT02252172) trial investigated the benefit of adding daratumumab to the standard Rd as frontline treatment. Participants were randomly assigned to receive D-Rd vs Rd. This study included 737 patients, 42% of whom were older than 75 years old, raising the external validity of the study as its population is relatively representative of the true myeloma population. Preliminary results are reported that patients in the D-Rd arm sustain better responses, as evident by the by higher rates of MRD negativity and the significantly better ORR. The PFS benefit was improved in the daratumumab arm as well, though not sustained in the subgroup of patients with high-risk cytogenetics. Risk for disease progression or death was double in the Rd group.⁶³ This trial led to the 2019 FDA approval of D-Rd for initial treatment of newly NDMM patients who are ineligible for ASCT⁶⁴. In real-world practice, D-Rd can be strongly considered as a reasonable alternative in cases of potentially increased toxicity with the well-established standard-of-care bortezomib-based regimens.

The pivotal ALCYONE (NCT02195479) trial is currently ongoing, investigating the potential benefit of four vs

Table 3 Pilot Phase III Trials Evaluating Daratumumab in Transplant-Ineligible Patients with NDMM

Study Name	Phase	N	Regimen	Results
MAIA	III	737	Arm 1: IV Dara-Rd Arm 2: Rd	<ul style="list-style-type: none"> • \geqCR: 47.6% vs 24.9% • \geqVGFR: 79.3% vs 53.1% • 30-mo-PFS: 70.6% vs 55.6% • mPFS: NR vs 31.9 months • MRD negativity: 24.2% vs 7.3%
ALCYONE	III	706	Arm 1: Dara-VMP Arm 2: VMP	<ul style="list-style-type: none"> • ORR: 90.9% vs 73.9% • \geqCR: 46% vs 25% • \geqVGPR: 73% vs 50% • 36-mo OS rate: 78% vs 67.9%; mOS NR • mPFS: 36.4 vs 19.3 months, • MRD negativity: 28% vs 7%
CEPHEUS	III	395	Arm 1: VRd, then mRd Arm 2: SC Dara-VRd, then mDara-Rd	Data not mature yet
GEM2017FIT	III	300	Arm 1: VMP, then Rd Arm 2: KRd Arm 3: Dara- KRd	Data not mature yet
LYRA ⁶⁹ (NCT02951819)	II	101 87 NDMM ASCT ineligible, 14 RRMM	Single Arm: D-VCd induction, then ASCT/consolidation (only eligible patients), then mDara	NDMM patients: <ul style="list-style-type: none"> • CR+VGPR 55.8% at the end of induction • mTime \geqPR: 10 months • mTime \geqVGPR: 46 months, • 12-month PFS: 87.9%, mPFS: NR • 12-month OS: 98.8%

Abbreviations: m, maintenance; NR, not reached; SC, subcutaneous; mPFS, median progression-free survival; OS, overall survival; CR, complete response; VGPR, very good partial response; OS, overall survival; MRD, minimal residual disease; VCd, Velcade–cyclophosphamide–dexamethasone; VTd, Velcade–thalidomide–dexamethasone; VMP, Velcade–melphalan–prednisone; KRd, Kyprolis–Revlimid–dexamethasone.

three drug regimens in patients who are ineligible for transplant. Here, patients were randomized to receive VMP, with or without daratumumab. The D-VMP arm has thus far shown a significantly longer PFS which, over time, translated into an OS benefit, improvement in hematologic response and sustained MRD negativity.^{65,66} PFS benefit was sustained for patients >75 years and those with poor prognosis (ISS stage III, renal failure, high-risk cytogenetics). OS benefit across all subgroups, but less pronounced in patients with high-risk cytogenetic profile. Most of the side effects were evenly balanced between the 2 arms, except for infections which were more frequent and severe in the daratumumab group; the most common grade 3/4 infection was pneumonia. Subsequently, the FDA has also approved the D-VMP combination in May 2018 for initial treatment of NDMM patients who are ineligible for ASCT.⁶⁴ It should be noted that patients in both arms received subsequent therapy

upon relapse, and so it is unclear whether the OS benefit was due to daratumumab or subsequent therapy.

Other ongoing phase III trials are underway to evaluate daratumumab's role for treatment of NDMM patients who cannot receive transplant. CEPHEUS (NCT03652064) is evaluating the combination daratumumab + VRd followed by dara-Rd maintenance.⁶⁷ GEM2017FIT (NCT03742297), is comparing three combinations: VMP followed by Rd, vs carfilzomib-Rd, vs carfilzomib-Rd plus daratumumab in fit elderly individuals between 65 and 80 years of age. Results of these studies are pending.

Most recently there are several ongoing studies investigating the combination of daratumumab with novel treatments such as the 2nd generation PIs (carfilzomib or ixazomib) as frontline for both transplant eligible and ineligible patients with NDMM. The most frequent combinations tested are daratumumab with

carfilzomib-lenalidomide-dexamethasone or daratumumab with ixazomib-lenalidomide-dexamethasone.⁶⁸

Interference with SPE/IFE

According to the IMWG criteria, treatment response assessment in MM is performed by periodic monitoring of the monoclonal paraprotein with serum protein electrophoresis (SPE) and immunofixation (IFE). Daratumumab is an IgG kappa monoclonal antibody, and thus may be detected on SPEP and/or IFE, similarly to endogenous monoclonal immunoglobulin, leading to false-positive results.^{70,71} This can be particularly problematic in cases of IgG kappa disease treated with daratumumab, since a positive assay result may represent daratumumab itself rather than the presence of an abnormal paraprotein. This often has negative impact on initial evaluation of complete responses and leads to an increased frequency of VGPR with underrepresentation of CR. It is highly likely that several of the above trials over-reported VGPRs that might actually be CRs. Therefore, it is possible that daratumumab has a greater efficacy than is being reported in the above studies. A recently developed daratumumab-specific IFE assay (DIRA) with an anti-daratumumab antibody has helped to overcome this interference and accurately classify hematologic response.⁷² Molecular mass spectrometry mechanisms have also been developed and are slowly being utilized to help differentiate between monoclonal antibodies and abnormal proteins, reducing the frequency of this phenomenon.^{73–75}

Blood Compatibility

Another challenge with daratumumab use comes from its ability to bind to CD38 on red blood cells. This interaction may result in pan-agglutination in vitro leading to pan-reactivity in indirect antiglobulin tests, antibody detection tests, antibody identification panels, and anti-human globulin crossmatches. However, the drug does not affect the patient's ABO blood typing and immediate spin crossmatch. In the clinical setting, this in vitro interference can translate to unanticipated delays in blood transfusions, raising safety concerns. One successful method to overcome this issue is dithiothreitol (DTT) treatment of RBC screening cells which eliminates the interference with daratumumab. DTT disrupts the extracellular bonds of CD38 and prevents daratumumab binding.⁷⁶ Another approach is, neutralization of daratumumab with recombinant human anti-daratumumab idiotype antibodies, but its use is still limited. An easy strategy is to perform a baseline type and screen and phenotype prior to starting daratumumab therapy.⁷⁷ These

patients should carry transfusion identification cards throughout their treatment with the novel antibody and up to 6 months after therapy completion. In emergency situations, blood banks should release non-crossed matched ABO and Rh compatible red cells.

Future Role and Applications SC Daratumumab

As daratumumab becomes a well-established medication in the treatment of multiple myeloma, investigators have begun to look into novel applications to utilize this medication further. A number of clinical trials are currently underway looking into the safety, efficacy and utility of SC administration of daratumumab. Additionally, these studies are investigating whether subcutaneous administration of daratumumab decreases infusion reactions and infusion times, improving patient tolerance of the agent. PAVO (NCT02519452) phase 1b was the first trial that confirmed the safety of SC daratumumab as monotherapy.^{26–28} A subsequent Chinese phase I clinical study is following 20 participants over 2 years to determine the rate of adverse effects in relation to the concentration of the drug at the beginning of each 28-day cycle. The phase III international trial COLUMBA (NCT03277105) with 522 participants is taking this further, comparing the ORR of SC daratumumab vs IV daratumumab. Interim data suggest that dara-SC is non-inferior to dara-IV and is associated with a lower rate of infusion reaction rate.⁷⁸ Additionally, the infusion time was decreased from hours to minutes.

Besides establishing the efficacy of monotherapy SC daratumumab monotherapy, there are other ongoing trials examining the efficacy of SC daratumumab in combination with other novel agents PLEIADES (NCT03412565) is a phase II trial that is currently adding SC daratumumab to various standard regimens (VRd, VMP, Rd, and Kd).⁷⁹ So far results reveal that SC daratumumab leads to similar efficacy as the IV formulation. Outcomes here will compare the treatment arms to phase III data on the established agents without daratumumab to again see how these novel regimens will help patients achieve a PR or better.

Smoldering MM (SMM)

There is also a move to consider the use of daratumumab in the treatment of monoclonal gammopathy of unknown significance (MGUS) and smoldering MM. The CENTAURUS (NCT02316106) phase II trial is evaluating 3 different daratumumab schedules/doses in an effort to

determine whether daratumumab monotherapy can delay progression to overt MM. Interim results suggest that daratumumab does have single-agent activity in this patient population; however, the primary endpoints of CR>15% and median PFS \geq 24 months were not met.⁸⁰ A phase II trial from Dana Farber is currently evaluating the efficacy of daratumumab for the treatment of high-risk MGUS or low-risk smoldering MM, following patients for 2 years to see how many will achieve VPGR or better. The active phase III AQUILA (NCT03301220) trial is randomly assigning patients with smoldering MM to either an active monitoring arm without intervention or an experimental arm in which they receive SC daratumumab for 39 cycles or 36 weeks.⁸¹ The primary outcome measure here is PFS, measured as time to development of active multiple myeloma, with all patients being screened for this transition every 12 weeks. Another ongoing phase III clinical trial (NCT03937635) with 288 participants is currently evaluating how daratumumab can be utilized with lenalidomide/dexamethasone in the treatment of high-risk Smoldering MM, this time looking at the OS between the two arms. Overall, while there is hope that daratumumab may be of value in the treatment of Smoldering MM, it is crucial to scrutinize its toxicity profile in this particular patient population, since the potential adverse effects of this agent may lead to increased morbidity and mortality relative to electing a periodic monitoring approach.

Conclusion

While daratumumab is a relatively new agent in the treatment of MM, studies continue to show the promise this medication brings to an incurable disease. We have already seen its efficacy in the treatment of RRMM and are now starting to use this agent for management of NDMM. Additionally, ongoing clinical trials are beginning to show decreased infusion reactions and infusion times when utilizing subcutaneous daratumumab versus the traditional intravenous formulation.

With all these positive results, it will be interesting to see other potential uses for this medication. The authors of this review have used daratumumab urgently as monotherapy in patients hospitalized with cast nephropathy and seen rapid improvements in renal function due to the medication's ability to reduce serum light chains rapidly, avoiding the need for plasmapheresis. Moving forward, it is possible to imagine daratumumab's role in the treatment of other plasma cell dyscrasias such as plasma cell leukemia, monoclonal gammopathy of renal significance (NCT03095118),

Waldenstrom macroglobulinemia (NCT03187262) and amyloidosis (NCT02841033, NCT03201965, NCT03283917, NCT04270175), as well as other hematologic malignancies such as plasmablastic lymphoma (NCT04139304), myelodysplastic syndrome (NCT03067571, NCT03011034), acute myeloid (NCT03537599, NCT03067571), acute lymphoblastic and chronic lymphocytic leukemia (NCT03734198, NCT04230304, NCT03447808), and possibly even in autoimmune disorders. Recently, MD Anderson is further exploring daratumumab's role in solid tumors including kidney, prostate and bladder cancer (NCT03473730, NCT03177460). Other potential uses include desensitization prior to kidney (NCT04204980) and heart (NCT04088903) transplantation as well. Further investigations into daratumumab's role in these diseases will be critical to help utilize this medication in clinical practice, develop new monoclonal antibodies, and help our patients avoid unnecessary morbidity and mortality.

Abbreviation

MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma; MRD, minimal residual disease; PFS, progression-free survival; OR, overall response; sCR, stringent complete response; VGPR, very good partial response; ASCT, autologous stem cell transplant; CyBorD, cyclophosphamide bortezomib dexamethasone; IMiD, immunomodulatory drug; IRR, Infusion-related reactions; IV, intravenous; Kd, carfilzomib dexamethasone; KRd, carfilzomib lenalidomide dexamethasone; PI, proteasome inhibitor; Rd, lenalidomide dexamethasone; Vd, bortezomib dexamethasone; VMP, bortezomib melphalan prednisone; VRd, bortezomib lenalidomide dexamethasone; SC, subcutaneous.

Disclosure

Dr Danai Dima and Dr Joshua Dower are co-first authors. Dr Raymond Comenzo reports a patent WO2016187546A1 issued. The authors report no other conflicts of interest in this work.

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