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ORIGINAL ARTICLE

Cross Fire: Daratumumab-Based Therapies Are Standard of Care in Newly Diagnosed Multiple Myeloma

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1. Introduction

The old adage of "less is more" has not always uniformly applied to upfront combination treatment options in newly diagnosed multiple myeloma (MM) patients. Historically, three-drug proteasome inhibitor/immunomodulatory (PI/IMiD) combinations have dominated two-drug regimens [1–3], whereas quadruplets have fallen short of deriving additional benefit [4,5]. Despite the evolution of MM therapeutics over the past two decades, the 5-year relative survival rate is 53.9%, and a need for strategic combinations *still* exists, especially in high-risk and fragile elderly transplant ineligible MM populations [6]. Daratumumab, first in class monoclonal antibody targeting CD38, was initially approved by the US Food and Drug Administration (FDA) in 2015 and subsequently by the European Medicines Agency in 2016 for treatment of relapsed or refractory MM in patients. The more recent arrival of daratumumab onto the frontline scene has challenged existing PI/IMiD canon in the newly diagnosed upfront treatment setting. The main difference this time is that daratumumab demonstrates a clear definitive synergistic advantage of efficacy with PIs and IMiDs without excessive toxicity.

Daratumumab is human monoclonal antibody, IgG1k, that targets CD38, a type II transmembrane glycoprotein widely expressed on plasma cells involved in calcium mobilization, nicotinamide-adenine dinucleotide (NAD) regulation, and cellular apoptosis/proliferation [7,8]. The anti-MM mechanisms of action by which daratumumab exerts its effects include direct effects (inhibition of CD38 activity), Fc-dependent effects (complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, cross-linking via Fcy receptor apoptosis), and immunomodulatory effects (regulation of T cells, B cells, and myeloid-derived suppressor cells) [8–12]. Preclinical models demonstrate synergism between daratumumab and PIs or IMiDs, likely through regulation of T cells and natural killer (NK) cells [13,14].

Moreover, this evidence of synergism has translated into compelling clinical data, culminating with the use of daratumamab in relapsed/refractory (R/R) MM with combination lenalidomide or bortezomib after reporting of the POLLUX and CASTOR trials, respectively [15,16]. In the Phase III POLLUX study, 569 patients receiving ≥ 1 prior line of therapy were randomized to daratumumab, lenalidomide, dexamethasone (DRd) versus lenalidomide, and dexamethasone (Rd). The DRd regimen demonstrated significant improved progression-free survival (PFS) over the Rd regimen, 18.5% versus

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41.0% events [hazard ratio (HR) = 0.37; 95% confidence interval (CI), 0.27–0.52; $p < .001$] [15]. In the CASTOR study, combination daratumumab, bortezomib, and dexamethasone (DVd) showed superior PFS over bortezomib and dexamethasone (Vd), reducing risk of death or progression by 61% with median PFS not reached in the DVd arm versus 7.2 months in the Vd arm after a median of 7.4 months of follow-up (HR = 0.39; 95% CI, 0.28–0.53; $p < .001$) [16]. The combination of daratumumab, pomalidomide, and dexamethasone (DPd) was approved in the United States by the FDA in R/R MM patients who have received at least two prior treatments including lenalidomide and a PI after the EQUULEUS trial (MMY1001) demonstrated an overall response rate (ORR) of 60% (58% in double-refractory MM patients) and 29% achieved a minimal residual disease (MRD) negative rate (10^{-5}) [17]. Finally, more recently, daratumumab, carfilzomib, and dexamethasone (KDd) was approved after the Phase III CANDOR study of KDd versus carfilzomib and dexamethasone (Kd) demonstrated improved PFS in the KDd arm, median PFS not reached versus 15.8 months after a median of 17 months of follow-up (HR = 0.63; 95% CI, 0.46–0.85; $p = .0027$) [18]. Given the success of daratumumab in R/R MM, the natural succession of testing and demonstrating the drug's efficacy in newly diagnosed MM followed suit.

2. Daratumumab in transplant ineligible newly diagnosed MM

Two randomized controlled trials have cemented daratumumab's placement in the armamentarium of treating transplant ineligible newly diagnosed MM patients (Table 1). The ALCYONE study randomized 706 patients to daratumumab, bortezomib, melphalan, and prednisone (D-VMP) or bortezomib, melphalan, and prednisone (VMP) and demonstrated 18-month PFS rates of 71.6% versus 50.2% after a median follow-up of 16.5 months, respectively (HR = 0.50; 95% CI, 0.38–0.65; $p < .001$) [19]. Notably, depth of response was deeper in D-VMP arm compared to the VMP arm with ≥ complete response (CR) rates of 46% versus 25% ($p < .0001$) and MRD negative rates (10^{-5}) reaching 28% versus 7% ($p < .0001$), respectively [19]. Treatments were generally tolerable, but D-VMP showed an increase in Grade 3/4 infections compared to VMP (23.1% vs. 14.7%) [19]. More recently, results were updated after a median follow-up of 40.1 months, and D-VMP demonstrated a significant overall survival (OS) benefit over VMP with a 40% reduction risk of death (HR = 0.60; 95% CI, 0.46–0.80; $p = .003$) [20]. Importantly, patients in the D-VMP received daratumumab as maintenance therapy compared to no maintenance after the nine cycles of VMP induction control arm and may have influenced long-term OS and PFS readouts on the study.

In the MAIA study, patients were randomly assigned to treatment arms; 368 patients received daratumumab, lenalidomide, and dexamethasone (DRd), whereas 369 patients received lenalidomide and dexamethasone (Rd). Again, notably, the daratumumab treatment arm (DRd) achieved deeper responses compared to the Rd group with a CR rate of 47.6% versus 24.9% ($p < .001$) and an MRD negative rate (10^{-5}) 24.2% versus 7.3% ($p < .001$), respectively [21]. In a recent updated analysis after a median follow-up of nearly 4 years, median PFS was not reached in DRd compared to 34.4 months in the Rd group (HR = 0.54; 95% CI, 0.43–0.67; $p < .0001$) [22]. Although neutropenia and infection rates were higher in the DRd group (50% Grade 3/4 neutropenia and 32.1% Grade 3/4 infection rate) compared to the Rd group (35.3% Grade 3/4 neutropenia and 23.3% Grade 3/4 infection rate), overall discontinuation of trial drugs were the same among each assigned groups and clear survival outcome benefit favoring the DRd arm [21].

Taken together, results to date demonstrate that the addition of daratumumab to initial therapy regimens offer a benefit to newly diagnosed transplant ineligible MM patients, providing increased depth of responses that translate to improved PFS and OS outcomes. Additional studies are being planned in this disease space. The MMY3019 CEPHEUS (NCT03652064) study is an ongoing Phase III multicenter randomized study that will be evaluating outcome differences between the subcutaneous version of daratumumab (daratumumab and hyauronidase; Darzalex Faspro), bortezomib, lenalidomide, and dexamethasone (SC D-RVd) versus bortezomib, lenalidomide, and dexamethasone (RVd) alone in transplant ineligible patients. The HOVON 143 study specifically evaluated the regimen of daratumumab, ixazomib, and dexamethasone in frail and unfit patients. In 2019, an interim analysis of HOVON 143 demonstrated an ORR of 74% in unfit MM patients with 9-month PFS of 78% and ORR of 78% in frail MM patients with 9-month PFS rate of 61% [23].

3. Daratumumab in transplant eligible newly diagnosed MM or transplant status undefined

In the transplant eligible and transplant undefined setting, daratumumab has been largely

Table 1. Pivotal trials using daratumumab in first-line therapy.

	Regimen	PH	*n*	AEs	Response rate	MRD	PFS/OS	Comments
Transplant ineligible								
ALCYONE	Dara-VMP vs. VMP [19,20]	III	706	Infections G3/4: 23.1 vs. 14.7%	≥CR: 46% vs. 25%, $p < .0001$	MRD neg by NGS (adaptive 2.0): 28% vs. 7%, $p < .0001$	Last median F/up: 40.1 mo PFS at 36 mo: 50.7% vs. 18.5%; HR = 0.42, $p < .0001$ OS at 36 mo: 78% vs. 67.9%; HR = 0.6, $p = .0003$	−9 × induction cycles −Dara vs. observation maintenance until progression
MAIA	Dara-Rd vs. Rd [21,22]	III	706	Neutropenia G3/4: 50% vs. 35.4% Infections G3/4: 32.1% vs. 23.3% Fatigue G3/4: 8.0% vs. 3.8%	≥VGPR: 79.3% vs. 53.1%, $p < .001$ ≥CR: 47.6% vs. 24.9%, $p < .001$	MRD neg by NGS (adaptive 2.0): 24.2% vs. 7.3%, $p < .001$	Last median F/up: 47.9 mo Median PFS: NR vs. 34.4, HR = 0.54, 95% CI 0.43−0.67, $p < .001$	−Treatment continued until progression −HR cytogenetics have not shown benefit in Dara arm at the 48-mo median follow-up
HOVON 143	Dara-IxaDex [23]	II	65 Frail; 65 Unfit		ORR: 74%—unfit ORR:78%—frail	–	9 mo PFS—78% unfit 9 mo PFS—61% frail	
AMaRC 03−16	Dara-CyBorD vs. CyBorD [35]		121		≥VGPR: 45% vs. 31% (p = NS)	–	Median PFS 23.2 vs. 18.9 mo (p = NS)	−Induction × 9 cycles −Dara maintenance only in Dara-CyBorD arm
NCT03993912	SC Dara-Rd vs. Rd	III	294	–	–	–	–	−Frail patients not eligible for ASCT −Treatment continued until progression
CEPHEUS	SC Dara RVd vs. RVd	III	360	–	–	–	–	−8 × induction cycles −Dara-Rd vs. Rd maintenance continued until progression
Transplant eligible								

(*continued on next page*)

Table 1. (continued)

	Regimen	PH	*n*	AEs	Response rate	MRD	PFS/OS	Comments
CASSIOPEIA	Dara-VTD vs. VTD [24]	III	085		≥VGPR: 83% vs. 78%, $p = .024$ ≥CR: 39.4% vs. 26%, $p < .0001$	MRD neg by NGS (adaptive 2.0): 64% vs. 44%, $p < .0001$	PFS: HR = 0.47, 95% CI 0.33−0.67, $p < .0001$ Median PFS: not reached in either groups	−First randomization: 4 × induction −ASCT included −2 × consolidation: Dara-VTD vs. VTD −Second randomization: Dara vs. observation maintenance
GRIFFIN	Dara-RVd vs. RVd [26,27]	II	207	Neutropenia G3/4: 43% vs. 24% URI G3/4: 4.5% vs. 2%	sCR: 42.4% vs. 32.0%; OR = 1.57; 95% CI, 0.87−2.82.	MRD neg by NGS (adaptive 2.0): 62.5% vs. 27.2%, $p < .0001$	PFS at 24 mo 95.8% vs. 89.8%, NS	−4 × Induction −ASCT included −2 × consolidation: Dara-RVd or RVD −Dara-R vs. R maintenance
PERSEUS	SC Dara-RVd vs. RVd	III	690	–	–	–	–	−4 × Induction −ASCT −2 × Consolidation: SC Dara-RVD or RVD −Dara-R vs. R maintenance −Continued Dara depends on sustained MRD neg rate
Transplant status not defined								
NCT03012880	Dara-IxaRd [28]	II	80	Lymphopenia G3/4: 36−47% Neutropenia G3/4: 17−23%	≥CR: 28−32%		Median PFS: not reached	−2 cohorts Cohort B limited dex dosing −12 × Induction cycles of Dara-IRD −24 × Maintenance cycles of Dara-Ixa
Manhattan	Dara-wKRd [30]	II	41	Neutropenia G3/4: 27% Lung infection Grade3/4: 7%	>VGPR: 95%	≥VGPR + MRD neg (10^{-5}) by MFC: 71%	Median PFS: not reached	
NCT04113018 LCI-HEM-MYE-KRdD-001[29]	SC Dara-KRd, response adapted	II	39	–	–	–	–	−Treatment algorithm using MRD (NGS) response adapted approach
ADVANCE NCT04268498	SC Dara-wKRd vs. KRd vs. RVd		462	–	–	–	–	−Primary endpoint is MRD response

Note. AEs = adverse evet; ASCT = autologous stem cell transplant; MFC = multicolor flow cytometry; MRD = minimal residual disease; NGS = next-generation sequencing; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PH = phase; VGPR = very good partial response.

studied in quadruplet regimens rather than triplet regimens (Table 1). The CASSIOPEIA trial assigned 1085 transplant eligible newly diagnosed MM patients to two treatment arms, 543 patients to daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) and 542 patients to bortezomib, thalidomide, and dexamethasone (VTd), with both groups receiving four cycles of induction treatment, autologous hematopoietic cell transplant (AHCT), two cycles of consolidation, followed by a second randomization of daratumumab or observation [24]. The D-VTD group demonstrated a favorable outcome over the VTD group for the primary endpoint (stringent CR rate after day 100 transplant), 29% versus 20%, respectively (OR = 1.60; 95% CI, 1.21–2.12; $p = .0010$), whereas the MRD negative rate (10^{-5}) was 64% versus 44%, respectively ($p < .0001$) [24]. Neither group reached median PFS after a median of 18.8 months of follow-up (HR = 0.47; 95% CI, 0.33–0.67; $p < .0001$); however, the probability of 18 month PFS for D-VTd vs. VTd was 93% versus 85% [24]. As with other studies, the daratumumab-containing arm demonstrated more clinically significant Grade 3/4 neutropenia (28% vs. 15%) and Grade 3/4 lymphopenia (17% vs. 10%); however, the Grade 3/4 infection rate did not differ between regimens (22% vs. 20%) [24]. Stem cell collection in the D-VTd arm was deemed adequate [24]. Furthermore, quality of life (QoL) data on the CASSIOPEIA study demonstrated that although both regimens improved European Organization for Research and Treatment of Cancer (EORTC) global health status scores, the D-VTd arm had greater improvement in pain, less cognitive decline, and higher emotional functioning domain scores compared to VTd [25].

The highly anticipated GRIFFIN study compared D-RVd to RVD in 207 newly diagnosed transplant eligible patients, in which patients received four cycles of induction therapy, AHCT, two cycles of consolidation, followed by 26 cycles of maintenance (daratumumab and lenalidomide vs. lenalidomide) [26]. The study demonstrated improved sCR rates after consolidation (primary endpoint) with the quadruplet regimen, favoring D-RVd 42.4% over RVd 32.0% (OR = 1.57; 95% CI, 0.87–2.82; one-sided $p = .068$) [26]. MRD negative (10^{-5}) rates after consolidation in patients receiving D-RVd compared to RVd were 47.1% versus 16.5%, respectively [26]. Similar to previously mentioned studies, although higher degree of cytopenias were noted in the daratumumab containing regimen (Grade 3/4 neutropenia 41.4% and thrombocytopenia 16.2%), no observable differences in Grade 3/4 upper respiratory infection rates between D-RVd and RVd (1.0% vs. 2.0%) were respectively seen [26]. An updated analysis with longer median follow-up of 27.4 months, including 12 months of maintenance, demonstrated that although 24-month PFS rates did not yet differ between D-RVd or RVd, the $\geq$ 12 month MRD negative sustainability rate was higher with D-RVd compared to RVd (28.2% vs. 2.9%, $p < .0001$) [27]. The next evolution of this combination will be studied in the MMY3014 PERSEUS (NCT0371063) trial, which is an ongoing Phase III study evaluating SC D-RVd versus RVd in 690 transplant eligible patients across Europe.

Other ongoing studies are incorporating daratumumab in the frontline setting regardless of transplant status. A Phase II single-center study of daratumumab, ixazomib, lenalidomide, and dexamethasone (D-IRd) was recently updated showing a $\geq$ CR rate of more than 28% and acceptable tolerability [28]. Smaller single-arm studies, including an MRD response adapted trial, are evaluating combination daratumumab, carfilzomib, lenalidomide, and dexamethasone (D-KRd) [29,30]. Early promising results of D-KRd are demonstrating a $\geq$ VGPR (very good partial response) rate of 98%, and an MRD negative rate of 71% without upfront AHCT [30]. The Phase II randomized ADVANCE study (NCT04268498) is ongoing and evaluating the difference in MRD rates between D-KRd, KRd, and RVD in 462 newly diagnosed MM patients.

Incorporation of daratumumab in upfront MM regimens is rapidly becoming the standard of care because of the drug's ability to synergize with existing backbone treatments, pushing response rates further down while leading to long-term sustained MRD negative remissions. Importantly, in the newly diagnosed MM setting, achievement and durability of MRD negative status has become a surrogate endpoint for improved PFS and OS outcomes [31]. As discussed above, several randomized clinical trials in both transplant ineligible and eligible MM patients have consistently demonstrated that daratumumab-containing regimens show higher MRD negative response rates and improved PFS compared to their non-daratumumab counterpart controls. The ALCYONE study has even boldly established an OS benefit with D-VMP, reducing the risk of death by 40% compared to VMP [20]. Further follow-up needs to demonstrate whether daratumumab can abrogate the influence of high-risk disease on clinical outcomes; however, a recent meta-analysis already suggests a benefit [32]. Importantly, the subcutaneous formulation of daratumumab has significantly offset the adverse events of infusion related reactions compared to the intravenous formulation, 13% versus 34%

(OR = 0.28; 95% CI, 0.18–0.44; $p < .0001$), while maintaining non-inferiority and improving patient satisfaction [33,34]. The inclusion of daratumumab has not resulted in worsening discernible clinical toxicities but rather added benefit to the scales of efficacy. Already designated with three separate FDA-approved regimens (DRd, D-VMP, D-VTd), daratumumab has catapulted to the frontline setting, while heralding the arrival of monoclonal antibody treatments in newly diagnosed MM.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NK, research funding-Amgen; consulting-Medimmune/Astra Zeneca; SZU, research funding-Amgen, Array Biopharma, BMS, Celgene, GSK, Janssen, Merck, Pharmacyclics, Sanofi, Seattle Genetics, SkylineDX, Takeda; consulting-Amgen, BMS, Celgene, Edo-Pharma, GSK, Janssen, Sanofi, Seattle Genetics, SecuraBio, SkylineDX, Takeda, TeneoBio; speaking fees-Amgen, BMS, Janssen, Sanofi.

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