





ORIGINAL PAPER

Haematological Malignancy – Clinical

MRD-negative conversion with daratumumab monotherapy in newly diagnosed multiple myeloma patients in \geq VGPR/MRD-positive after first-line therapy: Final analysis of the open-label, single-arm multicentric phase 2 trial DART4MM

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Funding information

Janssen Research and Development

Summary

Daratumumab is approved for front-line and relapsed myeloma therapy. Here, we evaluated daratumumab in multiple myeloma patients already in \geq very good partial response but minimal residual disease (MRD) positive by next-generation flow after first-line therapy and daratumumab naïve with the potential to eradicate the disease. In this prospective, single-arm phase 2 trial, we consecutively evaluated 110 eligible patients with newly diagnosed multiple myeloma for positivity at 10^{-6} in the bone marrow. Fifty patients were positive and were treated with 6 months of daratumumab. The primary end-point was at 6 months: MRD-negative patients stopped treatment, while positive patients continued for a total of 24 months. At the primary end-point, 15/50 (30%) patients became MRD negative. At 24 months, 11/50 (22%) patients were still MRD negative. At a median follow-up of 50 months, 29 (58%) patients relapsed. Median progression-free survival is reached at 45 months, and overall survival is not reached. Achieving at least one-time MRD negativity was significant (median progression-free survival of 61 vs. 26 months, $p=0.0009$). Of 50 patients, 21 did not progress at a median time of 44 months (range 31–73) and four of the relapsed patients are still in duration of response, not treated yet.

KEY WORDS

consolidation therapy, daratumumab, MRD, multiple myeloma

INTRODUCTION

Multiple myeloma (MM) is still considered an incurable disease, although much progress has been made in terms

of responses and survivals.^{1,2} Innovative drugs can induce deeper responses with respect to the past, and complete response (CR) achievement is not sufficient anymore to testify a durable response.³ Minimal residual disease (MRD)

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status measured both by next-generation flow (NGF) and next-generation sequencing (NGS) is a consolidated new prognostic parameter in multiple myeloma trials, with a threshold at 10^{-5} according to the International Myeloma Working Group (IMWG) guidelines.⁴⁻⁷ Recent trials have demonstrated that these techniques can reach even a higher sensitivity of 10^{-6} , providing a greater discriminatory power for progression-free survival (PFS) and helping to identify true 'functional cure' or very long-term, treatment-free remissions in multiple myeloma.⁸

Daratumumab (Dara) is an IgG/k monoclonal antibody that binds selectively to CD38 on MM plasma cells (PC) and is now approved in various combination regimens for transplant-eligible (daratumumab, bortezomib, thalidomide, dexamethasone, Dara-VTd) and transplant-ineligible (daratumumab, lenalidomide, dexamethasone, Dara-Rd; daratumumab, bortezomib, melphalan, prednisone, Dara-VMP) newly diagnosed multiple myeloma.^{9,10} A consolidation therapy with bortezomib, thalidomide and dexamethasone (VTd) after autologous stem cell transplant (ASCT) has been reported in a randomized trial to increase the level of responses measured by polymerase chain reaction (PCR),¹¹⁻¹³ and recently, the randomized study CASSIOPEIA showed that daratumumab given as maintenance therapy every 8 weeks for 24 months after ASCT was superior to observation in a population of MM patients treated with VTd with or without daratumumab as induction/consolidation.^{14,15} However, little is known about daratumumab monotherapy efficacy as consolidation/eradication therapy after a first line of therapy, if used in a very good responder group of patients with MRD positivity. Here, we present the results of the DART4MM study.

METHODS

Trial information

This is a non-profit, prospective, uncontrolled, open-label, single-arm phase 2 trial. An independent ethics committee or institutional review board at each site approved the study protocol. The Italian Agency for Drug (AIFA) approved (12 December 2018) this interventional study before the first patient was enrolled. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the principles originating from the Declaration of Helsinki. All patients provided written informed consent. The study was sponsored by a non-profit public institution (Azienda Ospedaliera Universitaria Senese, Siena, Italy) and was co-financed by Janssen Research & Development, LLC. The study was designed by the corresponding author, and data were collected and analysed by the investigators independently from Janssen. The trial was registered (EudraCT Number 2018-000386-36) before the first patient was enrolled on 31 December 2018. More information are described in the [Appendix S1](#).

Patients

We consecutively evaluated for MRD positivity daratumumab naïve newly diagnosed multiple myeloma patients in \geq very good partial response by NGF after a first line of therapy, between December 2018 and March 2022. Eligible patients had a treated newly diagnosed multiple myeloma at 12 weeks from therapy. Positron emission tomography (PET)/computed tomography (CT) was required 4 weeks before study entry and monitored during treatment. Additional eligibility criteria are listed in the Protocol and in the [Appendix S1](#).

Trial treatment

Patients were treated with daratumumab IV infusions 16 mg/kg weekly for eight times and biweekly for eight times (6 months total). At the first end-point, if MRD negative, they stopped treatment, and if still MRD positive by NGF, continued monthly daratumumab until month 24 ([Figure 1](#)). Patients received subcutaneous daratumumab from November 2020 (daratumumab 1800 mg co-formulated with recombinant human hyaluronidase).

End-points and assessments

The primary end-point was MRD negativity 10^{-6} at 6 months, since the clinical consensus is shifting towards 10^{-6} (1 in 1 000 000 cells) as the 'gold standard' for determining deeper, more durable remissions. MRD was assessed at 2-6-12-18-24 months, with analysis centralized and performed by NGF in the Siena lab. Key secondary end-points included safety, MRD-negativity rate during the study, progression-free survival and overall survival. If the patient was still MRD negative at the end of the study, MRD was evaluated every 6 months after patient consent was obtained until a positive result. Additional efficacy end-points are defined in the Protocol. Imaging (PET/CT) was not an end-point but was used to integrate marrow MRD negative status in response evaluation. Tumour response and disease progression were assessed following the IMWG response criteria.¹⁶

MRD evaluation

2-3 cc of blood bone marrow aspirate was obtained from patients. The first take from the iliac crest of patients was given to the laboratory to reduce the risk of haemodilution and ensure that samples had good cellularity. Evaluation of MRD has been done using the two 8-colour pre-titrated tubes, BD OneFlow PCST and BD OneFlow PCD (BD Biosciences), containing the markers needed to discriminate pathological PCs. Choice of this kit has been taken to guarantee the same processing and analytical steps for all the samples. Limit of

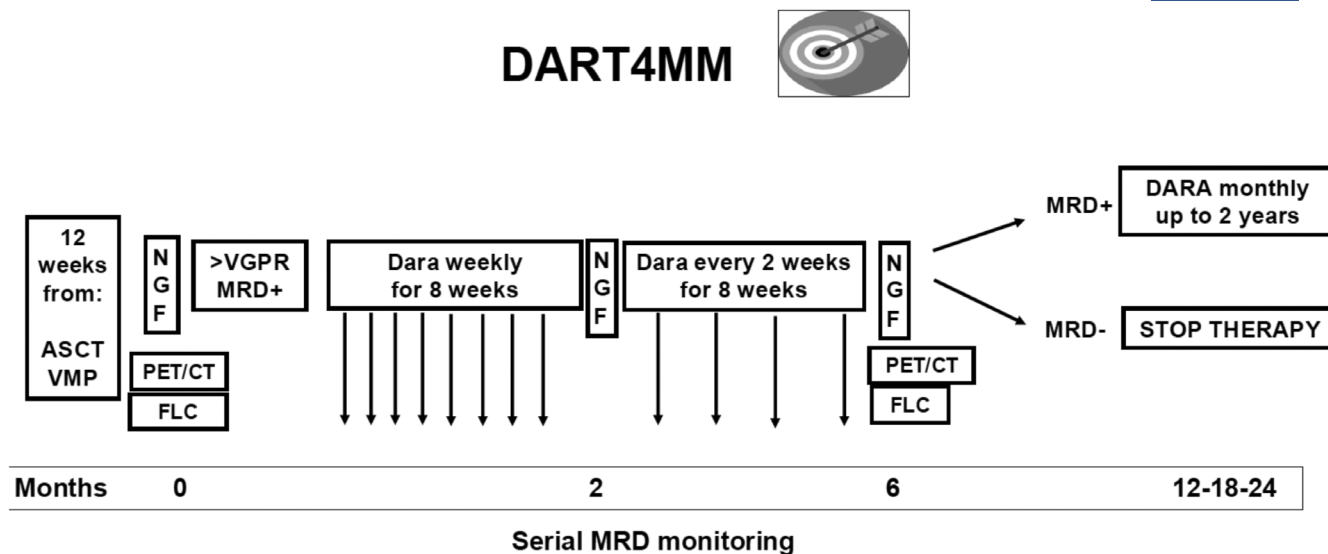


FIGURE 1 Trial design. The trial design is illustrated. Sequential minimal residual disease (MRD) was evaluated at times 0, 6, 12, 18 and 24 months with the next-generation flow (NGF). The daratumumab schedule is also reported, and the first end-point is at 6 months.

detection (LOD) and limit of quantification (LOQ) were defined according to the EuroFlow protocol.^{16–20} More is reported in [Appendix S1](#).

RESULTS

Patients and treatment

A total of 110 patients were evaluated; 53 (48.1%) were MRD positive (3 withdrew consent), and 50 were enrolled in the study. Demographic and clinical characteristics are listed in [Table 1](#). Median patient age was 61.0 years (range, 40–77); 16% had ISS stage III disease and 9 (18%) had high cytogenetic risk (t[4;14], t[14;16], amp (1q) with 4 or more signals or del[17p]). ASCT was received by 45 patients (one ASCT [1 ASCT] in 34; double ASCT [2 ASCT] in 11), and five patients were transplant ineligible (treated with proteasome inhibitor combinations). Patients had a median follow-up of 50 months (31–73).

Quality of bone marrow samples

A total of 273 MRD monitoring have been performed by NGF during the study, with no missing evaluations apart from one MRD corresponding to a 2-month time point. Considering the percentage of CD16+ bright neutrophils for the evaluation of haemodilution, 101/273 (37%) samples had a good quality (CD16+ cells <30%), 135/273 (49%) had a moderate haemodilution (CD16+ cells between 30 and 60%), while 37/273 (13%) BM samples had a percentage >60%, corresponding to high haemodilution. In particular, 5/37 (13%) samples were associated with very low cellularity, leading to the necessity to repeat the BM aspirate.

Efficacy

Of 50 evaluable patients, 15 (30%) were MRD negative at the first end-point of 6 months. One progressed before the end-point ([Table 2](#)). Other time points for MRD are listed in [Table 2](#), and sequential MRD evaluation is represented in [Figure 2](#) (analysis of different time points is reported in [Table S1](#)). At the end of the study, at 24 months, 11/50 (22%) patients were still MRD negative (11 patients progressed before the end-point). Interestingly, eight patients became MRD negative for the first time after 6 months during daratumumab therapy between months 6 and 24, and two patients had an MRD negativity detection at month 2 but not sustained later. At the cut-off study, 10 patients are still MRD negative. Three of these patients received daratumumab for 6 months, and seven for 24 months.

Progression-free survival (PFS) at 12–36 and 48 months was 90%, 61% and 44% respectively, 95% confidence interval (CI) 0.82–0.98 at 12 months; 0.48–0.76 at 36 months; 0.31–0.62 at 48 months. Overall survival (OS) at 12, 36 and 48 months was 100%, 88% and 80% respectively (95% CI 1.00–1.00 at 12 months; 0.79–0.97 at 36 months; 0.70–0.93 at 48 months).

At a median follow-up of 50 months (range, 31–73), disease progression occurred in 29 of 50 patients (58%), but four patients were still not treated, and in Duration of Response (DoR) at the time of analysis, at 22, 18, 10 and 8 months from relapse. Patients pretreated with VMP and later consolidated with daratumumab all relapsed at 21, 24, 61, 56 months, the first two patients with high-risk cytogenetics.

Death occurred in 10/50 (20%) patients (8 for progressive disease [PD], 1 for sepsis, 1 for acute myeloid leukaemia). Median PFS was reached at 45 months (range 3–64) (95% CI, 33–64) ([Figure 3A](#)). OS is not reached ([Figure 3B](#)).

Totally 27/50 (54%) MM patients had at least one MRD negativity detection. In particular, achieving at least one

TABLE 1 Demographic and clinical characteristics in the intention-to-treat population at baseline.

Characteristics	Total (N=50)
Age	
Median (range)—year	61 (40–77)
ECOG performance status—no. (%) ^a	
0	40 (80)
1	9 (18)
2	1 (2)
Type of measurable disease—no. (%)	
IgG	33 (66)
IgA	6 (12)
Other ^b	2 (4)
Detected in serum-light chains only	9 (18)
ISS disease stage—no. (%) ^c	(n=50)
I	30 (60)
II	12 (22)
III	8 (16)
Cytogenetic risk profile—no. (%) ^d	
Standard risk	32 (64)
High risk	9 (18)
Indeterminate	9 (18)
PET pos	4 (8)
Induction therapy (%)	
VTd	34 (68)
Vd, VCd, VRd	9 (18)
VMP	4 (8)
Other (KRd, Kd)	3 (6)
1 ASCT	34 (68)
2 ASCT	11 (22)
Response at enrolment of MRD+	
CR	17
VGPR	33

Abbreviations: 1 ASCT, one autologous stem cell transplantation; Kd, carfilzomib, dexamethasone; KRd, autologous stem cell transplantation; Kd, carfilzomib, dexamethasone; KRd, carfilzomib, lenalidomide, dexamethasone; VCd, bortezomib, cyclophosphamide, dexamethasone; Vd, bortezomib, dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone; VTd, bortezomib, thalidomide, dexamethasone.

^aEastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability. One patient had an ECOG performance status score of 0 at the time of randomization, which worsened to an ECOG performance status score of 3 at baseline.

^bIncludes IgD, not secreted.

^cInternational Staging System (ISS) disease stage is based on the combination of serum β_2 -microglobulin and albumin levels. Higher stages indicate more advanced disease.

^dCytogenetic risk was assessed by fluorescence in situ hybridization. High risk was defined as the presence of del(17p), t(4;14), and/or t(14;16).

MRD negativity proved a significantly longer PFS versus not reaching MRD negativity (PFS 61 vs. 26 months, HR 0.24; CI 0.10 to 0.56; $p=0.0009$) (Figure 4). While 7/11 (64%) patients who received 2 ASCT achieved one MRD negativity time point, 17/34 (50%) patients who had 1 ASCT and 1/5

(20%) patients not transplanted achieved MRD negativity at least once.

21/50 (42%) patients did not progress, and four more are still in DoR, making a total of 25/50 (50%) patients not treated for relapse at the data cut-off of this study. Regarding PET/CT positivity, Two of four patients who were positive at enrolment are still in DoR.

Safety

The most common adverse events of any grade and the grade 3 or 4 adverse events are shown in Table 3. Mostly grades 1–2 were transitory and solved. The most common were haematological, with lymphopenia in 38% of the patients and thrombocytopenia in 12%. Non-haematological grade 1 was mostly infections in 30% of the patients. Only one had a grade 4. COVID-19 occurred in seven patients (14%), only one patient required hospitalization because of infection (Table 3).

DISCUSSION

In the DART4MM study, daratumumab was added as monotherapy to test its efficacy to improve depth of response in a selected group of MM patients with \geq VGPR/MRD positivity and anti-CD38 naive. Although this is a small pilot phase 2 prospective study, it is the first one conceived with daratumumab monotherapy in a selected group of patients with at least VGPR and MRD positivity. It adds to the concept of daratumumab efficacy in consolidation and maintenance. It is important to remember that our population of patients was daratumumab-naive when the study started, and now the drug is approved in transplant-eligible (TE) and transplant-ineligible (TI) patients, making this strategy not useful anymore in clinical practice. However, our primary end-point was to test the efficacy of daratumumab monotherapy to eradicate a MRD in a 6-month period in 50 patients.

Treatment consolidation (defined usually by two cycles of therapy after ASCT to improve responses) and maintenance (defined by continuous therapy until disease progression) have been tested in the past to increase outcomes after ASCT as an alternative to a 2 ASCT, with the purpose of obtaining the same efficacy with less toxicity. In a pivotal study, VTD was used as consolidation therapy, and it increased CR from 15% to 49% in 39 bortezomib and thalidomide naive MM patients who were previously in VGPR after 2 ASCT.¹¹ Patients who achieved a molecular remission by allele-specific polymerase chain reaction (AS-PCR) after VTD treatment had better survival (PFS at 42 months was 100% vs. 57% for patients with a low tumour burden vs. patients with a higher tumour burden after VTD respectively). In the MM-BO2005 study, consolidation therapy with two cycles of TD or VTD was given after the second ASCT¹³ (CR rate increased from 40% to 47% in the TD arm and from 49% to 61% in the VTD arm).

TABLE 2 Time points and minimal residual disease (MRD) negativity in intention-to-treat.

Time point (months)	Total N	N progression at time point (%)	MRD- (%)	MRD+ (%)
2	50	0	13 (26%)	37 (74%)
6	50	1 (2%)	15 (30%)	34 (68%)
12	50	2 (4%)	10 (20%)	38 (76%)
18	50	9 (18%)	14 (28%)	27 (54%)
24	50	11 (22%)	11 (22%)	28 (56%)

Note: Progression at time point indicates N patients who progressed before the time point; MRD- indicates N patients who were negative for minimal residual disease; MRD+ indicates N patients who were minimal residual disease positive.

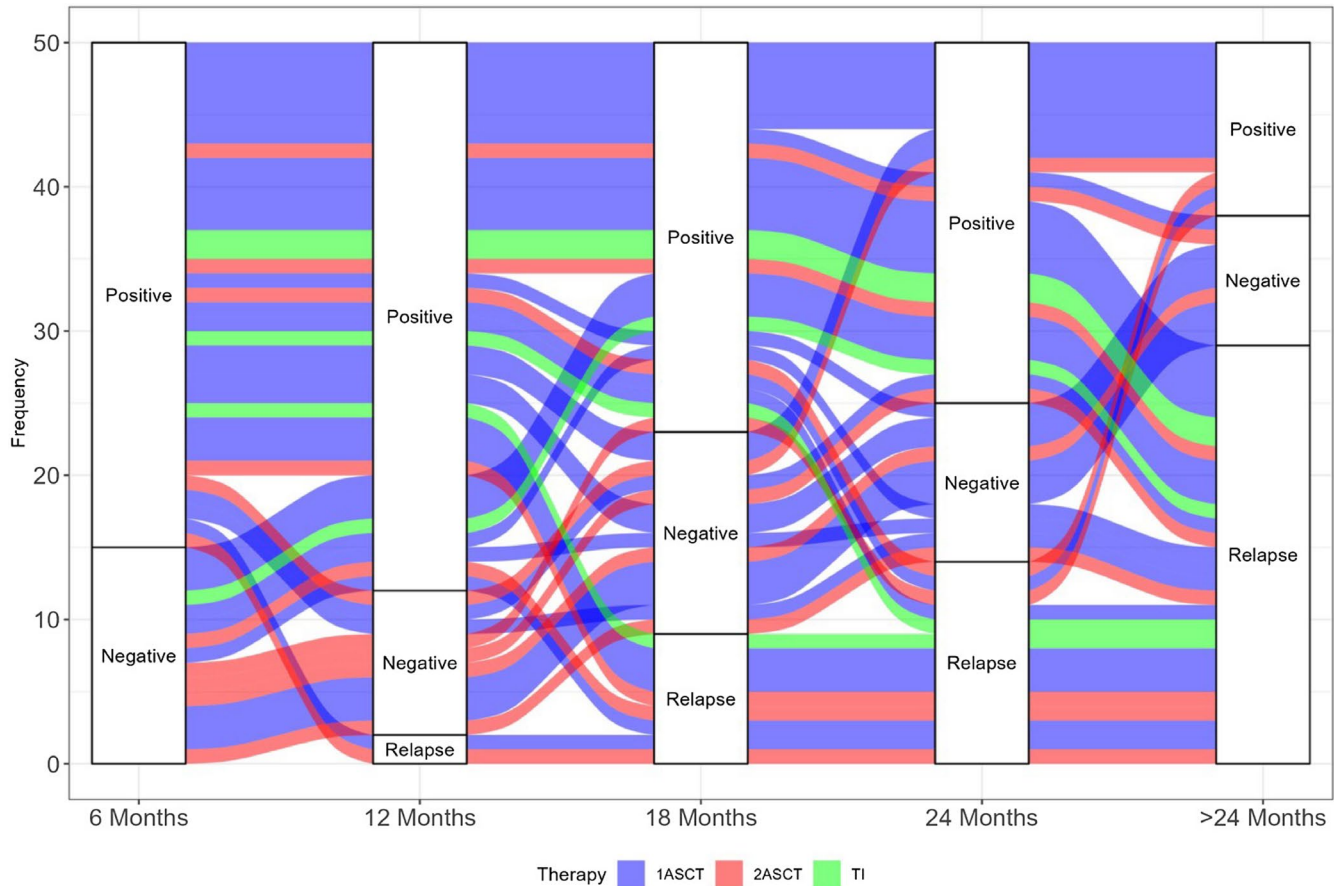


FIGURE 2 Alluvial plot. MRD status at different time points on intention-to-treat. Alluvial plot in intention-to-treat. Minimal residual disease (MRD) status, as well as relapsed patients, is reported. Patients who received 1 ASCT = one autologous stem cell transplantation. Patients who received 2 ASCT = double autologous stem cell transplantation and TI = transplant ineligible.

Based on this background but with a more powerful method for MRD detection, our study was conceived in 2018 with the idea to test the anti-CD38 antibody to eradicate MRD in the marrow. In the DART4MM study, a third of patients achieved MRD negativity at 10^{-6} at 6 months which could be the prerequisite for long-term survival.^{7,21} About 22% of patients, on intent to treat, were still negative at 24 months, and 10 are still MRD negative at a median of 56 months of follow-up (range 35–68). Considering that daratumumab was given for 6 months to three of them and for 24 months to seven of them, this seems particularly meaningful. Moreover,

21 patients did not progress, and four are still in DoR. Double ASCT seemed to give a more profound response, although in a small population of patients, since 64% of patients reached at least one MRD-negative time point, versus 50% and 20% of those that received 1 ASCT and VMP respectively. The safety profile of daratumumab after transplant was acceptable and consistent with previously reported safety profiles for this drug in multiple myeloma patients.²²

Daratumumab efficacy seems to be related to not only a direct apoptotic effect on monoclonal plasma cells but also a long-term or immunomodulatory effect of the drug via the

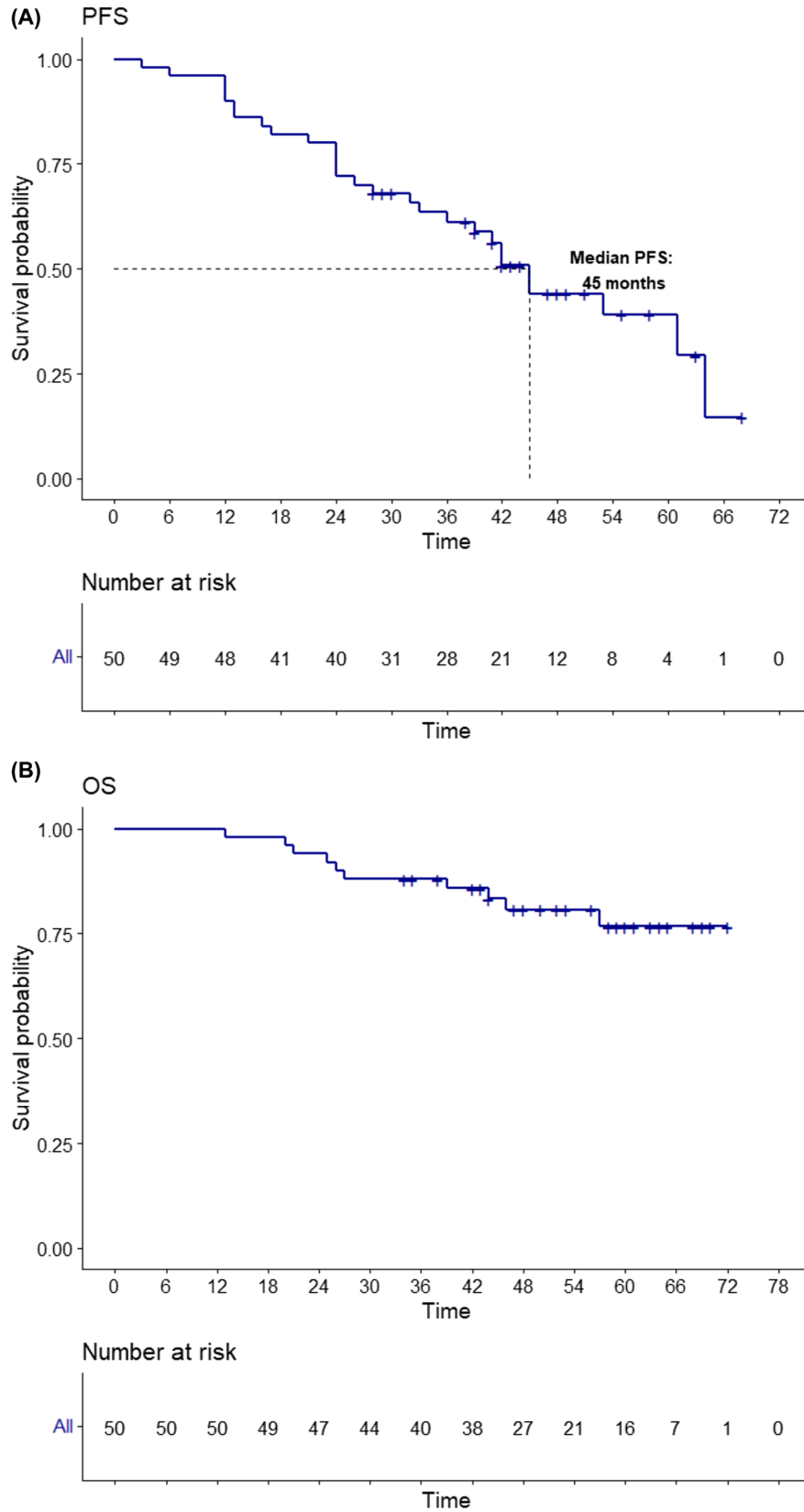


FIGURE 3 Progression-free survival and overall survival. (A) Results of the Kaplan–Meier estimates of progression-free survival among patients in the intention-to-treat population. The interim analysis of progression-free survival was performed after 29 events of disease progression had occurred. (B) Overall survival after 10 events for death occurred.

bone marrow microenvironment cannot be excluded, since a few patients become MRD negative months after the drug was stopped.^{23–27}

Different clinical trials since the beginning of the DART4MM study evaluated the anti-CD38 monoclonal antibody daratumumab as a combination therapy in NDMM patients in the TE and TI setting, although differently from our study. The MAIA study and the ALCYONE study were ongoing and ultimately determined the approval of Dara-Rd and Dara-VMP^{28,29} as standard treatment for TI NDMM patients with a median PFS of 61 and 36 months respectively. Our TI patients treated with VMP and later consolidated with daratumumab after a VGPR seem to be confirmatory of this trend of survival (all relapsed at 21, 24, 61, 56 months, the first two patients with high-risk cytogenetics). Regarding TE patients, when this study began, the standard of care in Europe was VTd, followed by ASCT.³⁰ At that time, lenalidomide maintenance was not allowed, and dexamethasone was used until progression or toxicity.

The phase 3 study CASSIOPEIA added daratumumab to bortezomib, thalidomide and dexamethasone induction and consolidation, followed by daratumumab maintenance therapy versus observation in a second randomization.¹⁵ Dara-VTd versus VTd increased response rates (complete response 73% vs. 61%; $p=0.0001$ and MRD negativity 59% vs. 47%; $p=0.0001$). Moreover, PFS was increased when daratumumab was added in the maintenance group versus the observation. In CASSIOPEIA, a small subgroup of patients ($N=66$) received VTd as induction/consolidation and later received daratumumab for maintenance, but it was different from our study. In fact, daratumumab was given every 2 months IV for 24 months (total doses 12), and the study was not MRD driven. At the latest cut-off date of September 2023, PFS was reported not reached. Our results seem inferior as the median PFS in our study was 45 months. This could be partly explained by the initial selection of all MM patients, MRD-positive after first therapy. Our population of patients could reflect a more aggressive group of myeloma patients.

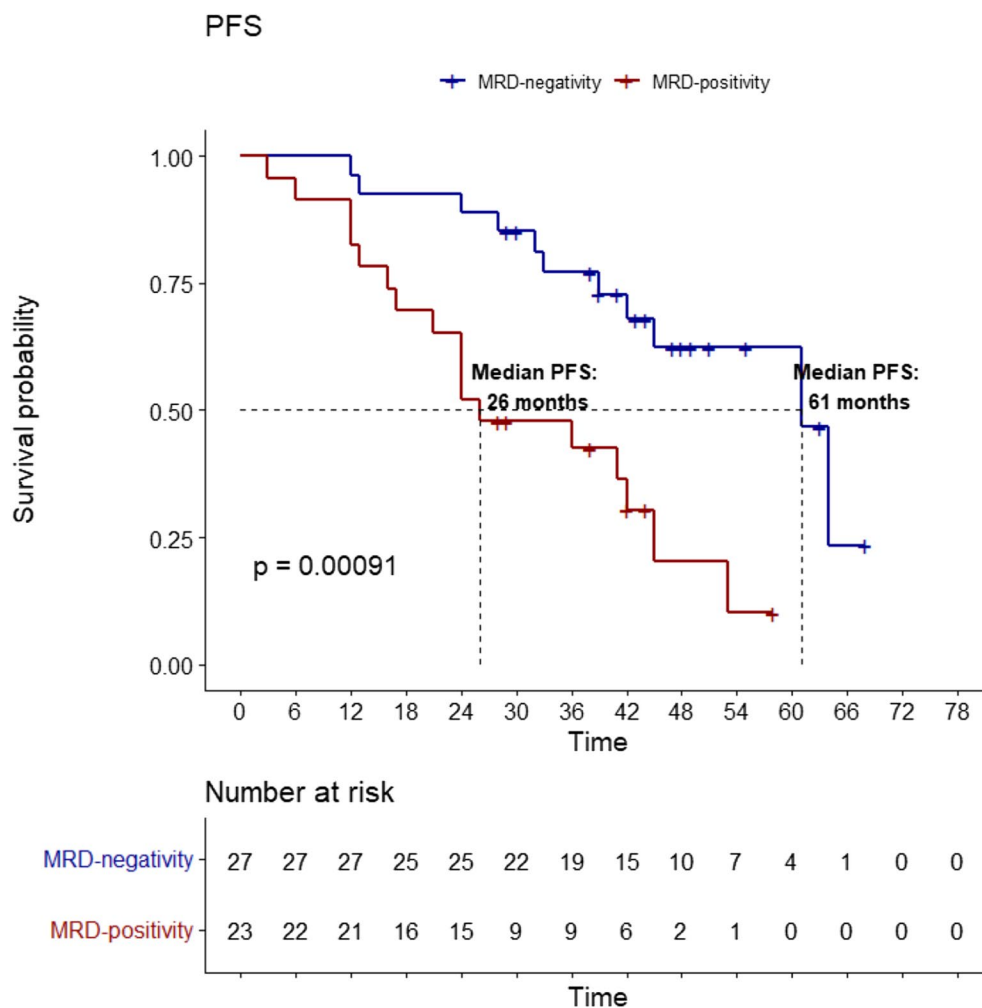


FIGURE 4 PFS for patients who reached at least one minimal residual disease (MRD) negativity. Results of the Kaplan–Meier estimates of progression-free survival in patients who reached at least one MRD negativity during the study ($N=11$ events) and patients who never reached MRD negativity ($N=17$ events), median 61 vs. 26 months; $p=0.0009$.

TABLE 3 Most common adverse events during daratumumab treatment.

Event	N=50	
	Any grade	Grade 3 or 4
	Number of patients (percent)	
Haematological adverse events		
Neutropenia	1 (2)	0
Thrombocytopenia	6 (12)	0
Anaemia	7 (14)	1 (2)
Febrile neutropenia	1 (2)	0
Lymphopenia	19 (38)	12 (24)
Non-haematological adverse events		
Diarrhoea	4 (8)	0
Peripheral sensory neuropathy	3 (6)	0
Constipation	1 (2)	0
Epigastric discomfort	2 (4)	0
Dysgeusia	1 (2)	0
Pyrexia	5 (10)	0
Arthralgia	1 (2)	0
Asthenia	6 (12)	0
Cough	4 (8)	0
Fatigue	1 (2)	0
Rash	5 (10)	0
Back pain	1 (2)	0
Peripheral oedema	1 (2)	0
Nausea	3 (6)	0
Tendonitis	1 (2)	0
Infections	15 (30)	1 (2)
COVID-19	7 (14)	0
Upper respiratory tract infection	2 (4)	1 (2)
Pneumonia	1 (2)	0
Herpes zoster	3 (6)	0
Second primary malignancy	1 (2)	NA
Any IRR iv	25 (65)	0
Any IRR sc	4 (33)	0
Hospitalization	0	1 (2)

Note: NA denotes not applicable.

Abbreviation: IRR, infusion-related reaction.

Daratumumab maintenance was also tested in the phase 3 study AURIGA, in which, differently from our study, daratumumab-lenalidomide (D-R) was compared to lenalidomide (R) as maintenance for 36 months in TE anti-CD38-naïve patients that obtained >VGPR but MRD-positive response after transplant.³¹ D-R proved to be significantly superior to R alone in MRD negativity conversion (50.5% vs. 18.8%). At median follow-up of 32.3 months, D-R achieved a

superior overall MRD-negative (10^{-5}) conversion rate, that is, D-R, 60.6% vs. R, 27.7%.

PERSEUS is a phase 3 study that evaluated daratumumab added to bortezomib, lenalidomide, and dexamethasone (VRd) as induction and consolidation and (differently from our study) followed by D-R maintenance. At a median follow-up of 47.5 months, D-VRd significantly increased PFS versus VRd induction-consolidation and R maintenance.³² Moreover, sustained MRD negativity rate at 12 months was superior with D-VRd versus VRd (64.8% vs. 29.7%; $p=0.0001$), and MRD negativity rate at 10^{-6} was significantly increased in the D-VRd group versus the VRd group (65.1% vs. 32.2%; $p=0.0001$).

D-VRd followed by D-R maintenance was also tested in the phase 2 GRIFFIN study, with improved PFS versus VRd induction/consolidation and R-only maintenance therapy³³ at a median follow-up of 49.6 months. Responses increased during the study, with complete response (67% vs. 48%; $p=0.0079$) and sustained MRD negativity lasting 12 months (44% vs. 14%; $p=0.0001$) with D-VRd and D-R maintenance versus VRd and R maintenance respectively. Dara-Lena maintenance is now acknowledged as an option by recent guidelines.³⁴

Finally, we should mention that lenalidomide is the only drug approved for maintenance after ASCT, and an OS benefit has been confirmed in different studies and meta-analyses.³⁵ However, all these studies did not include three or four drugs in the induction regimen, and the median PFS was inferior to 3 years.³⁵

Another point of interest is that MRD in our study was at 10^{-6} , which is one logarithm deeper than what is requested by the IMWG response criteria, since several recent studies⁸ settled the threshold at 10^{-6} for more accuracy. The FDA recently acknowledged MRD as an end-point for accelerated drug approval in clinical trials, making it easier to test drug efficacy in a shorter time. Unlike in the past, when disease disappearance was infrequent in multiple myeloma, it is now possible to look for an MRD-negative status not at a single time point but sustained at 2 or 3 years as the goal for prolonged survival and possibly cure. This is particularly important because sustained MRD could drive a more personalized treatment, that is, to stop maintenance therapy to avoid excessive toxicity if unnecessary. In that sense, one study evaluated disease recurrence in a group of 47 MRD-negative MM patients after ASCT and 36 months of lenalidomide maintenance. Relapse occurred only in 11 (23%) at a median follow-up of 30 months.³⁶ These data were confirmed by a similar study in which PET-CT was also added to bone marrow for MRD negativity evaluation.⁸

In conclusion, our study data are in favour of daratumumab as consolidation/maintenance after first-line therapy. It is the first study that evaluated the efficacy of daratumumab monotherapy as consolidation/maintenance in the peculiar setting of a very good responder group of MM patients. MRD-driven therapy will affect soon real-life treatments.³⁷

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in this contribution and take responsibility for the integrity of the data and the accuracy of the data analysis. AG, MB and DR substantially contributed to conception or design of the work. AG, FC, MB and VS drafted the work. AC, AG and LP involved in statistical analysis. MB and AG involved in supervision. All authors involved in acquisition, analysis or interpretation of data for the work; critical revision of the work for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGEMENTS

We thank the patients and staff members at the trial sites, Cristiana Caffarelli and Barbara Rappuoli, data manager, who were involved in data collection and protocol management.

FUNDING INFORMATION

Cofinanced by Janssen Research & Development, LLC.

CONFLICT OF INTEREST STATEMENT

AG received honoraria and research funding from Janssen, honoraria from Amgen, Menarini and Pfizer and served on an advisory board for Janssen, Amgen, Menarini and Pfizer; GB received honoraria from Janssen, Amgen, Menarini, Pfizer, GSK, Takeda, Oncopeptides, BMS; No conflicts to declare: EA; DR; LP; SC; MLD; PP; EB; DT; AS; FC; AS; AL; AMV; VC; MB; AML; FB; IA, VS, LP, MR; SG.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Gozzetti A, Pacelli P, Caroni F, Raspadori D, Bestoso E, Antonioli E, et al. MRD-negative conversion with daratumumab monotherapy in newly diagnosed multiple myeloma patients in \geq VGPR/MRD-positive after first-line therapy: Final analysis of the open-label, single-arm multicentric phase 2 trial DART4MM. *Br J Haematol*. 2026;00:1–10. <https://doi.org/10.1111/bjh.70448>