REGULAR ARTICLE

blood advances

Daratumumab, cyclophosphamide, bortezomib, and dexamethasone for transplant-ineligible myeloma: AMaRC 03-16

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Key Point

- The addition of daratumumab to the VCD chemotherapy backbone provides deeper hematological responses and improved PFS.

In newly diagnosed transplant-ineligible patients with myeloma, daratumumab has improved outcomes when added to the standard-of-care regimens. In a randomized trial, we tested whether similar improvements would be observed when daratumumab was added to the bortezomib, cyclophosphamide, and dexamethasone (VCD) regimen. Transplant-ineligible patients with untreated myeloma were randomized to receive VCD or VCD plus daratumumab (VCDD). A total of 121 patients were randomized: 57 in the VCD arm and 64 in the VCDD arm. Baseline characteristics were balanced between the 2 arms. The median progression-free survival (PFS) was 16.8 months (95% confidence interval [CI], 15.3-21.7) and 25.8 months (95% CI, 19.9-33.5) in the VCD and VCDD arms, respectively (hazard ratio, 0.67; log-rank test $P = .066$). In a preplanned analysis, it was demonstrated that the daratumumab-containing arm showed a significant improvement in PFS from 18 months onward, based on estimates at fixed time points after randomization. The proportions of patients who were progression-free at the following time points were: 18 months, 48% vs 68% ($P = .0002$); 24 months, 36% vs 52% ($P = .0001$); and 30 months, 27% vs 41% ($P < .0001$) in the VCD and VCDD arms, respectively. The best overall response and very good partial response rate were significantly higher in the daratumumab arm compared with the VCD and VCDD arms, respectively (65% vs 86%, $P = .007$; and 28% vs 52%, $P = .009$). Seventy-two percent of the VCDD patients completed the 9 cycles of induction therapy with no grade 3 or 4 peripheral neuropathy adverse events. This study supports VCDD as an option for the initial treatment of transplant-ineligible patients with myeloma. This trial was registered at the Australian New Zealand Clinical Trials Registry (ACTRN12617000202369).

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Original deidentified data are available on request from the corresponding author, Peter Mollee (peter.mollee@health.qld.gov.au). Deidentified individual participant data that underlie the reported results may be made available after publication of all study-related manuscripts through the Australasian Myeloma Research Consortium (AMaRC) trial office. Proposals for access should be sent to the corresponding author and will be reviewed by the AMaRC Steering Committee. The study protocol is included as a data supplement available with the online version of this article.

The full-text version of this article contains a data supplement.

Introduction

Treatment regimens for older patients with myeloma require agents that are both effective and well tolerated. Doses and schedules that are deliverable to transplant-eligible patients are often associated with excess nonhematological toxicity resulting in premature treatment discontinuation and poor efficacy, outcomes that worsen with increasing frailty.[1] Daratumumab has proven to be an ideal treatment for older patients because of its antimyeloma activity and safety profile. Daratumumab, when added to standard-of-care regimens for relapsed and untreated myeloma, has consistently demonstrated significant improvements in response rates and induction of minimal residual disease (MRD)–negative responses resulting in prolonged progression-free survival (PFS) and overall survival (OS) while proving highly tolerable, with minor increases in overall regimen toxicity.[2-7] In the setting of newly diagnosed transplant-ineligible patients with myeloma, this benefit of daratumumab was observed when it was added to the bortezomib, melphalan, and prednisolone (VMP), and lenalidomide and dexamethasone backbones.[3,6]

However, in many jurisdictions, the VMP regimen is not widely used, with the combination of bortezomib, cyclophosphamide, and dexamethasone (VCD) being favored because of concerns about the genotoxicity of melphalan and difficulty of dosing melphalan in renal impairment.[8] VCD has been widely used as initial therapy in older populations despite a lack of prospective studies in this population, with most publications having been conducted in the transplant-eligible setting.[9-11] Whether daratumumab improves outcomes in transplant-ineligible patients with newly diagnosed myeloma treated with VCD remains to be tested.

In this report, we present the results of a randomized, phase 2 trial of a dose-modified VCD regimen suitable for older patients, with or without daratumumab, for treating newly diagnosed myeloma in older patients who are not eligible for autologous stem cell transplantation.

Methods

Trial design

This was a prospective, multicenter, open-label, response-adapted randomized phase 2 trial of VCD induction compared with VCD and daratumumab (VCDD) induction followed by daratumumab maintenance until disease progression or toxicity. Participants were enrolled between August 2017 and December 2019 at 18 sites throughout Australia. The study was approved by a nationally approved human research ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guideline. All participants provided written informed consent. This study was registered under the Australian New Zealand Clinical Trials Registry (ACTRN12617000202369).

Patients

Patients had newly diagnosed myeloma and were not considered candidates for high-dose chemotherapy with autologous stem cell transplantation because of either age >65 years or the presence of comorbidities. No prior treatment was permitted with the exception of short-course corticosteroids (maximum total 160-mg dexamethasone or equivalent) or radiotherapy. Patients needed to have an Eastern Cooperative Oncology Group performance status of 0 to 2, and any degree of renal impairment, including dialysis dependence, was allowed. Conditions that excluded patients from trial eligibility included the following: AL amyloidosis, monoclonal gammopathy of uncertain significance, or smoldering myeloma; grade ≥3 peripheral neuropathy or grade 2 neuropathy with pain; and cancer within the prior 2 years (exceptions were squamous-cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix, and stage I prostate cancer). High-risk cytogenetics were defined as the presence of del(17p) and/or t(4;14) and/or t(14;16).

Treatments

VCD consisted of 9 cycles (cycle length, 35 days) of subcutaneous bortezomib (1.3 mg/m^2 on days 1, 8, 15, and 22), oral cyclophosphamide (300 mg/m^2 on days 1, 8, 15, and 22), and oral dexamethasone (20 mg on days 1, 8, 15, and 22). This schedule of bortezomib was based on a phase 3 Gruppo Italiano Malattie Ematologiche dell'Adulto trial where delivery of weekly bortezomib for 4 weeks during nine 5-week cycles significantly reduced neurotoxicity without affecting efficacy.[12] VCDD consisted of VCD plus intravenous daratumumab (16 mg/kg on days 1, 8, 15, and 22 of cycles 1 and 2; days 1 and 15 of cycles 3 to 6; and day 1 of cycles 7 to 9; followed by maintenance of 16 mg/kg daratumumab every 4 weeks until progression). The following medications were administered within 1 hour of daratumumab administration to mitigate the risk of infusion reactions: oral paracetamol (1000 mg), oral or intravenous diphenhydramine (25-50 mg or equivalent), oral dexamethasone (using the treatment dosing), and optional oral montelukast (10 mg). Antiviral prophylaxis, antibacterial prophylaxis, and bisphosphonates were mandatory and given according to individual institutional protocols.

Assessments and end points

Response was assessed by the International Myeloma Working Group response criteria[13] with the exception that for patients with disease not measurable by serum monoclonal immunoglobulin, the serum free light chain (FLC) assay, rather than urine Bence Jones proteinuria, was used to assess response.[14] A urine sample collected over a 24-hour period was only used to assess response in patients whose disease was not measurable by either serum protein electrophoresis (paraprotein <10 g/L) or serum FLC (involved FLC ≥100 mg/L and abnormal FLC ratio), but was still required to define complete response (CR). For patients with a small residual amount of IgG kappa band running in the same position as the original paraprotein, daratumumab interference was not resolved, and this was classified as a very good partial response (VGPR). Response assessments were performed at the end of each cycle of VCD and every 3 months thereafter until disease progression. MRD was assessed in a central laboratory by multiparameter 8-color flow cytometry[15] on bone marrow aspirate samples collected from patients achieving VGPR or better after 9 cycles of VCD(D). MRD-negative status was set at a threshold of 1 myeloma per 10^{-5} white blood cells. Patients whose samples were found to be either MRD-positive or of insufficient quality, or who were not assessed were considered to be MRD-positive. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).

The primary end point was PFS, defined as the time from randomization to either disease progression or death. Secondary end points were the overall response rates, MRD, OS, safety and toxicity, and global health status as measured by the patient-reported outcome instrument, EORTC QLQ-C30.[16]

Statistical analysis of the primary end point

The trial was designed to use a response-adaptive randomization (RAR) strategy. After a "burn-in" period of 1:1 randomized allocation of the first 30 patients to the 2 study arms, RAR was to be used to preferentially assign patients to the study arm that appeared to be superior as assessed by the VGPR rate after 4 cycles of therapy and regular updating of a model for the relationship between this short-term response end point and PFS (details are provided in the supplemental Protocol). After the trial had commenced, the Trial Management Committee reviewed the timeliness for reports of the short-term response end point and ultimately decided not to "switch on" RAR because of delays in reporting coupled with an acceleration in the accrual rate. Consequently, the comparison of PFS between the treatment arms was based on conventional statistical methods rather than a model-based approach that would have attempted to account for deviations from a 1:1 randomization and relied on an assumed model for a relationship between the response end point and PFS. This report uses conventional confidence intervals (CIs) for responses rates and hazard ratios (HRs).

The log-rank test was used to compare the PFS distributions of the 2 treatment arms. In anticipation of nonproportional hazards and either early or late differences between the treatment arms in their PFS, 3 comparisons of PFS between the arms were planned and conducted at 6, 12, and 18 months from randomization. To account for multiplicity of comparisons, a Bonferroni adjustment to the alpha-level of each test was implemented. Namely, a comparison between the treatment arms at 1 of these time points was judged to be statistically significant if the associated P value was $\leq \alpha/m$, where $\alpha = 0.05$ and $m = 3$; the threshold for statistical significance was accordingly 0.0167. Exploratory univariate and multivariate analyses of PFS and OS used Cox proportional hazards regression models to examine associations between treatment arms and the following baseline covariates: age dichotomized at 75 years, Revised International Staging System (R-ISS) stage, Chronic Kidney Disease Epidemiology Collaboration 2021 estimated glomerular filtration rate categories, sex, Eastern Cooperative Oncology Group performance status, frailty (2 levels: frail and nonfrail; and 3 levels: frail, intermediate, and fit), and cytogenetic risk (standard and high). A landmark analysis was used to assess the impact of posttreatment initiation outcomes (response rate, MRD) on PFS.

Sample size

A total sample size of 120 patients was selected on the basis of simulations of the trial design and the intended model-based analysis (details are provided in the supplemental Protocol). With the selected sample size, the false positive (ie, type 1) error rate was controlled below 5%, and the (Bayesian) power exceeded

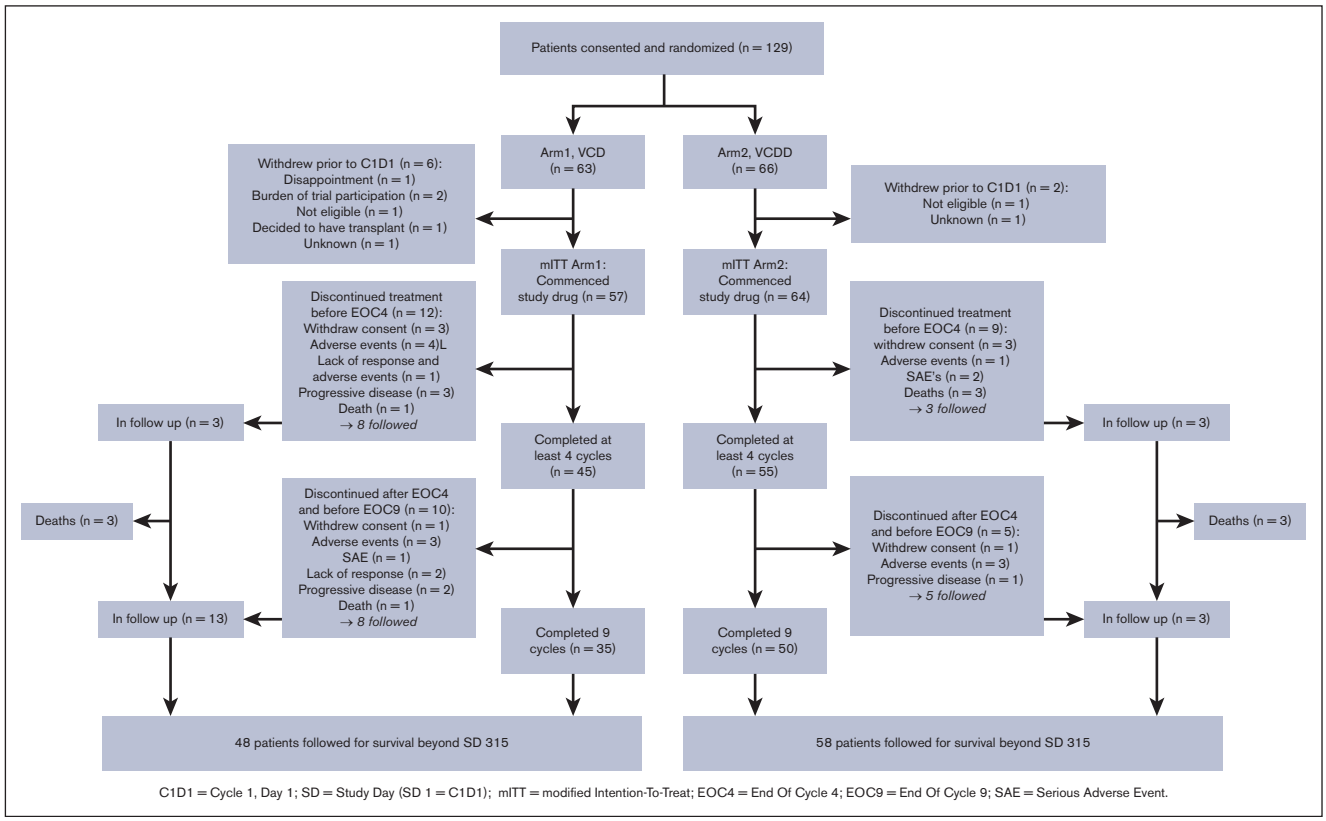


Figure 1. Consort diagram. Patient disposition until the end of cycle 9.

80% when the HR was 0.5 (eg, median PFS = 24 and 48 months in the VCD and VCDD treatment arms, respectively).

The study was approved by a nationally approved human research ethics committee (Alfred Hospital Ethics Committee) on April 28, 2017.

Results

Patient and treatment characteristics

A total of 129 patients were randomized, but 8 did not commence any trial therapy (6 from the VCD arm and 2 from the VCDD arm). The following modified intent-to-treat analysis is based on 121 patients (57 in the VCD arm and 64 in the VCDD arm), who commenced protocol therapy. The disposition of patients through the study is shown in Figure 1.

Baseline characteristics are presented in Table 1. Median age was 75 years (range, 62-91), with 18% being aged ≥80 years and 31% being female. Eastern Cooperative Oncology Group performance status was 0 (43%), 1 (36%), ≥2 (19%), and unknown (2%). ISS stage was I (21%), II (50%), III (29%), and unknown in 1 case. R-ISS stage was I (12%), II (70%), III (10%), and unknown (8%). Sixteen percent of patients were known to have high-risk cytogenetics. Disease characteristics were generally balanced between the 2 arms, although there was slightly less advanced-stage disease (5.3% vs 14.1%) and high-risk cytogenetics (12.3% vs 18.8%) in the VCD arm than in the VCDD arm. The median follow-up (by reverse Kaplan–Meier) was 44.7 months.

Efficacy

Median PFS for the entire cohort was 21.7 months (95% CI, 17.7-26.3), and was 16.8 months (95% CI, 15.3-21.7) and 25.8 months (95% CI, 19.9-33.5) in the VCD and VCDD arms, respectively (HR, 0.67; log-rank test $P = .066$, Figure 2). In a preplanned analysis, the estimated PFS at specific fixed time points after randomization demonstrated significantly improved PFS for the daratumumab-containing arm from 18 months onward. The proportions of patients who were progression-free at the following time points were: 18 months, 48% vs 68% ($P = .0002$); 24 months, 36% vs 52% ($P = .0001$); and 30 months, 27% vs 41% ($P < .0001$) in the VCD and VCDD arms, respectively.

Subgroup analyses of PFS (Figure 3) demonstrated what appeared to be a significant difference favoring the VCDD treatment arm in the younger age group ($P = .042$; HR, 0.508; 95% CI, 0.265-0.975) but not in the older age group ($P = .533$; HR, 0.834; 95% CI, 0.474-1.470). In the younger age group (age <75 years), median PFS was 16.3 months (95% CI, 10.3-26.5) and 29.8 months (95% CI, 18.7 to "not reached") in the VCD and VCDD treatment arms, respectively. In the older age group (age ≥75 years), median PFS was 19.0 months (95% CI, 15.0-28.5) and 23.0 months (95% CI, 17.7-31.6) in the VCD and VCDD treatment arms, respectively. In R-ISS stage II patients, the stage with the largest number of patients, there was evidence of a difference favoring VCDD patients ($P = .010$; HR, 0.512; 95% CI, 0.308-0.851). There was also an apparent difference in the small group of stage III patients ($P = .053$; HR, 0.202; 95% CI, 0.040-1.024). In all subgroups, there was an apparent benefit of daratumumab, with estimates of HR consistently below 1.

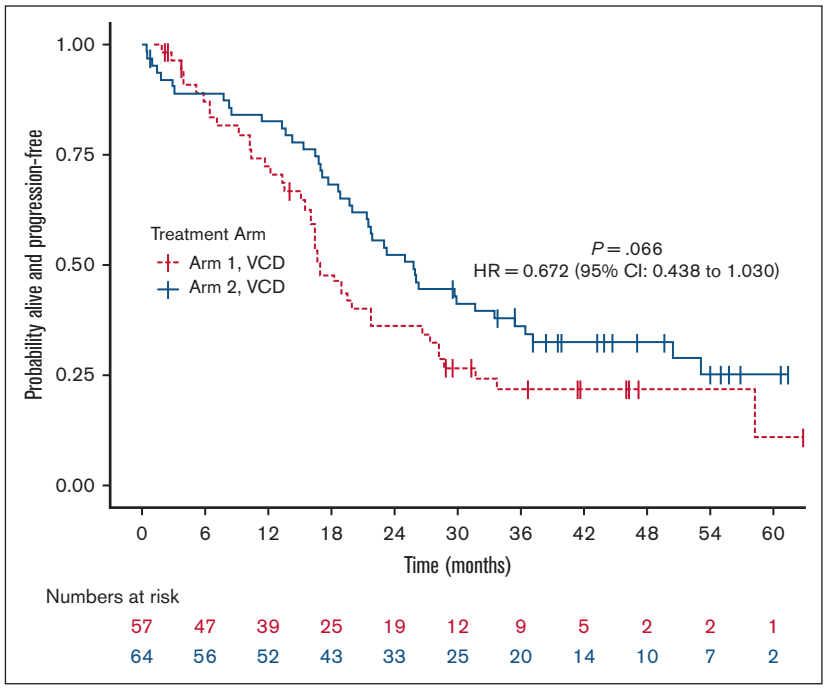
Table 1. Patient Characteristics

	VCD	VCDD
n	57	64
Age		
Median (range), y	75.4 (62-89)	75.9 (64-91)
Distribution, no (%)		
<70 y	8 (14.0)	9 (14.1)
≥70 y to <75 y	16 (28.1)	20 (31.3)
≥75 y to <80 y	24 (42.1)	22 (34.4)
≥80 y	9 (15.8)	13 (20.3)
Sex (% male)	59.7%	76.6%
ECOG Performance Status, n (%)		
0	26 (45.6)	26 (40.6)
1	20 (35.1)	24 (37.5)
≥2	10 (17.5)	13 (20.4)
Not known	1 (1.8)	1 (1.6)
Revised-ISS Stage, n (%)		
Stage I	6 (10.5)	8 (12.5)
Stage II	44 (77.2)	41 (64.1)
Stage III	3 (5.3)	9 (14.1)
Not known	4 (7.0)	6 (9.4)
Cytogenetics		
Standard risk	43 (75.4)	42 (65.6)
High risk	7 (12.3)	12 (18.8)
Not known	7 (12.3)	10 (15.6)
Renal function		
Median eGFR	65.2 mL/min	75.2 mL/min
Distribution, n (%)		
≥60 mL/min	34 (59.6)	42 (65.6)
≥45 and <60 mL/min	9 (15.8)	12 (18.8)
≥30 and <45 mL/min	13 (22.8)	6 (9.4)
<30 mL/min	1 (1.8)	4 (6.2)
IMWG Frailty Score, n (%)		
Frail	11 (19.3)	13 (20.3)
Intermediate	23 (40.4)	22 (34.4)
Fit	23 (40.4)	29 (45.3)

ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; IMWG, International Myeloma Working Group; ISS, International Staging System.

The best achieved overall response rate was 65% in the VCD arm and 86% in the VCDD arm ($P = .007$) (Table 2). The rate of ≥VGPR was significantly improved by daratumumab (28% in VCD arm vs 52% in VCDD arm; $P = .009$). Because assays to differentiate daratumumab from residual monoclonal immunoglobulin G kappa bands were not available in the study, we were not able to accurately assess the impact of daratumumab on CR rates. As a result, CR rates remained low in both arms (4% vs 6%; $P = .488$). MRD assessment by flow cytometry was hampered by delays in transporting samples to the central laboratory caused by the COVID-19 pandemic, which disproportionately affected the VCDD arm. At the end of induction, 11 of

Figure 2. **PFS by treatment arm.**



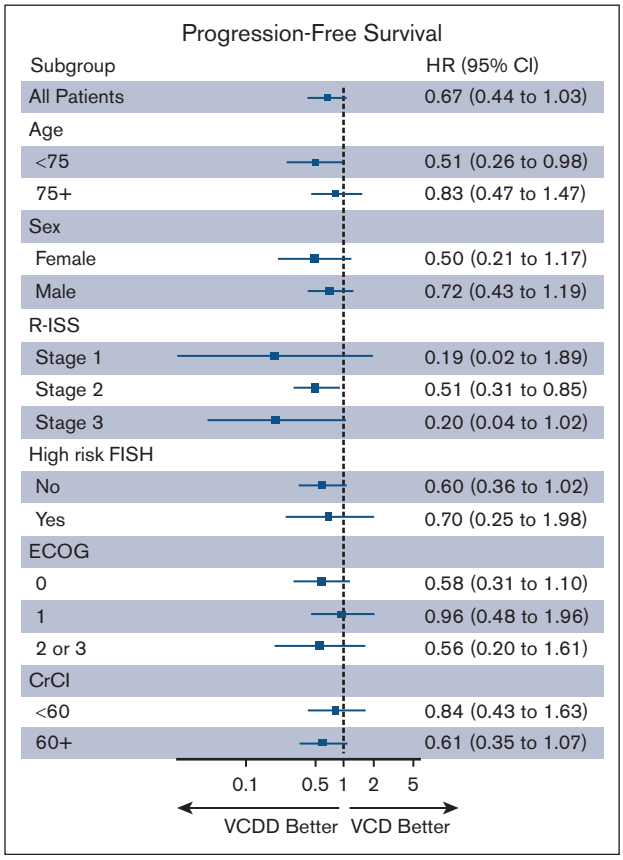


Figure 3. **Subgroup analysis of PFS.**

16 patients achieving VGPR in the VCD arm and 16 of 33 patients achieving VGPR in the VCDD arm had a successful MRD analysis performed. Thus, in the modified intent-to-treat analysis set, 5% of patients in the VCD group as opposed to 16% of patients in the VCDD arm were flow MRD-negative (P = .066). In a landmark analysis, achievement of flow MRD negativity did not affect PFS (P = .255).

The follow-up period is not yet long enough to adequately assess for any OS differences between the arms (Figure 4). Median OS is estimated to be 58.7 months (95% CI, 47.0-not available) in the VCD arm and "not reached" (95% CI, 41.7-not available) in the VCDD arm (P = .392).

Table 2. **Best responses to therapy**

	VCD (n = 57)		VCDD (n = 64)		
	%	95% CI	%	95% CI	*P* value
OR (PR or better)	64.91	51.13-77.09	85.94	74.98-93.36	.007
CR/sCR	3.51	0.43-12.11	6.25	1.73-15.24	.488
≥VGPR	28.07	16.97-41.54	51.56	38.73-64.25	.009
MR	10.53	3.96-21.52	6.25	1.73-15.24	.394
SD	12.28	5.08-23.68	0.00	0.00-5.60	.004
PD	1.75	0.04-9.39	0.00	0.00-5.60	.287
MRD-negative*	5.26	1.10-14.62	15.63	7.76-26.86	.066

MR, minimal response; PD, progressive disease; SD, stable disease.
*Patients not known to be MRD-negative, with a missing value, either through a missing or suboptimal sample, are assumed to be MRD-positive.

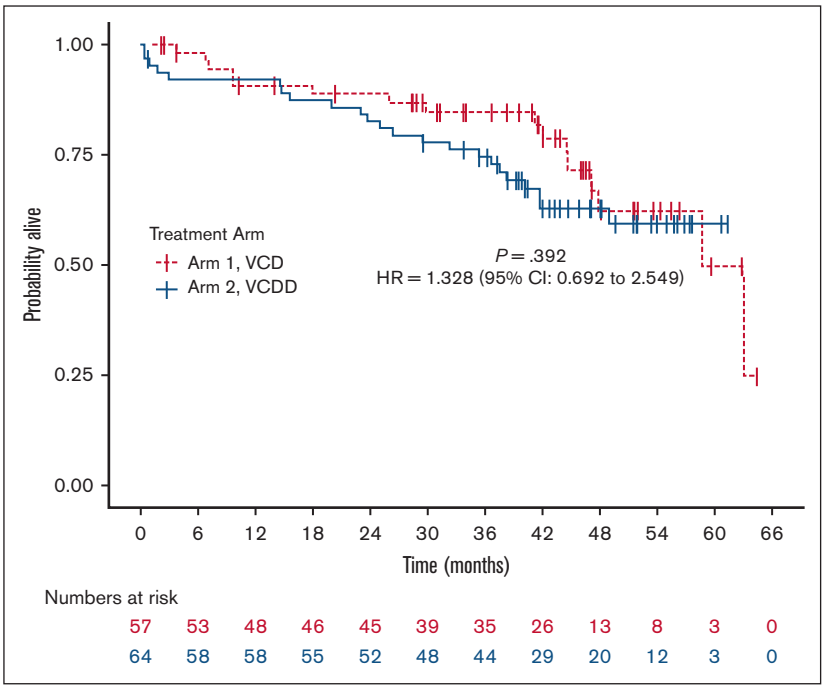


Figure 4. OS by treatment arm.

Safety

In all, 61% and 78% of patients in the VCD and VCDD groups, respectively, completed all 9 cycles of planned induction. Twenty-six percent and 13% completed ≤4 induction cycles, and 12% and 8% completed 5 to 8 cycles of induction, respectively.

In the VCD group, 82% of the patients had at least 1 adverse event reported as opposed to 89% in the VCDD treatment arm (Figure 5). There was 1 grade 5 adverse event (other infection) in the VCDD arm. The reporting period, which included the COVID-19 era, was significantly longer for the VCDD group, in which

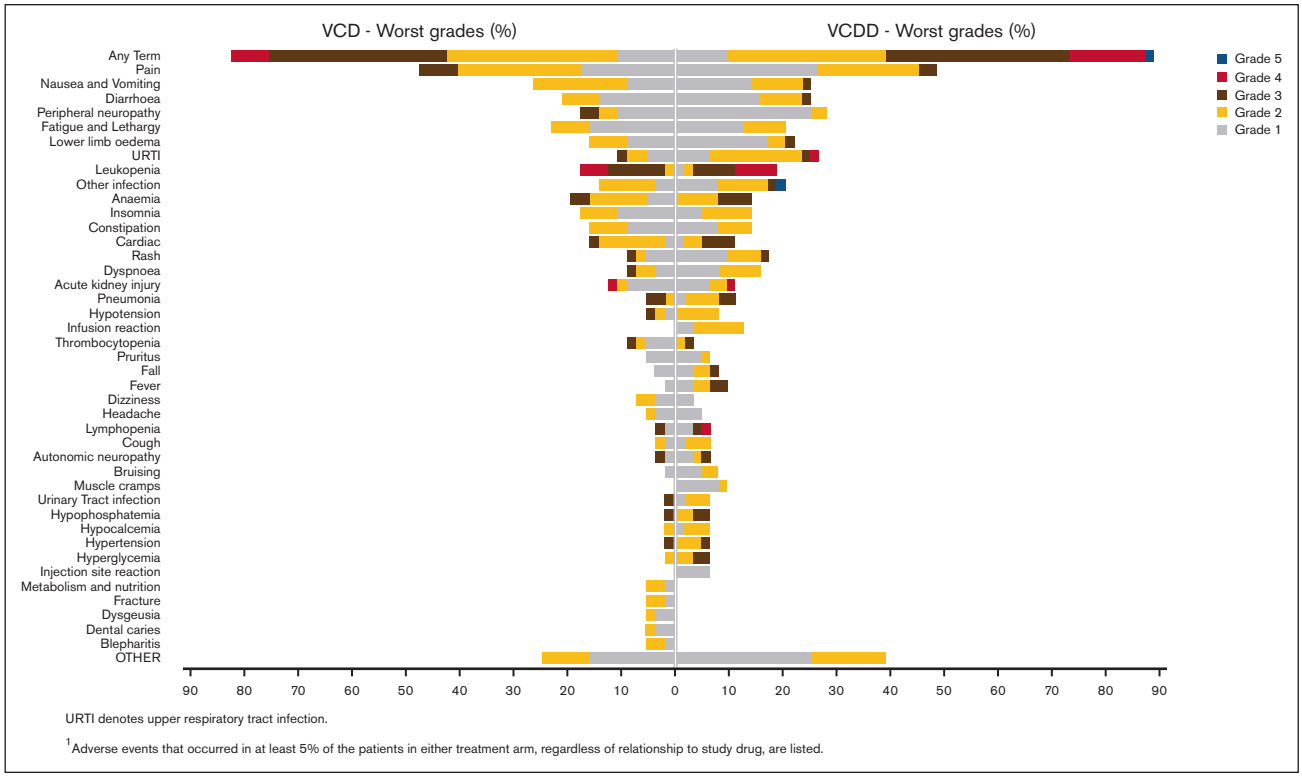


Figure 5. Adverse events according to treatment arm.

Table 3. Summary of adverse events

AE summary, n (%)	VCD (n = 57)	VCDD (n = 64)
Any AE	47 (82.5)	57 (89.1)
Grade ≥3 AE	23 (40.4)	32 (50.0)
Grade ≥4 AE	4 (7.0)	10 (15.6)
Therapy-related AE	37 (64.9)	47 (73.4)
Grade ≥3 TR-AE	13 (22.8)	21 (32.8)
Grade ≥4 TR-AE	2 (3.5)	8 (12.5)
Daratumumab-related AE		34 (53.1)
Grade ≥3 DR-AE		14 (21.9)
Grade ≥4 DR-AE		6 (9.4)
Drug-related AE leading to permanent discontinuation	4 (7.0)	2 (3.1)
Drug-related AE leading to dose interruption/delay	16 (28.1)	24 (37.5)
Any SAE	14 (24.6)	19 (29.7)
Fatal SAE	0 (0.0)	1 (1.6)
Therapy–related fatal SAE	0 (0.0)	1 (1.6)

AE, adverse event; SAE, serious adverse event.

adverse events continued to be reported during daratumumab maintenance, which continued until disease progression. The most common adverse events of any grade were pain (47% in the VCD group and 48% in the VCDD group), nausea and vomiting (26% and 25%, respectively), diarrhea (21% and 25%, respectively), peripheral neuropathy (18% and 28%, respectively), fatigue and lethargy (23% and 20%, respectively), lower limb edema (16% and 22%), and upper respiratory tract infections (11% and 27%). Pneumonia occurred in 5% of VCD patients and 11% of VCDD patients. Adverse events reported as "OTHER," although moderately frequent (25% and 39% in the VCD and VCDD arms, respectively), did not exceed grade 2.

Drug-related adverse events leading to permanent treatment discontinuation occurred in 7% and 3% of patients in the VCD and VCDD arms, respectively, and adverse events that required a temporary interruption of treatment occurred in 28% and 38%, respectively (Table 3). Serious adverse events occurred in 25% of the patients in the VCD treatment arm and 29% in the VCDD arm. There were 6 early deaths within 6 months from randomization: 1 in the VCD arm (respiratory failure n = 1) and 5 in the VCDD arm (progressive disease n = 2, infection n = 3).

Discussion

The addition of daratumumab to the VCD regimen improves the chance of deeper responses (VGPR or better) in older patients with myeloma. Although there is a trend of daratumumab improving PFS, the primary end point of the trial was not met, which may be related to the sample size not being large enough to detect a significant difference between the arms. It is also possible that imbalances in disease characteristics between the 2 treatment arms, such as a higher percentage of advanced-stage disease (14.1% vs 5.3%) and high-risk cytogenetics (18.8% vs 12.3%) in the VCDD arm, could have affected the primary end point analysis. However, in a preplanned analysis, daratumumab was clearly superior when assessed for PFS benefit at delayed time points after 12 months. The magnitude of improvement in PFS with VCDD vs VCD in this study was slightly lower than that observed in randomized trials of daratumumab added to bortezomib-based chemotherapy backbones: the HRs of PFS benefit were 0.50, 0.43, and 0.67 in the ALCYONE,[6] OCTANS,[17] and our study, respectively. In the context of these other randomized studies, there is clear evidence that daratumumab added to bortezomib-based regimens improves PFS in the initial therapy of transplant-ineligible patients with myeloma. Although these are active combinations, the most impressive outcomes with daratumumab in the initial treatment of older patients with myeloma, both in terms of PFS and OS, have been observed with the lenalidomide and dexamethasone backbone, in which the addition of daratumumab resulted in a 5-year PFS and OS of 52.5% and 66.3%, respectively.[3]

The median PFS of 25.8 months reported in our study appears lower than that reported in other trials of daratumumab with bortezomib-based backbones (Table 4). Although cross-study comparisons should be interpreted with caution, this could relate to our study containing an older, more frail population, which included patients with severe renal failure and comorbidities. The benefit of daratumumab for PFS was consistent across several subgroups examined, with the possible exception of the older-age subgroup. Because of our trial design, we could not determine the presence or degree of benefit associated with the continuation of daratumumab beyond the initial induction. We observed that the benefit of daratumumab was more pronounced in patients aged <75 years than in older patients. Similar trends were observed in the ALCYONE[6] and MAIA[3] trials, although the reasons for this lesser relative efficacy have not been explained. It could relate to increased infectious toxicity, especially respiratory tract infections, observed with the addition of daratumumab. The older and younger patients may not tolerate such infections, leading to dose delay or modification, early therapy cessation associated with loss of disease control, or premature death. Such an effect was observed in newly diagnosed, fit, older patients, for whom a recent trial reported increased rates of infections leading to death when daratumumab was added to the carfilzomib, lenalidomide, and dexamethasone regimen.[18] Otherwise, consistent with other randomized trials of chemotherapy with or without daratumumab, the benefit of daratumumab was observed in advanced disease stages, high-risk cytogenetics, poor performance status, and renal impairment subgroups.

Similar to other trials (Table 4), we observed an improvement in the overall hematological response rate with the addition of daratumumab (65% vs 86%), which included a near doubling of deeper responses (VGPR or better, 28% vs 52%). Assessment of MRD was affected by the COVID-19 pandemic. As a result, although the MRD-negative rate on an intent-to-treat basis was tripled in the daratumumab arm (5% in the VCD arm and 16% in the VCDD arm), similar to that observed in the ALCYONE trial[6] (6% vs 22% in the VMP and VMP + daratumumab groups, respectively), this difference was not statistically significantly different ($P = .066$). Possibly related to the small number of successful MRD specimens, and in contrast to the ALCYONE trial,[6] MRD negativity did not predict PFS.

An important issue in the treatment of older patients with myeloma is the tolerability and deliverability of the therapy. The improved tolerability of weekly compared with twice-weekly bortezomib in the context of the VMP regimen has been well described,[20] and the

Table 4. Trials of daratumumab with bortezomib-based chemotherapy in newly diagnosed transplant-ineligible patients with myeloma

	ALCYONE[6]		OCTANS[17]		VCDD		LYRA[19]
N	706		220		121		48
Median age	71 y		69 y		75 y		66 y
Age ≥75 y	30%		15%		50%		21%
ECOG ≥2	25%		17%		18%		8%
ISS stage							
Stage I	19%		25%		19%		33%
Stage II	42%		44%		46%		33%
Stage III	38%		30%		27%		33%
High-risk FISH	16%		22%		16%		43%
eGFR <30 mL/min	Excluded		0.50%		4%		Not stated
Therapy	**VMP**	**Dara + VMP**	**VMP**	**Dara + VMP**	**VCD**	**VCDD**	**VCDD**
Response							
ORR	74%	91%	78%	88%	65%	75%	83%
≥VGPR	50%	71%	43%	74%	32%	52%	70%
MRD-negative	6%	22%	7%	30%	5%	16%	Not stated
Median PFS	19.3 m	36.4 m	18.2 m	>18.2 m	18.9 m	25.8 m	>36 m

Dara + VMP, daratumumab and VMP; FISH, fluorescent in-situ hybridization cytogenetics; ORR, overall response rate.

ALCYONE trial[6] used biweekly bortezomib for cycles 1 to 2 followed by weekly bortezomib for cycles 3 to 9 in the VMP regimen in recognition of the difficulty of delivering twice-weekly bortezomib schedules to older patients. In the context of the VCD regimen, weekly delivery of bortezomib has been reported in transplant-eligible populations,[21-24] but there have only been a few small retrospective reports of a weekly VCD regimen for the initial treatment of older patients.[25,26] The schedule of VCD in our trial, using 4-weekly bortezomib doses in a 5-week cycle, proved highly tolerable despite the older and frail population. Approximately 80% of patients in the VCDD arm completed the planned 9 cycles of induction, with an all-grade peripheral neuropathy rate of 28% and no grade 3 or 4 events. Infective adverse events appeared more common in the daratumumab arm, particularly upper respiratory tract infections (27% vs 11%) and pneumonia (11% vs 5%), which is consistent with other studies of daratumumab in myeloma.[3,6] The extended safety monitoring in the VCDD treatment arm, which continued throughout maintenance, likely accounts for a proportion of the apparently higher infection rates in the daratumumab arm. However, this finding mandates close respiratory tract infection monitoring in patients treated with daratumumab and also argues for prospective trials of infection prophylaxis strategies.

In summary, in the initial treatment of older, frail patients with myeloma, the addition of daratumumab to this VCD chemotherapy backbone provides deeper hematological response rates and improved PFS from 18 months onward, although at the expense of increased infectious toxicity. The daratumumab, lenalidomide, and dexamethasone regimen remains the current standard-of-care because of its superior efficacy and toxicity profile. In jurisdictions where this combination is not reimbursed, however, this study supports VCDD along with daratumumab-VMP as alternative regimens for the initial treatment of transplant-ineligible patients with myeloma.

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Authorship

Contribution: P.M., J.R., and A.S. designed the trial; P.M. and J.R. were responsible for overall trial conduct, analysis, and writing of the manuscript; W.J., H.Q., P.C., S.G., S.L., E.L., K.T., T.C., C.W.-G., F.K., N.W., I.K., H.W., P.J.H., M.F.L., N.H., and A.S. contributed to patient care and accrual and review of the manuscript; and all authors had access to the primary clinical trial data.

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