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Health-related quality of life maintained over time in patients with relapsed or refractory multiple myeloma treated with daratumumab in combination with bortezomib and dexamethasone: results from the phase III CASTOR trial

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Summary

In the phase III CASTOR trial, daratumumab, bortezomib and dexamethasone (D-Vd) significantly extended progression-free survival compared with bortezomib and dexamethasone (Vd) alone in patients with relapsed/refractory multiple myeloma (RRMM). Here, we present patient-reported outcomes (PROs) from the CASTOR trial. PROs were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) and the EuroQol 5-dimensional descriptive system questionnaire. Treatment effects through Cycle 8 were measured by a repeated measures mixed-effects model. After Cycle 8, PROs were only collected for patients in the D-Vd group who continued on daratumumab monotherapy. Compliance rates for PRO assessments were high and similar between treatment groups. Mean changes from baseline were generally similar between treatment groups for EORTC QLQ-C30 global health status (GHS), functioning and symptoms, and did not exceed 10 points for either treatment group. Subgroup analyses were consistent with the results observed in the overall population. There was no change in patients' health-related quality of life for the first eight cycles of therapy; thereafter, patients treated with daratumumab over the long-term reported improvements in GHS and pain. These results complement the significant clinical benefits observed with D-Vd in patients with RRMM and support its use in this patient population.

Keywords: CASTOR, daratumumab, health-related quality of life, patient-reported outcomes, relapsed/refractory multiple myeloma.

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Introduction

Despite recent treatment advances, multiple myeloma (MM) remains an incurable disease with a substantial negative impact on patients' health-related quality of life (HRQoL).[1–9] MM treatment is associated with demanding administration and monitoring schedules[2] as well as adverse events.[1,2,5] Since treatment until disease progression (rather than a fixed-duration regimen) is recommended,[6,10] and because treatment with novel agents has extended progression-free survival (PFS),[11] assessment of the impact of treatment on patients' long-term HRQoL is warranted.[3,7,9,12,13] Moreover, MM is primarily a disease of older persons[1] for whom treatment selection may be complicated by co-morbidities, such as diabetes or cardiovascular disease.[14] Patient-reported outcomes (PROs), including evaluation of the impact of treatment on HRQoL, offer valuable insights to supplement clinical endpoints and aid in therapeutic decision-making.[1,3,11,13]

Daratumumab is an anti-CD38 monoclonal antibody with a direct on-tumour[15–18] and immunomodulatory[19–21] mechanism of action; daratumumab is approved by the US Food and Drug Administration in patients with relapsed or refractory MM (RRMM) as monotherapy or in combination with other agents.[22] The phase III CASTOR study (NCT02136134) compared daratumumab in combination with bortezomib and dexamethasone (D-Vd) with bortezomib and dexamethasone (Vd) alone in patients who had a median of two prior lines of therapy.[23] The study met its primary endpoint [PFS hazard ratio (HR) 0·39, 95% confidence interval (CI): 0·28–0·53; $P < 0·001$].[23] Treatment discontinuations occurred in 30·5% and 43·9% of patients in the D-Vd and Vd groups, respectively.[23] An updated analysis at a median follow-up of 19·4 months found that responses to D-Vd deepened over time, with no new treatment-emergent toxicities, and clinical benefits of D-Vd observed across all subgroups studied.[24] Here, we present the results of analyses evaluating the impact of D-Vd and Vd on PROs in the CASTOR trial.

Methods

Study design and patients

The full methods of the CASTOR study have been published previously.[23] In brief, CASTOR is a randomised, open-label, active-controlled, multicentre, phase III study of patients with RRMM. Each study site's independent ethics committee or institutional review board approved the study protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

Patients were randomised 1:1 to receive D-Vd or Vd alone. All patients received eight cycles of bortezomib (1·3 mg/m^2 subcutaneously on days 1, 4, 8 and 11) and dexamethasone (20 mg orally on days 1, 2, 4, 5, 8, 9, 11 and 12). Patients assigned to the D-Vd group received daratumumab 16 mg/kg intravenously once weekly in Cycles 1–3, day 1 of Cycles 4–8 and then every 4 weeks until disease progression, unacceptable toxicity or withdrawal of consent. Cycle durations were 21 days for Cycles 1–8 and 28 days thereafter. Patients in the Vd group received no further study treatment after Cycle 8. A protocol amendment after the primary analysis allowed patients who progressed on Vd to receive daratumumab monotherapy.

PRO measures

PROs were assessed for patients who were on study treatment. In all patients, PROs were assessed on day 1 of each treatment cycle to Cycle 8 to capture patients' HRQoL over the prior 3 weeks; assessments continued beyond Cycle 8 only for patients in the D-Vd group who remained on treatment. PROs were collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30)[25] and the EuroQol 5-dimensional descriptive system (EQ-5D-5L)[26] questionnaire, which were completed prior to study assessments or administration of the study drug.

The EORTC QLQ-C30 is a validated, cancer-specific instrument that contains 30 items resulting in five functional scales (physical, role, emotional, cognitive and social), one global health status (GHS) scale, three symptom scales (fatigue, nausea and vomiting, and pain) and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).[25] The EQ-5D-5L is a generic measure of health status that assesses five domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, plus a visual analogue scale (VAS) rating of 'health today.'[26]

Statistical methods

The primary endpoint was analysed in the intent-to-treat (ITT) population (all randomised patients). The PRO analysis set included all patients from the ITT population with a baseline PRO assessment and ≥1 post-baseline PRO assessment. Post-hoc subgroups were based on age (<65 and ≥65 years), baseline Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1, and 2) and depth of treatment response [best response of partial response or better (≥PR) or very good partial response or better (≥VGPR)].

Descriptive statistics (number, percentage, mean values) were used to report baseline demographic and clinical characteristics and change from baseline for individual treatment groups. Compliance with PRO assessments was calculated as the number of assessments received divided by the number of assessments expected (PRO assessments were expected from all patients who were on study treatment at each visit) at each time point.

The median time to improvement/worsening was calculated using the Kaplan–Meier method; improvement/worsening was

defined as an increase/decrease in score that was at least half one standard deviation from baseline values, where the standard deviation was calculated from the scores at baseline combining both treatment groups. HRs and 95% CIs were estimated based on the Cox proportional hazard model adjusted with stratification factors. *P*-values were based on the log-rank test stratified with the International Staging System, number of prior lines of therapy and prior bortezomib treatment.

Treatment effect for PRO scores was analyzed using a mixed-effects model with repeated measures that included patients as a random effect and baseline score, treatment group, time (weeks), treatment-by-time interaction, and stratification factors as fixed effects. Results are presented as least squares (LS) means with 95% CIs; *P*-values were based on the difference of the LS mean change from baseline (D-Vd − Vd). No imputation of missing data or adjustments for multiplicity were made. Nominal *P*-values are presented.

Thresholds for clinically meaningful change from baseline were defined *a priori*, based on published literature: ≥10 points for EORTC QLQ-C30 scores[27] and ≥7 points for the EQ-5D-5L score.[28]

Results

Baseline characteristics and PRO assessment compliance rates

A total of 498 patients with RRMM were randomised to D-Vd (n = 251) or Vd (n = 247). Baseline characteristics were well balanced between treatment groups (Table I). The median age was 64 years (range 30–88 years), 57·0% of patients were male and 48·9% had an ECOG performance status score of 1. Mean baseline EORTC GHS, functional and symptom scale scores and EQ-5D-5L VAS scores were comparable between groups (Table I). PRO compliance rates were high and similar in both treatment groups across all time points, with rates >87% at baseline and >85% through Cycle 8 (Table SI). Although compliance rates were similar between the two treatment groups, more patients in the D-Vd group than in the Vd group remained on study treatment and were, therefore, eligible to complete PRO assessments. In the D-Vd group, PRO compliance rates were >80% from Cycles 9 to 44, >50% from Cycles 45 to 47 and >10% from Cycles 48 to 52.

Treatment effect on EORTC QLQ-C30 scores

ITT population. Median time to a meaningful change in GHS score was 5·0 months vs. 5·1 months for the D-Vd vs. Vd groups (HR 0·99; 95% CI: 0·76–1·29; P = 0·9163). Median time to meaningful worsening of GHS score was 3·5 months vs. 3·7 months for the D-Vd vs. Vd groups (HR 0·93; 95% CI: 0·73–1·20; P = 0·5811).

Using a mixed-effects model with repeated measures, the LS mean (95% CI) change from baseline in GHS score was 2·2 (−0·5 to 5·0) with D-Vd and –0·9 (−4·6 to 2·8) with Vd (P = 0·1565) at Cycle 8 (Fig 1A). At Cycle 5, LS mean (95% CI) change from baseline pain score was significantly greater with Vd than D-Vd [−4·7 (−8·5 to 1·0) vs. 0·9 (−2·6 to 4·5), P = 0·0213; Fig 1B]. At Cycle 8, the last at which bortezomib was given, LS mean change (95% CI) from baseline in pain score was −4·7 (–8·3 to –1·1) with D-Vd and −1·4 (–6·3 to 3·6) with Vd (P = 0·2659). Similarly, changes in functional and symptom scale scores were not significantly different between groups at any assessment time point while patients were on treatment and point estimates favoured D-Vd (Fig 1C–I). Mean changes from baseline did not meet the clinically meaningful threshold (10 points) for either group at any time through Cycle 8, suggesting no change from the baseline health state.

While the mean changes for each treatment group as a whole did not meet the clinically meaningful threshold, the proportions of individual patients with GHS score changes of ≥10 points from baseline ranged from 21·2% to 32·0% in the D-Vd group and from 28·1% to 29·4% in the Vd group; differences between groups were not statistically significant (Fig 2A). Differences between groups were also not significant for any of the functional scales (Fig 2B–F). With the exception of fatigue score at Cycles 1 and 6 (Fig 2G), pain score at Cycle 6 (Fig 2H) and sleep disturbance score at Cycle 3 (Fig 2I), all significant in favour of Vd, between-group differences in proportion of patients with clinically meaningful symptom score changes were not statistically significant (Fig 2J–N). The proportion of patients with clinically meaningful improvements was greatest for pain scores (Fig 2H), with between 34·4% and 37·4% of patients in the D-Vd group and 39·3% and 48·9% of patients in the Vd group experiencing improvements of ≥10 points.

Subgroups. Changes from baseline GHS, functioning and symptom scores in subgroups based on age (<65 years vs. ≥65 years), ECOG performance status (0 or 1 vs. 2) and depth of response (≥VGPR vs. ≥PR) were largely consistent with the overall population (Table SII). Younger patients and those with better performance status tended to have greater improvement (or less worsening) in both treatment groups. Regardless of depth of clinical response (≥PR or ≥VGPR), HRQoL was unchanged from baseline.

Treatment effect on EQ-5D-5L scores

ITT population. Median time to a meaningful change in EQ-5D-5L VAS score was 5·0 months for both treatment groups (HR 1·03; 95% CI: 0·79–1·35; P = 0·8072). Median time to meaningful worsening of EQ-5D-5L VAS score was 3·6 months for both treatment groups (HR 0·97; 95% CI: 0·75–1·25; P = 0·8054).

EQ-5D-5L VAS scores followed a similar pattern as EORTC QLQ-C30 GHS scores, with LS mean (95% CI) change from baseline of 1·4 (−1·0 to 3·7) with D-Vd and −2·5 (−5·6 to 0·7) with Vd (P = 0·0427) at Cycle 8 (Fig 1J).

Table I. Baseline demographics and characteristics (ITT population).

Characteristic	D-Vd (n = 251)	Vd (n = 247)
Age, years, n (%)		
<65	132 (52·6)	125 (50·6)
65–74	96 (38·2)	87 (35·2)
≥75	23 (9·2)	35 (14·2)
Sex, n (%)		
Female	114 (45·4)	100 (40·5)
Male	137 (54·6)	147 (59·5)
Baseline ECOG PS, n (%)		
0	106 (42·4)	116 (47·0)
1	131 (52·4)	112 (45·3)
2	13 (5·2)	19 (7·7)
EORTC QLQ-C30 scores, mean (SD)*	n = 227	n = 219
Global health status	59·1 (20·2)	58·4 (23·3)
Physical functioning	71·9 (20·9)	70·0 (23·4)
Role functioning	69·8 (27·1)	66·1 (31·3)
Emotional functioning	75·9 (21·0)	75·7 (20·4)
Cognitive functioning	83·3 (20·2)	82·7 (19·9)
Social functioning	75·0 (25·3)	74·9 (27·6)
Pain	34·4 (28·7)	36·8 (29·5)
Fatigue	36·8 (23·1)	38·8 (25·6)
Nausea/vomiting	5·0 (12·4)	4·8 (13·1)
Dyspnoea	18·9 (26·4)	21·3 (27·0)
Sleep disturbance	26·4 (28·7)	28·9 (31·2)
Appetite loss	14·8 (25·5)	13·4 (24·4)
Constipation	12·9 (24·5)	10·5 (22·3)
Diarrhoea	10·6 (20·2)	10·1 (20·2)
Financial difficulties	25·1 (31·7)	19·9 (29·5)
EQ-5D-5L scores, mean (SD)	n = 225	n = 216
VAS†	64·2 (19·1)	64·6 (20·3)

D-Vd, daratumumab, bortezomib and dexamethasone; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item; EQ-5D-5L, EuroQol 5-dimensional descriptive system; ITT, intent-to-treat; PS, performance status; SD, standard deviation; VAS, visual analogue scale; Vd, bortezomib and dexamethasone.

*Scores range from 0–100; higher scores represent better health status, better physical functioning and more (worse) symptoms.

†Scores range from 0–100; higher scores represent better self-evaluated health status.

Between-group differences were not significant at other assessment time points. The mean change from baseline did not meet the clinically meaningful threshold (7 points) in either treatment group at any time through Cycle 8.

Subgroups. Subgroup analyses demonstrated stability of baseline EQ-5D-5L VAS scores regardless of age (<65 years vs. ≥65 years) or depth of response (≥VGPR vs. ≥PR; Table SII). Changes from baseline in EQ-5D-5L VAS scores tended to favour younger patients, while changes were similar between subgroups based on depth of response. These patterns were consistent between treatment groups. Subgroups based on baseline ECOG performance status were very imbalanced in size, precluding meaningful conclusions.

Assessments after Cycle 8

Following Cycle 8, patients in the Vd group did not receive further study treatment and PROs were not collected. Patients in the D-Vd group received treatment with daratumumab alone and reported HRQoL improvements from baseline, with a trend for higher mean GHS, pain and VAS scores at subsequent treatment cycles (Fig 3). Improvements in these scores were observed at every assessment time point from Cycle 9 to Cycle 48. Improvements were clinically meaningful at Cycle 14 for GHS score, at 19 time points for pain score and at 14 time points for VAS score. The largest changes from baseline were 14·2, 19·4 and 12·9 points for GHS, pain and VAS scores, respectively.

Discussion

In the CASTOR study, changes in PROs from baseline to Cycle 8 in both treatment groups were not clinically meaningful, suggesting that baseline HRQoL was maintained over time. With few exceptions, differences between treatment groups were not statistically significant. Although there were a few instances when a greater proportion of patients in the Vd group than the D-Vd group achieved a clinically meaningful improvement in fatigue, pain or sleep disturbance scores, the mean changes for each treatment group were not clinically meaningful for any scales at any time through Cycle 8. Not surprisingly, younger patients and those with better baseline ECOG performance status experienced greater improvements (or less worsening) of PROs. Although no clear pattern emerged regarding PROs by depth of response, previous studies have found better HRQoL in patients with deeper responses.[9,29,30] PRO data were also collected in the D-Vd group beyond Cycle 8 and revealed HRQoL improvements from baseline to Cycle 49.

Overall, baseline EORTC QLQ-C30 scores were worse than those of a non-cancer population,[31] reflective of the impaired HRQoL typical of patients with MM. Emotional and cognitive functioning scores were similar to those of non-cancer patients. Interestingly, baseline scores for the EORTC QLQ-C30 scales were better in patients from the CASTOR study than in a reference population of patients with MM[32]; this is consistent with a pooled analysis of six randomised controlled trials, which found that HRQoL was generally better among patients with RRMM than those with newly diagnosed MM.[5]

Between-group differences in mean change for patients who stayed on treatment were not significant for GHS, functioning or symptom scores during this period, unlike clinical outcomes (PFS, overall response rate and rates of ≥CR), which were significantly better in D-Vd *versus* Vd.[23] The lack of significant between-group differences in PROs may be due

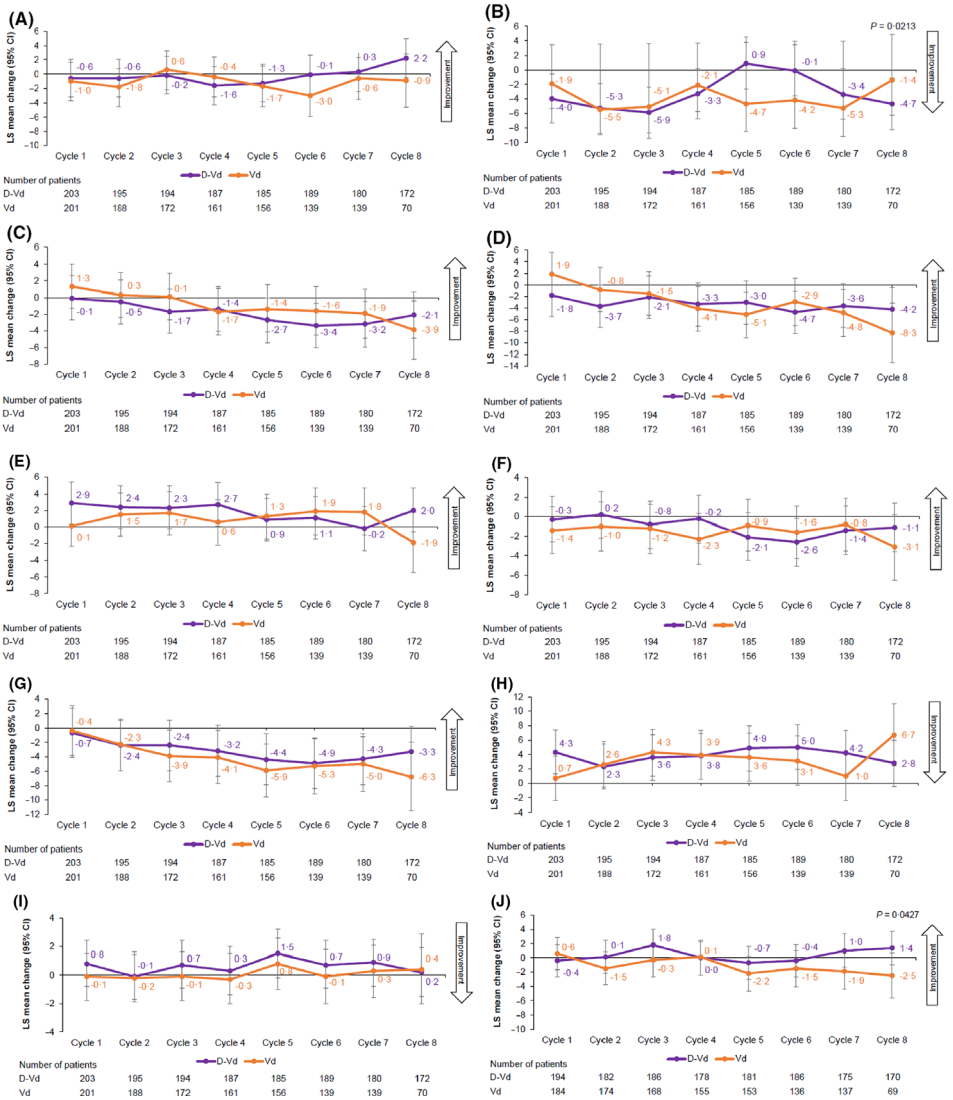

Fig 1. Least squares (LS) mean change from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item. (A) Global health status, (B) pain, (C) physical functioning, (D) role functioning, (E) emotional functioning, (F) cognitive functioning, (G) social functioning, (H) fatigue, (I) nausea and vomiting and (J) EuroQol 5-dimensional descriptive system visual analogue scale scores through Cycle 8. CI, confidence interval; D-Vd, daratumumab, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

in part to the benefits conferred by bortezomib treatment. Patients in both groups received bortezomib as study treatment and about 65% of patients had received bortezomib previously[24]; therefore, it is possible that there was little additional room for HRQoL improvement from the addition of daratumumab. Furthermore, this was an on-treatment analysis and a greater proportion of patients in the D-Vd group than the Vd group remained on treatment.

In the D-Vd group, PRO assessments were conducted beyond Cycle 8 and showed improvements from baseline in GHS, pain and VAS scores. This delay in HRQoL improvements may be due to a response shift (i.e., a change in patients' expectations after prolonged experience with a disease[4,5]). Additionally, less frequent clinic visits following the discontinuation of bortezomib may have resulted in improvements in patients' moods, which then translated into better PROs. Furthermore, while clinical responses may have been rapid, organ and skeletal recovery may take much longer; once this recovery occurred, it is reasonable to assume that PROs would also improve. Reduced toxicity following discontinuation of dexamethasone may also have had an impact on HRQoL. Finally, unlike bortezomib, side effects with daratumumab tend not to be cumulative, meaning that side effects from long-term treatment with daratumumab are likely to have remained consistent and did not worsen over time.

PROs are an increasingly important metric for evaluating MM treatment, but are inconsistently and sub-optimally reported; drawing conclusions is often impossible because of

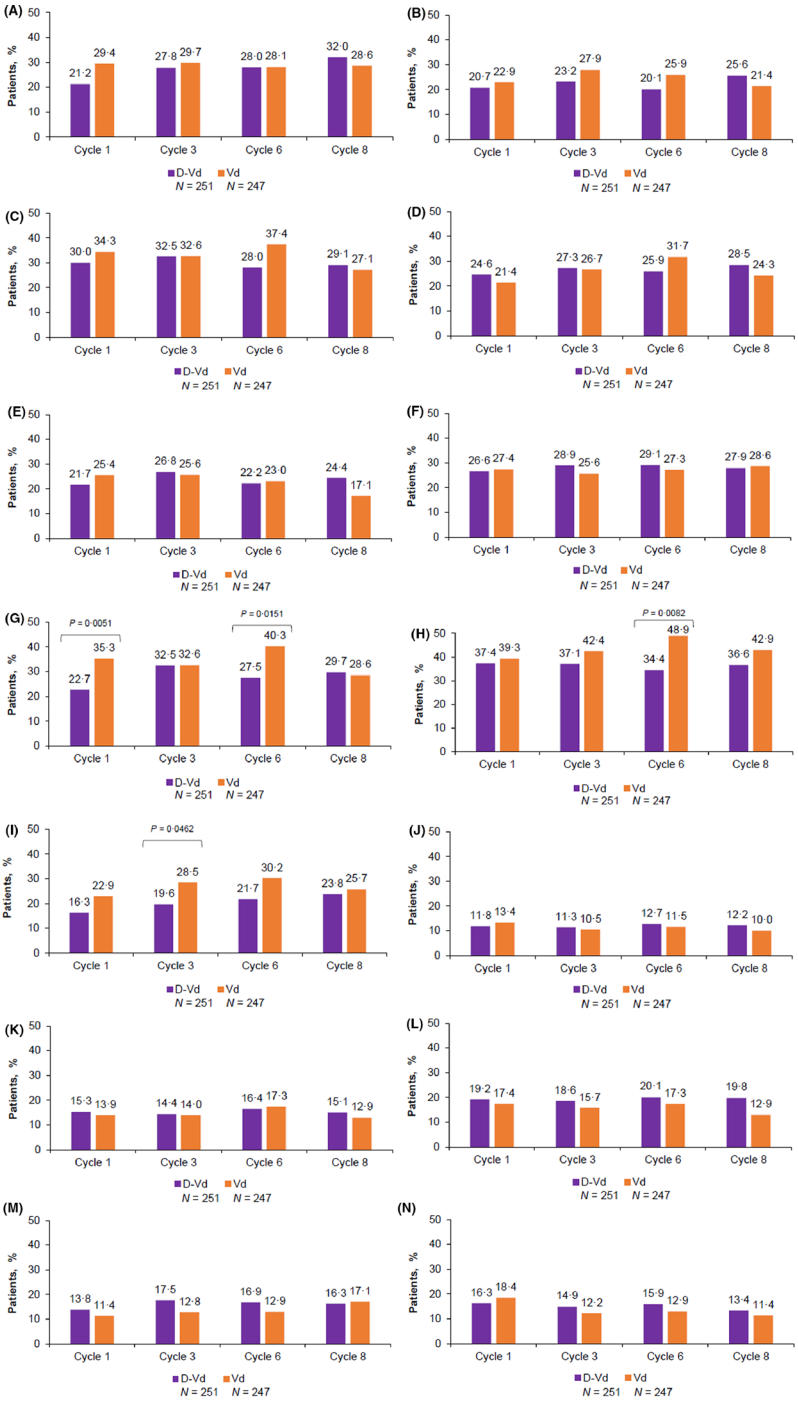

Fig 2. Proportion of patients with ≥10-point improvement from baseline in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item. (A) Global health status, (B) physical functioning, (C) role functioning, (D) emotional functioning, (E) cognitive functioning, (F) social functioning, (G) fatigue, (H) pain, (I) sleep disturbance, (J) nausea and vomiting, (K) dyspnoea, (L) appetite loss, (M) constipation and (N) diarrhoea scores through Cycle 8. D-Vd, daratumumab, bortezomib and dexamethasone; Vd, bortezomib and dexamethasone.

the limited information reported.[13] There are few published studies regarding the impact of Vd-based regimens on HRQoL in patients with RRMM. In general, rather than improvement, these studies have found no change from baseline HRQoL. The HRQoL results from the D-Vd arm of the CASTOR study represent the longest follow-up period in patients with RRMM.

The OPTIMISMM study compared pomalidomide + Vd (P-Vd) *versus* Vd alone.[8] Overall, HRQoL remained unchanged from baseline in both groups through 26 cycles. Mean changes from baseline in GHS, physical functioning and fatigue scores were similar between groups. Worsening of the GHS score was significantly greater with P-Vd than Vd at Cycles 5 and 9, but differences were not clinically meaningful. A similar proportion of patients in both groups experienced clinically meaningful worsening GHS scores. Over time, the proportion of patients with worsening physical functioning and fatigue scores decreased in the P-Vd

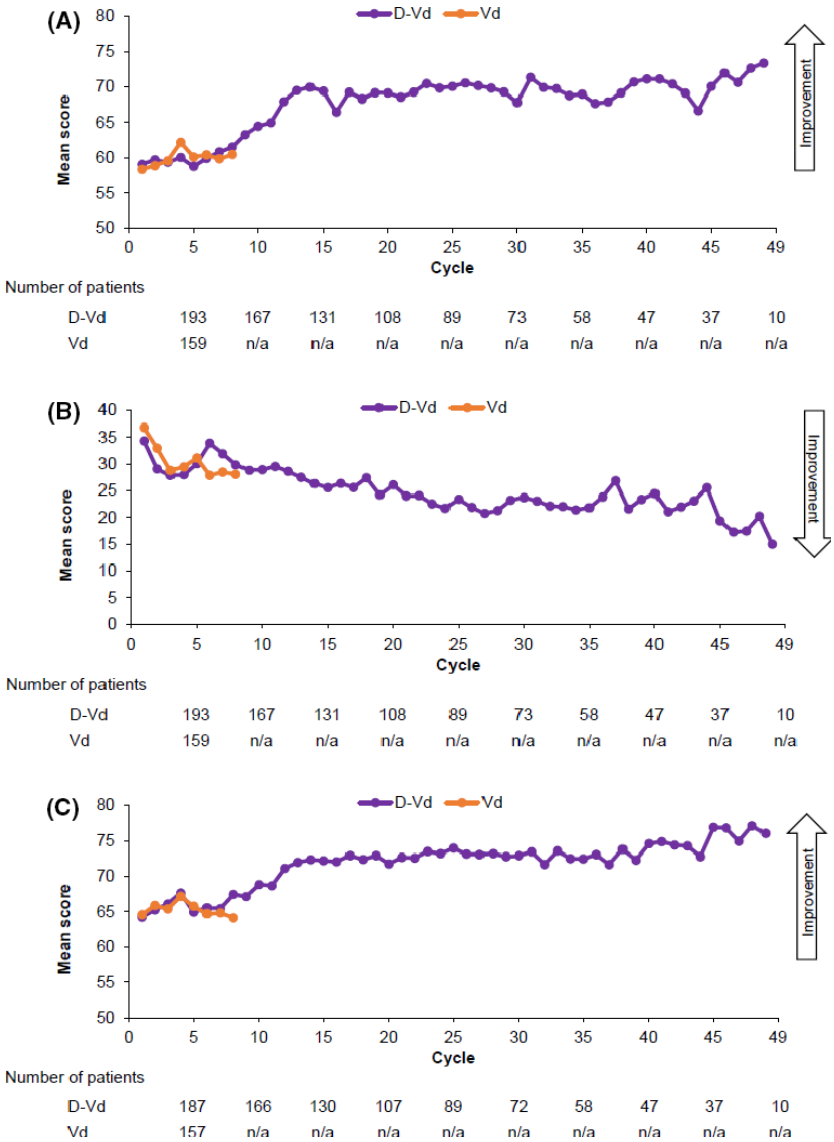

Fig 3. Mean scores over time for (A) European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30) global health status scale, (B) EORTC QLQ-C30 pain scale and (C) EuroQol 5-dimensional descriptive system visual analogue scale. D-Vd, daratumumab, bortezomib and dexamethasone; n/a, not available; Vd, bortezomib and dexamethasone.

group and increased in the Vd group. Richardson et al. reported on HRQoL from a subset of patients in the PANORAMA study who were treated with ≥2 prior lines of therapy.[7] Patients who received panobinostat + Vd experienced declines in GHS through Week 24, after which scores returned to levels similar to baseline; there were no differences in GHS score*versus* the Vd group at Week 48.

Several other studies have shed light on HRQoL in patients treated with bortezomib. The ENDEAVOR trial compared carfilzomib and dexamethasone (Kd) *versus* Vd.[12] Kd-treated patients experienced statistically significant improvements in GHS, pain and fatigue scores *versus* those treated with Vd; however, the differences were not clinically meaningful. There was an overall trend toward declining HRQoL in both groups over 72 weeks, with a longer time to GHS score worsening with Kd *versus* Vd. In the VISTA trial of bortezomib, melphalan and prednisone (VMP) *versus* MP in patients with transplant-ineligible newly diagnosed MM, transient decrements in HRQoL were observed with VMP during the early treatment cycles, and HRQoL was lower in these patients than in the MP group.[9] These findings were likely due to the toxicities associated with bortezomib. Despite these initial outcomes, HRQoL in the VMP group was generally improved from baseline and was comparable to that of the MP group at the end of treatment.

There are several limitations that should be considered when interpreting the current study results. PROs were evaluated as secondary endpoints and were not powered to detect differences between groups. Subgroup analyses by age, ECOG performance status and depth of response were post hoc. These analyses were done for patients who remained on treatment and the rates of discontinuation were higher with Vd than D-Vd. PROs beyond Cycle 8 were only assessed in the D-Vd group; it is unknown how PROs in the Vd group might have compared with those of the D-Vd group over the long-term. Finally, patients were aware of their treatment

assignment, which may have influenced their responses to HRQoL assessments, although only limited data in the literature suggest widespread open-label bias regarding PROs in the oncology setting.[33]

In patients with RRMM treated with D-Vd and Vd, HRQoL was unchanged from baseline, with no significant between-group differences for the first eight cycles of therapy. Following long-term daratumumab dosing, patients reported improvements in HRQoL, including GHS, pain and VAS scores. These PROs complement the significant clinical improvements observed with D-Vd treatment *versus* Vd treatment in the CASTOR study.

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Conflict of interest

VH served in a consulting or advisory role and on a speakers' bureau for AbbVie, Amgen, Celgene, Janssen, Takeda and Bristol-Myers Squibb. MB served in a consulting or advisory role and on a speakers' bureau for Amgen, Janssen and Takeda. KCW received honoraria from GlaxoSmithKline, Sanofi, Adaptive, Amgen, Bristol-Myers Squibb, Celgene, Janssen and Takeda; served in a consulting or advisory role for GlaxoSmithKline, Amgen, Adaptive, Bristol-Myers Squibb, Celgene, Janssen, Takeda, Sanofi and Juno; and received institutional research funding from Amgen, Celgene, Sanofi and Janssen. AN received honoraria from and served in a consulting or advisory role for Janssen, GlaxoSmithKline, Celgene, Amgen, Takeda, Spectrum, Bristol-Myers Squibb, Karyopharm, Oncopeptides and Adaptive; and received research funding from Janssen, GlaxoSmithKline, Celgene, Amgen, Takeda, Karyopharm and Bristol-Myers Squibb. MM received honoraria from Janssen, Bristol-Myers Squibb, Celgene and Amgen; served in a consulting or advisory role for Janssen, Bristol-Myers Squibb, Takeda, Celgene, Amgen and Heidelberg Pharma; received research funding from Incyte and Bristol-Myers Squibb; and had travel, accommodations or other expenses paid or reimbursed by Janssen, Bristol-Myers Squibb, Takeda, Celgene and Amgen. M-VM received honoraria from and served in a consulting or advisory role for Janssen, Celgene, Amgen, Takeda, GlaxoSmithKline, AbbVie, Seattle Genetics and Adaptive. TMM holds stock in AbbVie; received honoraria and research funding from Celgene; and served in a consulting or advisory role for Janssen, Takeda and Adaptive. MQ, XQ, JF, WG and KSG are employees of Janssen. AS received honoraria from Celgene, Janssen, Amgen, AbbVie, Servier and Takeda; served in a consulting or advisory role for Celgene, Janssen, Servier and AbbVie; and served on a speakers' bureau for and received institutional funding from Janssen, Takeda and Celgene. PS received honoraria and research funding from Amgen, Celgene, Janssen, SkylineDx and Takeda. IS and TM have no conflicts of interest to declare.

Author contributions

VH, MB, KCW, AKN, TM, IS, MM, M-VM, TMM, AS and PS contributed to the conception, design, collection and assembly of data and data analysis and interpretation; MQ, XQ, JF, WG, TR and KSG contributed to the conception and design and data analysis and interpretation. All authors drafted and reviewed the manuscript, approved the final version and vouch for data accuracy and completeness.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. PRO compliance rates from baseline through Cycle 8.

Table SII. Change from baseline in EORTC QLQ-C30 GHS, functioning and symptom scale scores and EQ-5D-5L VAS scores in subgroups by age, baseline ECOG performance status and depth of response.

References

1. Ramsenthaler C, Kane P, Gao W, Siegert RJ, Edmonds PM, Schey SA, et al. Prevalence of symptoms in patients with multiple myeloma: a systematic review and meta-analysis. *Eur J Haematol*. 2016;**97**(5):416–29.
2. Baz R, Lin HM, Hui AM, Harvey RD, Colson K, Gallop K, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on health-related quality of life. *Support Care Cancer*. 2015;**23**(9):2789–97.
3. Osborne TR, Ramsenthaler C, Siegert RJ, Edmonds PM, Schey SA, Higginson IJ. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur J Haematol*. 2012;**89**(6):437–57.
4. Nielsen LK, Stege C, Lissenberg-Witte B, van der Holt B, Mellqvist UH, Salomo M, et al. Health-related quality of life in transplant ineligible newly diagnosed multiple myeloma patients treated with either thalidomide or lenalidomide-based regimen until progression: a prospective, open-label, multicenter, randomized, phase 3 study. *Haematologica*. 2020;**105**(6):1650–9.
5. Robinson D Jr, Esseltine DL, Regnault A, Meunier J, Liu K, van de Velde H. The influence of baseline characteristics and disease stage on health-related quality of life in multiple myeloma: findings from six randomized controlled trials. *Br J Haematol*. 2016;**174**(3):368–81.
6. Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. *Haematologica*. 2015;**100**(6):826–33.

7. Richardson PG, Schlossman RL, Roy AN, Panneerselvam A, Acharyya S, Sopala M, et al. Patient-reported outcomes of multiple myeloma patients treated with panobinostat after ≥2 lines of therapy based on the international phase 3, randomized, double-blind, placebo-controlled PANORAMA-1 trial. *Br J Haematol*. 2018;**181**(5):628–36.
8. Weisel K, Dimopoulos M, Moreau P, Yagci M, Larocca A, Kanate AS, et al. Health-related quality-of-life results from the phase 3 OPTIMISMM study: pomalidomide, bortezomib, and low-dose dexamethasone versus bortezomib and low-dose dexamethasone in relapsed or refractory multiple myeloma. *Leuk Lymphoma*. 2020;**61**(8):1850–9.
9. Delforge M, Dhawan R, Robinson D Jr, Meunier J, Regnault A, Esseltine DL, et al. Health-related quality of life in elderly, newly diagnosed multiple myeloma patients treated with VMP vs. MP: results from the VISTA trial. *Eur J Haematol*. 2012;**89**(1):16–27.
10. Szabo AG, Iversen KF, Möller S, Plesner T. The clinical course of multiple myeloma in the era of novel agents: a retrospective, single-center, real-world study. *Clin Hematol Int*. 2019;**1**(14):220–8.
11. Jordan K, Proskorovsky I, Lewis P, Ishak J, Payne K, Lordan N, et al. Effect of general symptom level, specific adverse events, treatment patterns, and patient characteristics on health-related quality of life in patients with multiple myeloma: results of a European, multicenter cohort study. *Support Care Cancer*. 2014;**22**(2):417–26.
12. Ludwig H, Moreau P, Dimopoulos MA, Mateos MV, Kaiser M, Hajek R, et al. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. *Blood Cancer J*. 2019;**9**(3):23.
13. LeBlanc MR, Hirschey R, Leak Bryant A, LeBlanc TW, Smith SK. How are patient-reported outcomes and symptoms being measured in adults with relapsed/refractory multiple myeloma? A systematic review. *Qual Life Res*. 2020;**29**(6):1419–31.
14. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol*. 2014;**32**(6):587–600.
15. de Weers M, Tai YT, van der Veer MS, Bakker JM, Vink T, Jacobs DC, et al. Daratumumab, a novel therapeutic human CD38 monoclonal antibody, induces killing of multiple myeloma and other hematological tumors. *J Immunol*. 2011;**186**(3):1840–8.
16. Lammerts van Bueren J, Jakobs D, Kaldenhoven N, Roza M, Hiddingh S, Meesters J, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood*. 2014;**124**(21):3474.
17. Overdijk MB, Jansen JH, Nederend M, Lammerts van Bueren JJ, Groen RW, Parren PW, et al. The therapeutic CD38 monoclonal antibody daratumumab induces programmed cell death via Fcγ receptor-mediated cross-linking. *J Immunol*. 2016;**197**(3):807–13.
18. Overdijk MB, Verploegen S, Bogels M, van Egmond M, Lammerts van Bueren JJ, Mutis T, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. *MAbs*. 2015;**7**(2):311–21.
19. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. *Blood*. 2016;**128**(3):384–94.
20. Chiu C, Casneuf T, Axel A, Lysaght A, Bald J, Khokhar NZ, et al. Daratumumab in combination with lenalidomide plus dexamethasone induces clonality increase and T-cell expansion: results from a phase 3 randomized study (POLLUX). *Blood*. 2016;**128**(22):4531.
21. Adams HC 3rd, Stevenaert F, Krejcik J, Van der Borght K, Smets T, Bald J, et al. High-parameter mass cytometry evaluation of relapsed/refractory multiple myeloma patients treated with daratumumab demonstrates immune modulation as a novel mechanism of action. *Cytometry A*. 2019;**95**(3):279–89.
22. Janssen Biotech, Inc. DARZALEX® (daratumumab) injection, for intravenous use [prescribing information]. Horsham, PA 2019.
23. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;**375**(8):754–66.
24. Spencer A, Lentzsch S, Weisel K, Avet-Loiseau H, Mark TM, Spicka I, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. *Haematologica*. 2018;**103**(12):2079–87.
25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;**85**(5):365–76.
26. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;**20**(10):1727–36.
27. Kvam AK, Fayers PM, Wisloff F. Responsiveness and minimal important score differences in quality-of-life questionnaires: a comparison of the EORTC QLQ-C30 cancer-specific questionnaire to the generic utility questionnaires EQ-5D and 15D in patients with multiple myeloma. *Eur J Haematol*. 2011;**87**(4):330–7.
28. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;**5**:70.
29. Seitzler S, Finley-Oliver E, Simonelli C, Baz R. Quality of life in multiple myeloma: considerations and recommendations. *Expert Rev Hematol*. 2019;**12**(6):419–24.
30. Dimopoulos MA, Palumbo A, Hajek R, Kropff M, Petrucci MT, Lewis P, et al. Factors that influence health-related quality of life in newly diagnosed patients with multiple myeloma aged ≥65 years treated with melphalan, prednisone and lenalidomide followed by lenalidomide maintenance: results of a randomized trial. *Leuk Lymphoma*. 2014;**55**(7):1489–97.
31. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. *Eur J Cancer*. 2019;**107**:153–63.
32. Scott NW, Fayers PM, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, et al. EORTC QLQ-C30 reference values. EORTC Quality of Life Group; 2008 [cited July 2008]. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf.
33. Roydhouse JK, Fiero MH, Kluetz PG. Investigating potential bias in patient-reported outcomes in open-label cancer trials. *JAMA Oncol*. 2019;**5**(4):457–8.