Open access • Journal Article • DOI:10.1080/10428194.2020.1747066

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. — Source link

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Published on: 09 Apr 2020 - Leukemia & Lymphoma (Taylor & Francis)

Topics: Pomalidomide, Bortezomib, Lenalidomide, Multiple myeloma and Progression-free survival

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

Running head: HRQoL of PVd in Patients With RRMM

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Abstract

In the randomized phase 3 OPTIMISMM study, the addition of pomalidomide to bortezomib and low-dose dexamethasone (PVd) resulted in significant improvement in progression-free survival (PFS) in lenalidomide-pretreated patients with relapsed or refractory multiple myeloma (RRMM), including lenalidomide refractory patients. Here we report health-related quality of life (HRQoL) results from this trial. Patients received PVd or Vd in 21-day cycles until disease progression or discontinuation. HRQoL was assessed using the EORTC QLQ-C30, QLQ-MY20, and EQ-5D-3L instruments on day 1 of each treatment cycle. Mean score changes for global QoL, physical functioning, fatigue, side effects of treatment domains, and EQ-5D-3L index, were generally stable over time across treatment arms. Proportion of patients who experienced clinically meaningful worsening in global QoL and other domains of interest were similar. These HRQoL results with PVd along with previously demonstrated improvement in PFS vs Vd continue to support its use in patients with RRMM.

Key Words (3-6 allowed): quality of life; HRQoL; multiple myeloma; pomalidomide; bortezomib; dexamethasone

Abstract word count: 148/150

Table/figure count (6 max): 4 tables/3 figures

Word count: 3291/3500

Target journal: *Leukemia & Lymphoma*

Research Availability of Data and Materials

Celgene is committed to responsible and transparent sharing of clinical trial data with patients, healthcare practitioners, and independent researchers in order to both improve scientific and medical knowledge as well as to foster innovative treatment approaches. Researchers interested in obtaining access to documents and/or data can make their requests on the Celgene portal at: https://www.vivli.org.

Introduction

The global incidence of multiple myeloma (MM) increased by an estimated 126% between 1990 and 2016 [1]. In 2016, MM was responsible for nearly 100,000 deaths worldwide with an age-adjusted standardized death rate of 1.5 per 100,000 persons. MM is characterized by hyperproliferation of malignant plasma cells in the bone marrow and immune dysfunction [2,3] The natural course of MM is one of relapse and remittance [4,5]. With each subsequent relapse, patient prognosis and quality of life (QoL) worsen [6-8]. Moreover, the burden of illness in MM is high. Complications include hypercalcemia, renal impairment, anemia, and lytic bone lesions, which affect approximately 13%, 20% to 40%, 70%, and 80% of patients with MM, respectively [9].

Given the burden of disease, it is not surprising that patients with MM have a lower health-related QoL (HRQoL) compared with normative populations [10]. In assessing HRQoL up to 10 years after diagnosis of MM, Mols et al. found that the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 subscales for QoL, dyspnea, and physical, role, and social functioning were most affected, irrespective of time since diagnosis [10]. Gulbrandsen et al. also found that patients with MM have worse HRQoL than the general population [11], with more pain and fatigue, reduced physical and role functioning, and worse overall QoL. Although QoL scores appeared to improve with treatment, patients continued to experience reduced physical and role functioning after 3 years of therapy.

Management of relapsed or refractory MM (RRMM) necessitates multiple lines of therapy [4,12]. Evidence shows that with each additional line of therapy, disease resistance increases, resulting in reduced treatment response, immune system impairment, and worsened HRQoL

[4,6,13-15]. As with most cancer treatments, anti-myeloma treatment regimens aim to achieve maximum response and enhance survival while improving or maintaining HRQoL and minimizing treatment-related toxicity and patient discomfort [16,17].

Lenalidomide is a standard of care in patients with newly diagnosed MM who are transplant-eligible [18,19] or transplant-ineligible [20–22]. In the post–autologous stem cell transplant settings, lenalidomide monotherapy is the only approved treatment [22–26]. Moreover, continuous therapy with lenalidomide until disease progression is now standard practice based on improved survival outcomes demonstrated in randomized phase 3 clinical trials [20,21]. As a result, most patients in current clinical practice will become refractory to lenalidomide in early lines of treatment [27]. Until OPTIMISMM, phase 3 clinical data regarding subsequent treatment regimens in this patient population were lacking [24,28,29].

OPTIMISMM was the first phase 3 trial to prospectively evaluate a triplet regiment in early RRMM (median of 2 prior lines of therapy) and to demonstrate improved efficacy in patients who were all lenalidomide pretreated and a majority of whom were lenalidomide refractory (70%). In this trial, PVd significantly reduced the risk of disease progression or death by 39% (median PFS 11.2 vs 7.1 months [hazard ratio 0.61, 95% CI 0.49-0.77, $P < .0001$]) and led to a significantly higher overall response rate (82.2% vs 50.0%) compared with Vd [30]. The safety of PVd was consistent with the known profile of each component.

The objective of this analysis was to evaluate the effect of PVd versus Vd on HRQoL in patients with RRMM who had previously been treated with lenalidomide. Specifically, this analysis sought to address whether adding pomalidomide to Vd would maintain the same HRQoL as that achieved with Vd alone.

Methods

Study Design and Data Source

The OPTIMISMM study was a phase 3, multicenter, randomized, open-label, active-controlled trial that compared PVd with Vd in patients with RRMM. Details of the study design and

primary results, have been previously described [30]. Key enrolment and treatment information is outlined below.

The study enrolled adult patients with RRMM who had received 1 to 3 prior anti-myeloma regimens and had previously been treated with a lenalidomide-containing regimen. Patients were randomly assigned to receive PVd (n = 281) or Vd (n = 278) in 21-day treatment cycles until disease progression or treatment discontinuation. In cycles 1 to 8, bortezomib (1.3 mg/m^2) was administered intravenously or subcutaneously on days 1, 4, 8, and 11, and oral dexamethasone (20 mg/day for patients aged ≤ 75 years, 10 mg/day for patients > 75 years) was administered on days 1, 2, 4, 5, 8, 9, 11, and 12. From cycles 9 on, bortezomib was administered on days 1 and 8, and oral dexamethasone was administered on days 1, 2, 8, and 9. Patients in the PVd group additionally received oral pomalidomide (4 mg/day) on days 1 to 14 of each 21-day cycle.

Outcomes of Interest

HRQoL was assessed using the EORTC QLQ-C30 and MM module (QLQ-MY20) and the EQ-5D-3L instrument on day 1 of each 21-day cycle (before treatment administration) and at the end-of-treatment visit.

The QLQ-C30 and QLQ-MY20 scales range from 1 to 100. For QLQ-C30, a higher score for the global QoL or functional domains indicates better functioning or health status. For QLQ-MY20, a higher score for disease symptoms and side effects of treatment indicates worsening symptoms or adverse events.

The primary domain of interest was the global health status/QoL domain of the QLQ-C30. Secondary domains of interest included the physical functioning, pain, and fatigue domains of the QLQ-C30; disease symptoms and side effects of treatment domains of the QLQ-MY20; and health utility index of the EQ-5D-3L. Exploratory domains of interest included the remaining QLQ-C30 and QLQ-MY20 domains. Results from the exploratory analyses are provided in **Table S2** and **Figure S3**.

For the QLQ-C30 and QLQ-MY20, an improvement of ≥ 10 points was used to define a responder [31]. To facilitate interpretation of the results, mean QLQ-C30 scores from an international study of 15,386 individuals from the general population were used as a reference [32]. A deterioration of ≥ 0.10 points from baseline was used as the cutoff value for the EQ-5D-3L health utility index [33].

Statistical Analysis

Data from the OPTIMISMM study obtained up to October 26, 2017 were used for the present HRQoL analyses. All statistical analyses were performed using SAS version 9.4 or higher. A detailed HRQoL analysis plan was signed on January 25, 2018, before the study database lock.

Adherence rates for completion of the HRQoL assessments were assessed at each visit. For QLQ-C30 and QLQ-MY20, adherence was defined as completion of ≥ 50% of the items. For the EQ-5D-3L, adherence was defined as completion of the 5 dimensions. A 2-sided Fisher exact test was used to compare the proportion of adherent patients at each visit between treatment groups.

The intent-to-treat (ITT) population comprised all patients randomized in the study. The primary analyses of HRQoL data were based on the HRQoL-evaluable population: all randomized patients who completed the QLQ-C30 at baseline and ≥ 1 post-baseline assessment. Descriptive statistics for baseline scores for each HRQoL domain, key demographics, and disease characteristics were summarized for each treatment group based on the HRQoL-evaluable population. Changes in HRQoL scores from baseline at each post-baseline visit were also summarized descriptively for each treatment (cross-sectional analysis). A 2-sample *t* test was used to compare treatment groups.

As a post hoc analysis of the HRQoL-evaluable population, area under the curve (AUC) for change from baseline was calculated for each QLQ-C30 and QLQ-MY20 domain using the trapezoidal rule, with adjustment for time between baseline and each patient's last visit. Descriptive statistics were calculated. There was no imputation for missing intermittent assessments when calculating the AUC. Differences in AUCs between treatment groups were

assessed by analysis of covariance with adjustment for randomization strata. The least-square (LS) mean treatment group difference (PVd − Vd) and corresponding 95% CI were calculated. Hedges *g* effect size and corresponding 95% CI were also calculated.

A mixed-model repeated measure (MMRM) analysis was used to estimate the treatment effects over time for each QLQ-C30 and QLQ-MY20 domain (longitudinal analysis) and the EQ-5D-3L health utility index and to assess the differences in treatment effects between groups. Within-group and between-group differences were assessed at each visit by calculating the LS mean change from baseline and 95% CI.

Instrument scoring and missing items were handled in accordance with the developer's instructions [34,35]. Missing domain scores for a given assessment visit were not imputed in the primary HRQoL analyses. However, post hoc analyses were conducted to investigate missing data/dropout patterns and examine whether imputation of missing data using pattern-mixture models altered the findings of the primary analyses.

For each QLQ-C30 and QLQ-MY20 domain and the EQ-5D-3L health utility index, the proportion of HRQoL-evaluable patients with a clinically meaningful change was calculated based on change from baseline score at day 1 of cycles 5, 9, 19, and 25. Cumulative distribution function curves for patients experiencing different degrees of change in global QoL at day 1 of cycles 5, 9, 19, and 25 were generated for each treatment group. The proportions of patients experiencing a clinically meaningful change were compared between treatment groups using the Cochran-Mantel-Haenszel test with modified ridit scores [36]. Adjusted odds ratios and 95% CIs were calculated. For each Cochran-Mantel-Haenszel analysis, the Breslow-Day test was used to assess the homogeneity of the odds ratios within each stratification level [37,38].

Results

Patients

The ITT population consisted of 559 patients: 281 (50.3%) in the PVd group and 278 (49.7%) in the Vd group (**Figure 1**). Of these patients, 15% did not have a QLQ-C30 assessment at the baseline visit (cycle 1 day 1), and 14% had no assessments at subsequent visits. Overall,

approximately 20% of the ITT population was excluded from the primary HRQoL analyses, as they did not meet the inclusion criteria for the HRQoL, resulting in an evaluable population of 240 patients (85.4%) from the PVd group and 209 patients (75.2%) from the Vd group.

Baseline demographics and clinical characteristics for the HRQoL-evaluable population are provided in **Table 1**. Most patients were ≤ 75 years old (84.2%) and had an ECOG PS of 0-1 (96.0%); 69.9% of patients were refractory to lenalidomide, and 76.2% of patients had received 1 or 2 prior anti-myeloma regimens. Baseline characteristics were similar for both treatment groups. Key differences in baseline characteristics between the HRQoL-evaluable and -nonevaluable populations are listed in the **Supplemental Results**.

Adherence rates are provided in **Figure S1**. When the number of eligible patients at each given visit was used as the denominator, adherence rates in the PVd group were high (≥ 80%) at all assessment visits except the end-of-treatment visit (**Figure S1A**). Adherence rates in the Vd group were high (≥ 80%) until cycle 20. Adherence rates were generally lower in the Vd group than in the PVd group and were significantly lower ($P < .05$) at cycles 1, 2, and 27. Only approximately half of patients in both groups completed the QLQ-C30 at the end-of-treatment visit.

HRQoL at Baseline

HRQoL scores at baseline are presented in **Table 2**. Mean (SD) baseline scores for the global QoL domain of the QLQ-C30 were similar in the 2 treatment groups: 61.0 (23.2) for the PVd group and 63.5 (21.3) for the Vd group.

Compared with an age- and gender-matched general reference population, patients in this study had worse HRQoL scores across most domains (**Table 2**), indicating that HRQoL was impaired at baseline [32]. Generally, patients in the PVd group had worse mean baseline scores for the QLQ-C30 and QLQ-MY20 domains and EQ-5D-3L than the Vd group. However, the differences were not clinically meaningful.

Treatment Effects on HRQoL

Global Health Status, Function Domains, and Symptom Domains

Mean changes in the QLQ-C30 global QoL domain were similar between treatment groups across all scheduled visits (**Figure 2A**). In the PVd group, the global QoL score showed a slight decrease during the first few cycles of treatment.

Mean changes from baseline for the secondary domains of interest are provided in **Figure 2 (B-G)**. The physical functioning, fatigue, and side effects of treatment domains exhibited similar trends in changes in scores from baseline, with small, non–clinically meaningful worsening during the first few cycles of treatment. For these domains, no significant differences between treatment groups were observed at any assessment visit. For the QLQ-MY20 disease symptoms domain, scores in both treatment groups showed trends of improvement over time; no statistically significant differences between treatment groups were observed. The EQ-5D-3L health utility index score was also maintained for the duration of the treatment period for both groups.

MMRM analyses showed statistically significant worsening in the LS mean QLQ-C30 global QoL domain score in patients in the PVd group compared with the Vd group at cycle 5 (difference = −2.883; P = .0219) and cycle 9 (difference = −2.914; P = .0272) (**Figure 3A**). However, these differences were not clinically meaningful. After imputing missing data using a pattern-mixture model, the differences between treatment groups in LS mean changes from baseline were reduced and were not statistically significant at any assessment visit (**Figure 3B**).

For the secondary domains of interest, results from the MMRM analysis were similar to those observed from the cross-sectional analysis (**Figure 3C**). There were no significant or clinically meaningful differences in the LS mean changes from baseline between treatment groups (**Figure 3C**). For most secondary domains of interest, the differences between treatment groups were smaller when missing data were imputed (**Figure 3D**).

AUC Analysis

For the emotional functioning domain of the QLQ-C30, the adjusted LS mean AUC (95% CI) was −2.4 (−4.07 to −0.75) with PVd and 0.2 (−1.73 to 2.15) with Vd (P = .039) (**Table 3**). The effect size (Hedges g) was −0.20 (95% CI, −0.39 to −0.01), suggesting a "small" effect size. None of the other QLQ-C30 or QLQ-MY20 domains showed a treatment difference that was statistically significant or clinically meaningful.

Clinically Meaningful Change

The proportion of patients who experienced clinically meaningful worsening of the global QoL score was similar for both treatment groups: 23.9% to 33.0% with PVd and 28.8% to 50.0% with Vd (P > .05 for all cycles) (**Table 4**). The cumulative distribution function plots (**Appendix Figure 2**) show that use of different cutoffs for the definition of clinically meaningful worsening did not alter the results.

For the secondary domains of interest, the proportion of patients who experienced clinically meaningful worsening showed no significant differences between treatment groups across all assessment visits (**Table 4**). The proportion of patients experiencing clinically meaningful worsening generally decreased over time in the PVd group but increased over time in the Vd group.

Discussion

Impaired HRQoL profoundly affects patients with RRMM. Considering changes to treatment regimens with the addition of novel agents and a move toward continuous therapy [39,40], this analysis assessed whether the addition of pomalidomide to the Vd combination would maintain the same HRQoL as that achieved with Vd alone in patients with RRMM treated previously with lenalidomide, including those refractory to lenalidomide after first- or early-line treatment. Overall, the results indicate that the addition of pomalidomide to Vd did not decrease HRQoL in this patient population. HRQoL was maintained over time in both the Vd and PVd treatment groups as measured with the QLQ-C30, QLQ-MY20, and EQ-5D-3L.

Consistent with previous reports from other clinical trials, HRQoL in patients from the OPTIMISMM study was lower at baseline compared with the general population [11,12,32,40,41]. This is expected since patients with RRMM experience symptoms each time their disease progresses [15]. Thus, patients are likely to have diminished HRQoL before treatment for relapsed or refractory disease begins [42].

No difference in clinically meaningful worsening of symptoms between treatment groups was observed during the study. However, non–clinically meaningful worsening in scores for the global QoL, physical functioning, role functioning, social functioning, fatigue, and side effects of treatment domains was observed during the first few cycles of treatment. This observation may be related to the safety profiles of the treatment regimens. Twice-weekly bortezomib dosing during the first 8 treatment cycles may have also attributed to these results. Similar trends were reported in both the VISTA and TOURMALINE-MM1 studies [40, 43]. However, VISTA was not designed to assess HRQoL differences between patients who received bortezomib once versus twice weekly and in TOURMALINE-MM1, an initial slight HRQoL worsening consistent with the toxicity profile of the investigational drugs was observed. Although an initial decline in HRQoL may have resulted from the incremental toxicity of adding pomalidomide to Vd, the subsequent improvement in HRQoL is likely the result of improved PFS with the PVd regimen. Furthermore, the observed differences became smaller when missing data were imputed in a post hoc analysis, suggesting that the difference between treatment groups in the primary analysis may have been overestimated. Typically, between-group improvements are not observed when comparing triple-therapy regimens with double-therapy combinations [40,41]. The results presented in this study indicate that the addition of pomalidomide to Vd did not adversely affect HRQoL.

It is important that treatment regimens delay relapse or progression and prolong survival while maintaining or improving HRQoL [16,17]. However, no proven treatment strategy exists to manage RRMM in patients who have previously received lenalidomide and have experienced relapse [27]. Although the availability of several agents with unique modes of action has given clinicians multiple options for managing RRMM, selecting the right class or combination of agents to achieve optimal efficacy is complex and challenging. Moreover, selecting the best

treatment regimen for specific subgroups of patients with RRMM (eg, those with high-risk cytogenetics) is made more challenging by the lack of clarity in current treatment approaches [5].

Pomalidomide has demonstrated improved efficacy when combined with Vd, and the results from this analysis show that the addition of pomalidomide to the Vd combination maintains the HRQoL of patients with RRMM, including those who were refractory to lenalidomide in early lines of therapy. Notably, while maintaining HRQoL, PVd increased PFS in the OPTIMISMM study [30]. This is important because MM disease progression is associated with deterioration of HRQoL. An appropriate treatment for RRMM should achieve improved disease control while maintaining HRQoL.

The present study has certain limitations that may affect interpretation of the results. OPTIMISMM was an open-label study which may have influenced the HRQoL scores. In addition, approximately 15% of patients in the PVd group and 25% of patients in the Vd group were excluded from the HRQoL-evaluable population due to missing data. Excluded patients were sicker and had poor treatment outcomes, indicating that the primary analysis population for HRQoL (the HRQoL-evaluable population) may not have been representative of the overall OPTIMISMM study population (**Table S1**). The exclusions likely biased the results against the PVd treatment group, because patients excluded from the Vd group had worse treatment outcomes than patients excluded from the PVd group. To address these concerns, a post hoc sensitivity analysis was performed using pattern-mixture models to impute missing HRQoL data. Observed differences in HRQoL between treatment groups became smaller as a result of this imputation. Finally, across all assessment time points, fewer patients in the Vd treatment group than the PVd group were considered in the analyses based on the HRQoL-evaluable population. This could have been due to disease progression, and these patients were likely to be sicker and with a suboptimal response to treatment. The slight worsening of the global QoL score in the PVd group during the first few cycles of treatment may have been confounded by this.

In summary, these data add valuable insight regarding HRQoL with PVd and complement the previously reported results on the efficacy and safety of this regimen [30]. It is important to consider that any potential survival benefits should be weighed against the overall burden of

treatment with respect to HRQoL. The results presented here indicate that addition of pomalidomide to Vd maintained HRQoL across all subgroups of patients with RRMM, suggesting that a longer progression-free interval can be achieved without compromising HRQoL. These results may be worth considering when making MM treatment decisions, as they may allow for individualization of the patient experience and help patients maintain HRQoL while achieving prolonged survival and a longer progression-free interval.

Disclosure of Interest

KW: advisory board for and honoraria from Amgen, Adaptive Biotech, Celgene, Bristol-Myers Squibb, Janssen, Juno, Takeda, Sanofi and research funding from Amgen, Celgene, Sanofi, Janssen; MD: honoraria, consulting fees, and lecture fees from Celgene, Amgen, Takeda; PM: personal fees from Celgene, Janssen; MY: nothing to disclose; AL: honoraria and personal fees from Amgen, honoraria, advisory board, and personal fees from Bristol-Myers Squibb, Celgene, Janssen, and advisory board for Takeda; ASK: nothing to disclose; FV: nothing to disclose; NC: nothing to disclose; SB: nothing to disclose; PJ: nothing to disclose; PB: stock ownership in Merck, Bristol Myers Squibb, Pfizer, Teva, Johnson & Johnson and honoraria from Merck, Astra Zeneca, Celgene; MH: nothing to disclose; PRO: personal fees, lectures, and advisory boards for Celgene, Janssen and personal fees and advisory boards for Kite Pharma, Abbvie, Sanofi; EM: nothing to disclose; PA: nothing to disclose; PH: nothing to disclose; MTK: consultancy for and honoraria from Amgen, Bristol-Myers Squibb, Celgene, Takeda, Novartis, and Janssen; PL: advisory board for and honoraria from Amgen, Celgene, Janssen, Takeda, Sanofi; DBY: nothing to disclose; LM: nothing to disclose; SG: consulting fees from Celgene; XY: employee for and salary/compensation from Celgene; LG: employment with Celgene; TB: employment and equity ownership in Celgene International Sarl, Boundary, Switzerland; SD: employment and equity ownership in Celgene; PR: grants from Bristol Myer Squibb, grants and personal fees from Oncopeptides, Celgene, Takeda, and personal fees from Karyopharm, Amgen, Janssen, Sanofi.

Role of the Funding Source

This work was supported by Celgene Corporation.

Acknowledgements

- The authors thank the patients and their families, as well as all participating clinical investigators
- Medical writing support was provided by Nora Tu, PharmD, and Stephen Gilliver, PhD, of Evidera and was funded by Celgene Corporation.

References

1. Cowan AJ, Allen C, Barac A, et al. Global burden of multiple myeloma: a systematic analysis for the Global Burden of Disease Study 2016. JAMA Oncol. 2018;4:1221–1227.
2. Bianchi G, Munshi NC. Pathogenesis beyond the cancer clone(s) in multiple myeloma. Blood. 2015;125:3049-3058.
3. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364:1046-1060.
4. Terpos E, Suzan F, Goldschmidt H. Going the distance: Are we losing patients along the multiple myeloma treatment pathway? Crit Rev Oncol Hematol. 2018;126:19–23.
5. Cook G, Zweegman S, Mateos MV, et al. A question of class: treatment options for patients with relapsed and/or refractory multiple myeloma. Crit Rev Oncol Hematol. 2018;121:74–89.
6. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc. 2004;79:867–874.
7. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicentre international myeloma working group study. Leukemia. 2012;26:149-157.
8. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol. 2016;175:252-264
9. Eslick R, Talaulikar D. Multiple myeloma: from diagnosis to treatment. Aust Fam Physician. 2013;42:684–688.
10. Mols F, Oerlemans S, Vos AH, et al. Health-related quality of life and disease-specific complaints among multiple myeloma patients up to 10 yr after diagnosis: results from a population-based study using the PROFILES registry. Eur J Haematol. 2012;89:311–319.
11. Gulbrandsen N, Hjermstad MJ, Wisløff F, et al. Interpretation of quality of life scores in multiple myeloma by comparison with a reference population and assessment of the clinical importance of score differences. Eur J Haematol. 2004;72:172–180.
12. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. Leukemia. 2016;30:1005–1017.
13. Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis. 2009;49:1211–1225.

14. Rajkumar SV, Kumar S. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc. 2016;91:101–119.
15. Despiégel N, Touboul C, Flinois A, et al. Health-related quality of life of patients with multiple myeloma treated in routine clinical practice in France. Clin Lymphoma Myeloma Leuk. 2019;19:e13–e28.
16. San Miguel JF, Mateos MV. Advances in treatment for newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation. Leuk Suppl. 2013;2:S21–S27.
17. Palumbo A, Mina R. Part II: role of maintenance therapy in transplant-ineligible patients. J Natl Compr Canc Netw. 2013;11:43–49.
18. Roussel M, Avet-Loiseau H, Moreau P, et al. Frontline therapy with bortezomib, lenalidomide, and dexamethasone (VRD) induction followed by autologous stem cell transplantation, VRD consolidation and lenalidomide maintenance in newly diagnosed multiple myeloma patients: primary results of the IFM 2008 phase II study [abstract]. Blood. 2010;116:624.
19. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371:895–905.
20. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371:906–917.
21. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389:519–527.
22. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv52–iv61.
23. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem cell transplant in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol. 2017;35:3279–3289.
24. Kumar SK, Callander NS, Alsina M, et al. NCCN Guidelines Insights: Multiple Myeloma, version 3.2018. J Natl Compr Canc Netw. 2018;16:11–20.

25. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018;131:301–310.
26. Revlimid (lenalidomide) [summary of product characteristics]. Utrecht, the Netherlands: Celgene Distribution B.V.; 2019.
27. Moreau P, Zamagni E, Mateos MV. Treatment of patients with multiple myeloma progressing on frontline-therapy with lenalidomide. Blood Cancer J. 2019;9:38.
28. Raab MS, Cavo M, Delforge M, et al. Multiple myeloma: practice patterns across Europe. Br J Haematol. 2016;175:66–76.
29. Moreau P, de Wit E. Recent progress in relapsed multiple myeloma therapy: implications for treatment decisions. Br J Haematol. 2017;179:198–218.
30. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:781–794.
31. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16:139–144.
32. Nolte S, Liegl G, Petersen MA, 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 United States. Eur J Cancer. 2019;107:153–163.
33. 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;87:330–337.
34. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35:1095–1108.
35. Cocks K, Cohen D, Wisløff F, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-MY20) in assessing the quality of life of patients with multiple myeloma. Eur J Cancer. 2007;43:1670–1678.
36. Bross I. How to use Ridit Analysis. Biometrics. 1958;14:18–38.

37. Breslow N, Day N. The analysis of case-control studies. In: International Agency for Research on Cancer. Statistical Methods in Cancer Research. Lyon, France: IARC Press; 1980.
38. Breslow N, Day N. The design and analysis of cohort studies. In: International Agency for Research on Cancer. Statistical Methods in Cancer Research. Lyon, France: IARC Press; 1987.
39. Fouquet G, Tardy S, Demarquette H, et al. Efficacy and safety profile of long-term exposure to lenalidomide in patients with recurrent multiple myeloma. Cancer. 2013;119:3680–3686.
40. Leleu X, Masszi T, Bahlis NJ, et al. Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma. Am J Hematol. 2018 [4 May]. DOI: 10.1002
41. Stewart AK, Dimopoulos MA, Masszi T, et al. Health-Related quality-of-life results from the open-label, randomized, phase III ASPIRE Trial evaluating carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed multiple myeloma. J Clin Oncol. 2016;34:3921–3930.
42. Weisel K, Dimopoulos M, Song KW, et al. Pomalidomide and low-dose dexamethasone improves health-related quality of life and prolongs time to worsening in relapsed/refractory patients with multiple myeloma enrolled in the MM-003 randomized phase III trial. Clin Lymphoma Myeloma Leuk. 2015;15:519–530.
43. Delforge M, Dhawan R, Robinson D Jr, 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;89:16–27.

Tables

Table 1. Baseline Demographics and Clinical Characteristics of HRQoL-Evaluable Patients

Characteristic	PVd (n = 240)	Vd (n = 209)	Overall (n = 449)
Age, years, n (%)			
≤ 75	202 (84.2)	176 (84.2)	378 (84.2)
> 75	38 (15.8)	33 (15.8)	71 (15.8)
Sex, n (%)			
Male	135 (56.3)	108 (51.7)	243 (54.1)
Female	105 (43.8)	101 (48.3)	206 (45.9)
Region, n (%)			
US	33 (13.8)	35 (16.8)	68 (15.1)
Non-US	207 (86.3)	174 (83.3)	381 (84.9)
Prior anti-myeloma regimens, n (%)			
1	86 (35.8)	71 (34.0)	157 (35.0)
2	104 (43.3)	81 (38.8)	185 (41.2)
3	50 (20.8)	57 (27.3)	107 (23.8)
ECOG PS, n (%)			
0	139 (57.9)	114 (54.6)	253 (56.4)
1	94 (39.2)	84 (40.2)	178 (39.6)
2	7 (2.9)	11 (5.3)	18 (4.0)
β2M at screening, mg/L, n (%)			
< 3.5	133 (55.4)	116 (55.5)	249 (55.5)
≥ 3.5 to ≤ 5.5	69 (28.8)	60 (28.7)	129 (28.7)
> 5.5	38 (15.8)	33 (15.8)	71 (15.8)
ISS stage, n (%)			
I	128 (53.3)	109 (52.2)	237 (52.8)
II	74 (30.8)	67 (32.1)	141 (31.4)
III	38 (15.8)	33 (15.8)	71 (15.8)

Characteristic	PVd (n = 240)	Vd (n = 209)	Overall (n = 449)
Refractory to lenalidomide, n (%)			
Yes	172 (71.7)	142 (67.9)	314 (69.9)
No	68 (28.3)	67 (32.1)	135 (30.1)
Prior exposure to bortezomib, n (%)			
Yes	169 (70.4)	153 (73.2)	322 (71.7)
No	71 (29.6)	56 (26.8)	127 (28.3)
Baseline cytogenetic risk assessment, n (%)			
High	51 (21.3)	36 (17.2)	87 (19.4)
Not high	119 (49.6)	105 (50.2)	224 (49.9)
Missing	70 (29.2)	68 (32.5)	138 (30.7)
Prior bone marrow or stem cell transplant, n (%)			
Yes	133 (55.4)	122 (58.4)	255 (56.8)
No	107 (44.6)	87 (41.6)	194 (43.2)

β2M, β2-microglobulin; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ISS, International Staging System; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; US, United States; Vd, bortezomib and low-dose dexamethasone.

Table 2. Mean HRQoL Scores at Baseline (HRQoL-evaluable population)

Domain	Patient Scores, mean (SD)			General Population Scores, mean [30][a]
	PVd (n = 240)	Vd (n = 209)	Overall (n = 449)	Reference (N = 15,386)
QLQ-C30				
Global QoL	61.0 (23.2)	63.5 (21.3)	62.2 (22.4)	66.4
Physical functioning	73.9 (23.7)	76.7 (22.0)	75.2 (22.9)	83.0
Role functioning	74.4 (27.9)	77.0 (27.5)	75.6 (27.7)	83.7
Cognitive functioning	84.0 (21.1)	87.2 (17.5)	85.5 (19.5)	86.9
Emotional functioning	82.8 (20.5)	82.8 (19.0)	82.8 (19.8)	79.7
Social functioning	79.4 (25.0)	83.4 (21.5)	81.3 (23.5)	88.5
Fatigue	33.2 (26.1)	29.1 (22.8)	31.3 (24.7)	25.9
Nausea and vomiting	5.6 (15.8)	4.1 (12.7)	4.9 (14.4)	3.1
Pain	28.3 (28.9)	26.8 (25.6)	27.6 (27.4)	24.0
Dyspnea	19.4 (25.9)	17.4 (23.8)	18.5 (25.0)	16.8
Insomnia	23.1 (27.7)	22.3 (27.6)	22.7 (27.6)	25.5
Appetite loss	13.5 (25.0)	13.1 (24.4)	13.3 (24.7)	7.3
Constipation	12.9 (25.1)	9.7 (20.0)	11.4 (22.9)	10.9
Diarrhea	12.1 (22.8)	10.7 (20.4)	11.4 (21.7)	6.8
Financial difficulties	13.4 (24.2)	10.4 (22.0)	12.0 (23.2)	8.4
QLQ-MY20				
Disease symptoms	23.5 (22.1)	21.3 (19.2)	22.5 (20.8)	NR
Side effects	16.0 (15.3)	12.9 (13.1)	14.5 (14.4)	NR
Future perspective	66.8 (24.3)	65.6 (27.3)	66.2 (25.7)	NR
Body image	85.3 (25.3)	86.5 (25.4)	85.8 (25.4)	NR
EQ-5D-3L				
Health utility index	0.71 (0.30)	0.73 (0.28)	0.72 (0.29)	NR

NR, not reported; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; QLQ-MY20, Quality-of-Life Questionnaire for Patients With Multiple Myeloma; QoL, quality of life; Vd, bortezomib and low-dose dexamethasone.

[a] Weighted mean value adjusted for age and sex per MM-007 population.

Table 3. Area Under the Curve for Change From Baseline for the QLQ-C30 and QLQ-MY20 Domains

	PVd (n = 240)	Vd (n = 209)	PVd vs Vd		
Domain	**Mean (95% CI)**	**Mean (95% CI)**	**Mean difference (95% CI)[a]**	**Effect size (95% CI)[b]**	***P* value**
QLQ-C30					
Global QoL	−2.0 (−4.04 to 0.04)	−1.1 (−3.32 to 1.13)	−0.92 (−3.93 to 2.09)	−0.06 (−0.24 to 0.13)	.549
Physical functioning	−3.1 (−4.81 to −1.45)	−1.9 (−3.64 to −0.07)	−1.32 (−3.77 to 1.14)	−0.10 (−0.29 to 0.09)	.291
Role functioning	−4.7 (−7.08 to −2.38)	−3.8 (−6.45 to −1.16)	−1.05 (−4.54 to 2.45)	−0.06 (−0.24 to 0.13)	.556
Cognitive functioning	−2.8 (−4.62 to −1.04)	-1.8 (−3.54 to -0.11)	−0.95 (−3.44 to 1.54)	−0.07 (−0.26 to 0.12)	.453
Emotional functioning	−2.4 (−4.07 to −0.75)	0.2 (−1.73 to 2.15)	−2.67 (−5.20 to −0.14)	−0.20 (−0.39 to −0.01)	.039[c]
Social functioning	−3.5 (−5.69 to −1.25)	−3.4 (−5.71 to −1.01)	−0.11 (−3.35 to 3.14)	−0.01 (−0.19 to 0.18)	.949
Fatigue	4.1 (1.94-6.25)	4.1 (1.74-6.47)	0.05 (−3.13 to 3.24)	0.00 (−0.18 to 0.19)	.973
Nausea and vomiting	−0.9 (−2.61 to 0.82)	0.1 (−1.51 to 1.70)	−0.99 (−3.37 to 1.39)	−0.08 (−0.27 to 0.11)	.415
Pain	−1.0 (−3.50 to 1.43)	−1.5 (−4.15 to 1.15)	0.46 (−3.16 to 4.09)	0.02 (−0.16 to 0.21)	.801
Dyspnea	3.8 (1.34-6.34)	2.9 (0.86-4.91)	1.00 (−2.29 to 4.28)	0.06 (−0.13 to 0.24)	.551
Insomnia	−0.5 (−3.31 to 2.23)	1.7 (−1.24 to 4.70)	−2.28 (−6.34 to 1.78)	−0.11 (−0.29 to 0.08)	.270
Appetite loss	0.6 (−1.99 to 3.28)	−0.6 (−3.11 to 1.98)	1.29 (−2.37 to 4.95)	0.07 (−0.12 to 0.25)	.488
Constipation	5.5 (2.76-8.17)	3.4 (1.12-5.68)	2.04 (−1.57 to 5.65)	0.11 (−0.08 to 0.29)	.267
Diarrhea	0.1 (−2.63 to 2.83)	−0.5 (−2.68 to 1.59)	0.68 (−2.88 to 4.24)	0.04 (−0.15 to 0.22)	.709
Financial difficulties	1.7 (−0.42 to 3.81)	−1.0 (−3.10 to 1.02)	2.73 (−0.25 to 5.72)	0.17 (−0.01 to 0.36)	.073
QLQ-MY20					
Disease symptoms	−4.3 (−6.12 to −2.49)	−3.8 (−5.59 to −2.05)	−0.45 (−3.01 to 2.12)	−0.03 (−0.22 to 0.16)	.733
Side effects	4.0 (2.63-5.40)	3.3 (1.87-4.68)	0.72 (−1.27 to 2.71)	0.07 (−0.12 to 0.26)	.476
Future perspective	4.6 (2.45-6.83)	7.0 (4.37-9.66)	−2.47 (−5.84 to 0.90)	−0.14 (−0.33 to 0.05)	.150
Body image	−3.5 (−5.94 to −1.06)	−2.9 (−5.76 to 0.03)	−0.53 (−4.26 to 3.21)	−0.03 (−0.21 to 0.16)	.782

PVd, pomalidomide, bortezomib, and low-dose dexamethasone; QLQ-MY20, Quality of Life Questionnaire for Patients with Multiple Myeloma; QoL, quality of life; Vd, bortezomib and low-dose dexamethasone.

[a] Least-square mean difference, adjusted for age (≤ 75 vs > 75 years), number of prior anti-myeloma regimens (1 vs > 1), and β2-microglobulin at screening (< 3.5 vs ≥ 3.5 mg/L to ≤ 5.5 vs > 5.5 mg/L).

[b] Hedges *g*.

[c] $P < .05$.

Table 4. Proportions of Patients Experiencing Clinically Meaningful Worsening by Treatment Group and Visit

Domain	Visit	PVd		Vd		OR	95% CI	*P* value
		n	% Worsening	n	% Worsening			
Global QoL								
	C5D1	200	33.0	146	28.8	1.18	0.73-1.89	.504
	C9D1	158	31.0	86	31.4	0.99	0.55-1.79	.982
	C19D1	67	23.9	24	29.2	0.90	0.30-2.70	.848
	C25D1	36	25.0	8	50.0	0.21	0.03-1.57	.109
Physical functioning								
	C5D1	200	37.5	146	32.9	1.23	0.78-1.95	.366
	C9D1	158	31.6	86	39.5	0.73	0.42-1.27	.265
	C19D1	67	29.9	24	29.2	1.00	0.34-2.90	.993
	C25D1	36	22.2	8	25.0	0.23[a]	0.03-1.97	.091
Fatigue								
	C5D1	200	51.5	146	44.5	1.36	0.88-2.12	.169
	C9D1	158	44.3	86	44.2	0.96	0.56-1.65	.889
	C19D1	67	41.8	24	41.7	1.22	0.44-3.41	.713
	C25D1	36	33.3	8	37.5	0.79	0.11-5.58	.813
Pain								
	C5D1	200	29.0	146	28.1	1.03	0.64-1.67	.889
	C9D1	158	25.9	86	26.7	0.98	0.53-1.81	.948
	C19D1	67	25.4	24	16.7	1.91	0.52-7.05	.34
	C25D1	36	25.0	8	50.0	0.31	0.05-1.97	.169
Disease symptoms								
	C5D1	199	15.6	144	16.0	0.95	0.52-1.73	.865
	C9D1	159	17.0	84	17.9	0.95	0.46-1.96	.897
	C19D1	67	20.9	23	13.0	2.25	0.51-9.97	.271
	C25D1	36	13.9	8	25.0	0.68	0.06-7.62	.746
Side effects of treatment								
	C5D1	199	37.2	144	33.3	1.13	0.72-1.78	.595
	C9D1	159	33.3	84	34.5	0.89	0.5-1.57	.692
	C19D1	67	28.4	23	34.8	0.53	0.18-1.58	.257
	C25D1	36	25.0	8	25.0	0.47	0.07-3.24	.401
EQ-5D-3L health utility index								
	C5D1	200	32.5	146	31.5	1.1	0.69-1.74	.694
	C9D1	159	30.2	85	30.6	1.01	0.55-1.84	.979
	C19D1	67	25.4	24	33.3	0.8	0.26-2.43	.705
	C25D1	36	27.8	8	37.5	0.32	0.04-2.29	.261

C, cycle; D, day; OR, odds ratio; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; Vd, bortezomib and low-dose dexamethasone.

A ≥ 10-point worsening from baseline was considered clinically meaningful for the QLQ-C30 and QLQ-MY20; a ≥ 0.10-point worsening from baseline was considered clinically meaningful for the EQ-5D-3L.

OR was estimated using the Cochran-Mantel-Haenszel test with modified ridit scores stratified by randomization stratification factors.

[a] A common OR at the C25D1 visit was reported, but the Breslow-Day test shows significant heterogeneity of ORs across stratification levels.

Figures

Figure 1

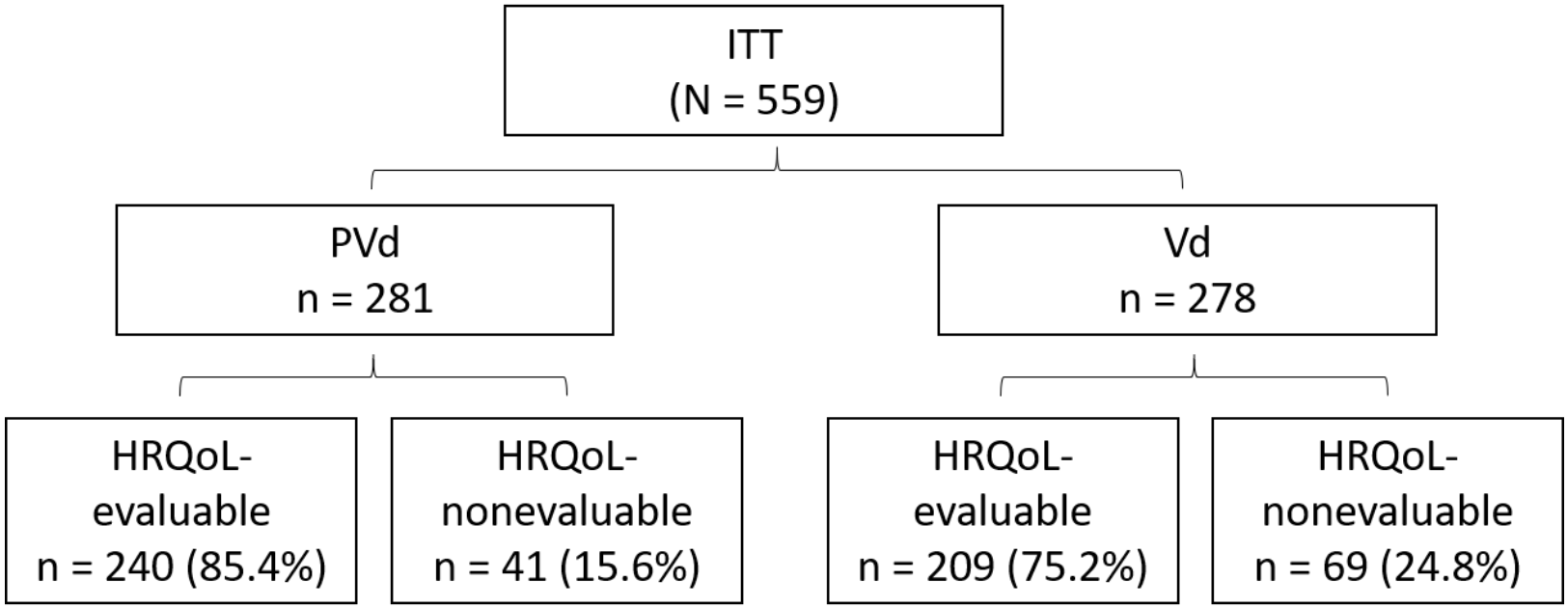
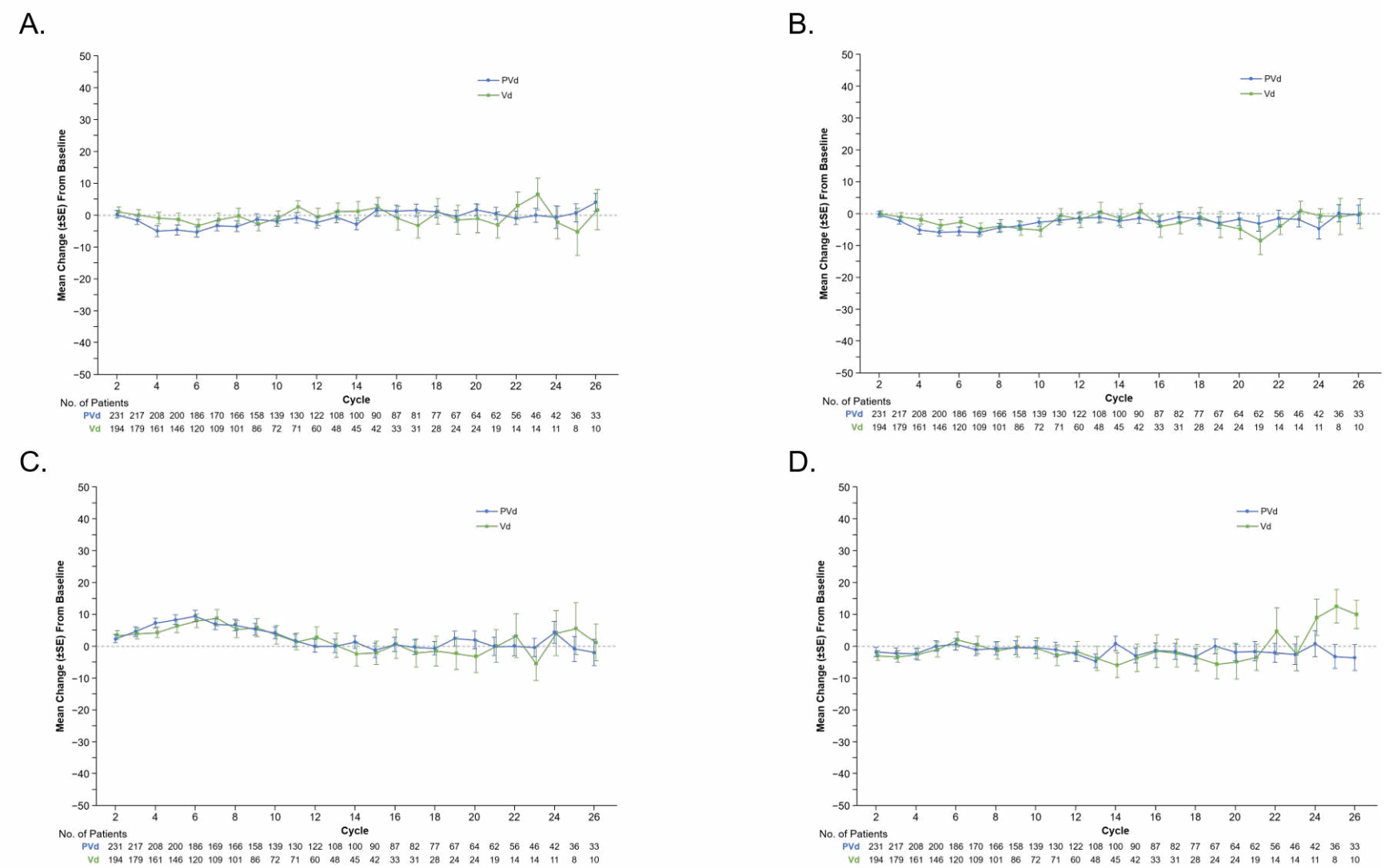
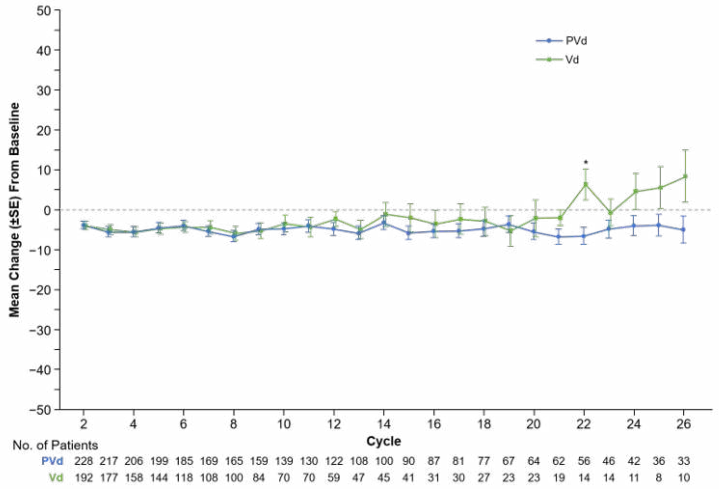


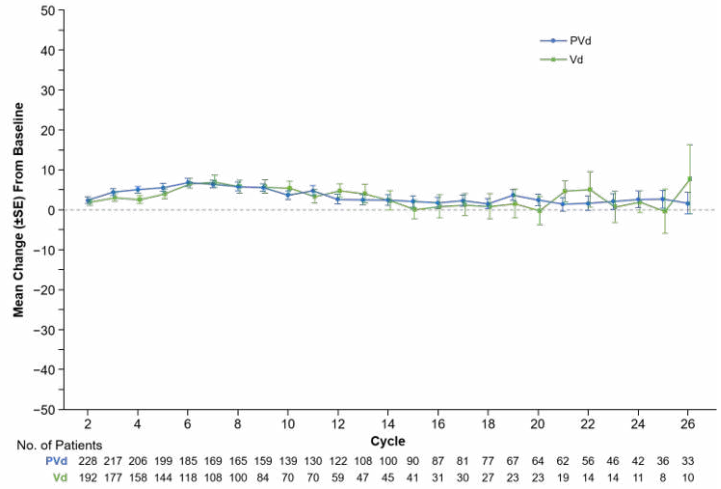
Figure 2


A.
B.
C.
D.
PVd
Vd
Mean Change (±SE) From Baseline
Cycle
No. of Patients
PVd 231 217 208 200 186 170 166 158 139 130 122 108 100 90 87 81 77 67 64 62 56 46 42 36 33
Vd 194 179 161 146 120 109 101 86 72 71 60 48 45 42 33 31 28 24 24 19 14 14 11 8 10
PVd 231 217 208 200 186 169 166 158 139 130 122 108 100 90 87 82 77 67 64 62 56 46 42 36 33
Vd 194 179 161 146 120 109 101 86 72 71 60 48 45 42 33 31 28 24 24 19 14 14 11 8 10
PVd 231 217 208 200 186 169 166 158 139 130 122 108 100 90 87 82 77 67 64 62 56 46 42 36 33
Vd 194 179 161 146 120 109 101 86 72 71 60 48 45 42 33 31 28 24 24 19 14 14 11 8 10
PVd 231 217 208 200 186 170 166 158 139 130 122 108 100 90 87 82 77 67 64 62 56 46 42 36 33
Vd 194 179 161 146 120 109 101 86 72 71 60 48 45 42 33 31 28 24 24 19 14 14 11 8 10

E.


PVd
Vd
Mean Change (±SE) From Baseline
Cycle
No. of Patients
PVd 228 217 206 199 185 169 165 159 139 130 122 108 100 90 87 81 77 67 64 62 56 46 42 36 33
Vd 192 177 158 144 118 108 100 84 70 70 59 47 45 41 31 30 27 23 23 19 14 14 11 8 10

F.


PVd
Vd
Mean Change (±SE) From Baseline
Cycle
No. of Patients
PVd 228 217 206 199 185 169 165 159 139 130 122 108 100 90 87 81 77 67 64 62 56 46 42 36 33
Vd 192 177 158 144 118 108 100 84 70 70 59 47 45 41 31 30 27 23 23 19 14 14 11 8 10

G.

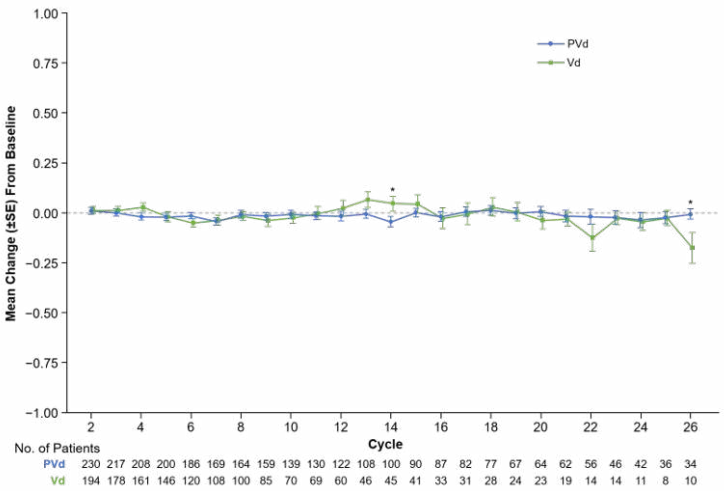

PVd
Vd
Mean Change (±SE) From Baseline
Cycle
No. of Patients
PVd 230 217 208 200 186 169 164 159 139 130 122 108 100 90 87 82 77 67 64 62 56 46 42 36 34
Vd 194 178 161 146 120 108 100 85 70 69 60 46 45 41 33 31 28 24 23 19 14 14 11 8 10

Figure 3

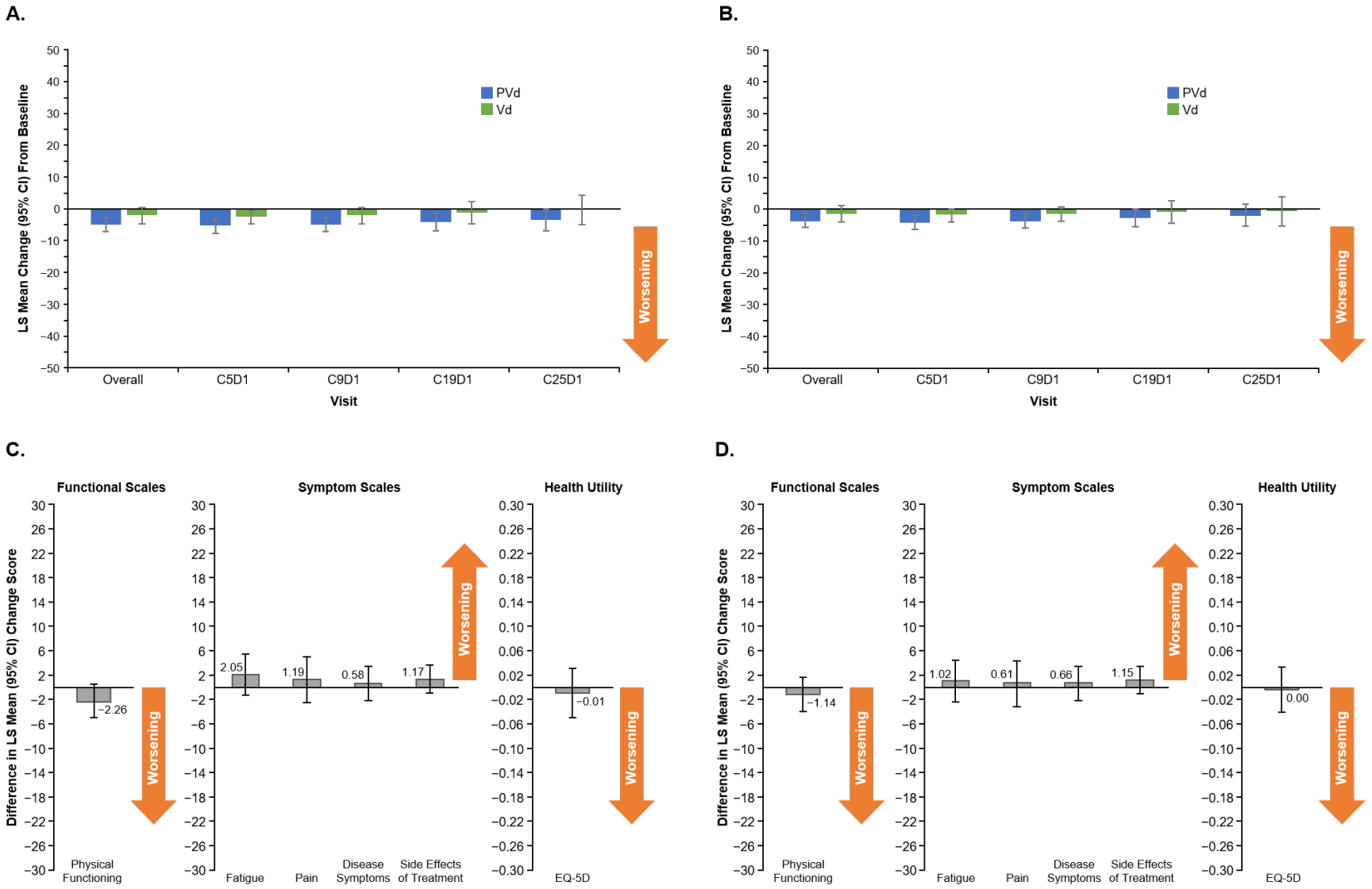

A.
LS Mean Change (95% CI) From Baseline
PVd
Vd
Worsening
Overall
C5D1
C9D1
C19D1
C25D1
Visit
B.
LS Mean Change (95% CI) From Baseline
PVd
Vd
Worsening
Overall
C5D1
C9D1
C19D1
C25D1
Visit
C.
Difference in LS Mean (95% CI) Change Score
Functional Scales
Symptom Scales
Health Utility
−2.26
2.05
1.19
0.58
1.17
−0.01
Worsening
Physical Functioning
Fatigue
Pain
Disease Symptoms
Side Effects of Treatment
EQ-5D
D.
Difference in LS Mean (95% CI) Change Score
Functional Scales
Symptom Scales
Health Utility
−1.14
1.02
0.61
0.66
1.15
0.00
Worsening
Physical Functioning
Fatigue
Pain
Disease Symptoms
Side Effects of Treatment
EQ-5D

Figure Captions

Figure 1. Patient disposition in the HRQoL analysis based on the OPTIMISMM study.

HRQoL, health-related quality of life; ITT, intent to treat; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; Vd, bortezomib and low-dose dexamethasone.

Figure 2. Observed change from baseline in HRQoL. A. Global QoL. B. Physical functioning. C. Fatigue. D. Pain. E. Disease symptoms. F. Side effects of treatment. G. EQ-5D-3L health utility index. For global QoL, physical functioning, and EQ-5D-3L health utility index, a negative value indicates worsening from baseline; for the other domains, a negative value indicates improvement from baseline.

PVd, pomalidomide, bortezomib, and low-dose dexamethasone; SE, standard error; Vd, bortezomib and low-dose dexamethasone.

* Difference in mean change between treatments significant at $P < .05$ (2-sample t test). Results are displayed up to the last cycle with $n \geq 10$ in both treatment arms.

Figure 3. Change from baseline in HRQoL: longitudinal analyses. A. Global QoL. B. Global QoL with missing data imputed. C. Secondary domains of interest. B. Secondary domains of interest with missing data imputed. LS mean changes and CIs were estimated based on a random intercept/slope model under the assumption of unstructured covariance and with the following covariates as fixed

effects: baseline domain score, age, number of prior anti-myeloma regimens, β2-microglobulin, treatment, visit, treatment-by-visit interaction, and baseline domain score-by-visit interaction.

LS, least square; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; Vd, bortezomib and low-dose dexamethasone.

Supplemental Materials

Results

Key Baseline Differences Between Health-Related Quality of Life–Evaluable and –Nonevaluable Populations

Compared with the health-related quality of life (HRQoL)–evaluable population, the HRQoL-nonevaluable population was, on average, older (20.0% vs 15.8% were older than 75 years), had more severe disease based on Eastern Cooperative Oncology Group performance status (13.6% vs 4.0% of patients had an Eastern Cooperative Oncology Group performance status of 2) and International Staging System stage (23.64% vs 15.81% of patients had stage III disease), and was more likely to live in the United States (49.1% vs 15.1%) (**Table S1**). The HRQoL-nonevaluable population also had worse overall survival, progression-free survival, and best overall response rate (44.6% of patients had a complete or partial response compared with 71.5% of the HRQoL-evaluable population; data not shown).

Treatment Effects on HRQoL: Exploratory Domains of Interest

The remaining functional and symptom domains of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-MY20 were evaluated as an exploratory analysis. HRQoL domain scores were maintained over time in both treatment groups, with the exception of the role functioning, social functioning, dyspnea, and constipation domains, which showed evidence of worsening during the first few cycles of treatment (data not shown). Scores for the future perspectives domain of the QLQ-MY20 improved over time in both treatment groups (data not shown).

Overall, the pomalidomide, bortezomib, and low-dose dexamethasone (PVd) group exhibited worse least-squares (LS) mean changes from baseline than the bortezomib and low-dose dexamethasone (Vd) group. However, based on an MMRM analysis of all exploratory functional domains, the differences in LS mean changes from baseline between treatment groups were neither significant nor clinically meaningful (**Figure S3A**). No clinically meaningful between-group differences in LS mean changes from baseline were observed for symptom domains (**Figure S3B**), despite statistically significant ($P < .05$) worsening of constipation and financial difficulties in the PVd group. Patients in the PVd group also experienced transient, clinically meaningful worsening of constipation during the first few cycles of treatment (data not shown).

Across all domains, the proportions of patients who experienced clinically meaningful worsening were similar between treatment groups for all the assessment visits (**Table S2**). Exceptions were the financial difficulties domain at cycle 19, for which 7.5% and 16.7% of patients in the PVd and Vd groups, respectively, experienced clinically meaningful worsening ($P = .050$), and the body image domain, also at cycle 19, for which 20.9% and 39.1% of patients in the PVd and Vd groups, respectively, experienced clinically meaningful worsening ($P = .031$).

Time to the first clinically meaningful worsening for the HRQoL-evaluable population was calculated as the time between randomization and the first time a patient's change in a given domain was, at a minimum, 10 points worse than at baseline. In Cox proportional hazard regression analyses, time to first clinically meaningful worsening for all exploratory domains was similar between the 2 treatment groups (data not shown).

Table S1. Baseline Demographics and Clinical Characteristics Comparing Evaluable and Nonevaluable Patients

	PVd		Vd		Overall	
	HRQoL Evaluable (n = 240)	**HRQoL Nonevaluable (n = 41)**	**HRQoL Evaluable (n = 209)**	**HRQoL Nonevaluable (n = 69)**	**HRQoL Evaluable (n = 449)**	**HRQoL Nonevaluable (n = 110)**
Age, years, n (%)						
≤ 75	202 (84.2)	33 (80.5)	176 (84.2)	55 (79.7)	378 (84.2)	88 (80.0)
> 75	38 (15.8)	8 (19.5)	33 (15.8)	14 (20.3)	71 (15.8)	22 (20.0)
Sex, n (%)						
Male	135 (56.3)	20 (48.8)	108 (51.7)	39 (56.5)	243 (54.1)	59 (53.6)
Female	105 (43.8)	21 (51.2)	101 (48.3)	30 (43.5)	206 (45.9)	51 (46.4)
Region, n (%)						
US	33 (13.8)	20 (48.8)	35 (16.8)	34 (49.3)	68 (15.1)	54 (49.1)
Non-US	207 (86.3)	21 (51.2)	174 (83.3)	35 (50.7)	381 (84.9)	56 (50.9)
Prior anti-myeloma regimens, n (%)						
Missing	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.5)	0 (0.0)	2 (1.8)
1	86 (35.8)	12 (29.3)	71 (34.0)	24 (34.8)	157 (35.0)	36 (32.7)
2	104 (43.3)	14 (34.2)	81 (38.8)	26 (37.7)	185 (41.2)	40 (36.4)
3	50 (20.8)	14 (34.2)	57 (27.3)	18 (26.1)	107 (23.8)	32 (29.1)
ECOG PS, n (%)						
0	139 (57.9)	10 (24.4)	114 (54.6)	23 (33.3)	253 (56.4)	33 (30.0)
1	94 (39.2)	27 (65.9)	84 (40.2)	35 (50.7)	178 (39.6)	62 (56.4)
2	7 (2.9)	4 (9.8)	11 (5.3)	11 (15.9)	18 (4.0)	15 (13.6)

	PVd		Vd		Overall	
	HRQoL Evaluable (n = 240)	**HRQoL Nonevaluable (n = 41)**	**HRQoL Evaluable (n = 209)**	**HRQoL Nonevaluable (n = 69)**	**HRQoL Evaluable (n = 449)**	**HRQoL Nonevaluable (n = 110)**
β2M at screening, mg/L, n (%)						
< 3.5	133 (55.4)	23 (56.1)	116 (55.5)	31 (44.9)	249 (55.5)	54 (49.1)
≥ 3.5 to ≤ 5.5	69 (28.8)	9 (22.0)	60 (28.7)	21 (30.4)	129 (28.7)	30 (27.3)
> 5.5	38 (15.8)	9 (22.0)	33 (15.8)	17 (24.6)	71 (15.8)	26 (23.6)
ISS stage, n (%)						
I	128 (53.3)	21 (51.2)	109 (52.2)	29 (42.0)	237 (52.8)	50 (45.5)
II	74 (30.8)	11 (26.8)	67 (32.1)	23 (33.3)	141 (31.4)	34 (30.9)
III	38 (15.8)	9 (22.0)	33 (15.8)	17 (24.6)	71 (15.8)	26 (23.6)
Refractory to lenalidomide, n (%)						
Yes	172 (71.7)	28 (68.3)	142 (67.9)	49 (71.0)	314 (69.9)	77 (70.0)
No	68 (28.3)	13 (31.7)	67 (32.1)	20 (29.0)	135 (30.1)	33 (30.0)
Prior exposure to bortezomib, n (%)						
Yes	169 (70.4)	32 (78.1)	153 (73.2)	50 (72.5)	322 (71.7)	82 (74.6)
No	71 (29.6)	9 (22.0)	56 (26.8)	19 (27.5)	127 (28.3)	28 (25.5)
Baseline cytogenetic risk assessment, n (%)						
High	51 (21.3)	10 (24.4)	36 (17.2)	13 (18.8)	87 (19.4)	23 (20.9)
Not high	119 (49.6)	18 (43.9)	105 (50.2)	27 (39.1)	224 (49.9)	45 (40.9)
Missing	70 (29.2)	13 (31.7)	68 (32.5)	29 (42.0)	138 (30.7)	42 (38.2)

	PVd		Vd		Overall	
	HRQoL Evaluable (n = 240)	**HRQoL Nonevaluable (n = 41)**	**HRQoL Evaluable (n = 209)**	**HRQoL Nonevaluable (n = 69)**	**HRQoL Evaluable (n = 449)**	**HRQoL Nonevaluable (n = 110)**
Prior bone marrow or stem cell transplant, n (%)						
Yes	133 (55.4)	28 (68.3)	122 (58.4)	41 (59.4)	255 (56.8)	69 (62.7)
No	107 (44.6)	13 (31.7)	87 (41.6)	28 (40.6)	194 (43.2)	41 (37.3)

β2M, β2-microglobulin; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; ISS, International Staging System; PVd, pomalidomide, bortezomib, and low-dose dexamethasone; US, United States; Vd, bortezomib and low-dose dexamethasone.

Table S2. Proportions of Patients Experiencing Clinically Meaningful Worsening by Treatment Group and Visit (exploratory domains of interest)

Domain	Visit	PVd		Vd		OR	95% CI	*P* value
		n	% Worsening	n	% Worsening			
Role functioning								
	C5D1	200	36.5	146	37.0	0.99[a]	0.64-1.55	.979
	C9D1	158	33.5	86	39.5	0.74	0.42-1.30	.300
	C19D1	67	28.4	24	33.3	0.99	0.35-2.77	.979
	C25D1	36	27.8	8	25.0	0.56	0.07-4.69	.586
Emotional functioning								
	C5D1	200	25.0	146	17.1	1.59	0.93-2.71	.089
	C9D1	158	26.6	86	19.8	1.41	0.73-2.71	.305
	C19D1	67	20.9	24	20.8	1.14	0.35-3.75	.830
	C25D1	36	2.8	8	12.5	0.20	0.01-4.17	.276
Cognitive functioning								
	C5D1	200	28.0	146	26.7	1.07	0.66-1.74	.788
	C9D1	158	29.1	86	33.7	0.81	0.46-1.43	.461
	C19D1	67	32.8	24	20.8	2.04	0.61-6.85	.260
	C25D1	36	22.2	8	37.5	0.41	0.06-2.59	.352
Social functioning								
	C5D1	200	36.5	146	33.6	1.13	0.72-1.77	.599
	C9D1	158	38.0	86	32.6	1.29	0.73-2.27	.386
	C19D1	67	25.4	24	20.8	1.29	0.41-4.10	.649
	C25D1	36	33.3	8	12.5	1.61	0.15-16.79	.695
Nausea and vomiting								
	C5D1	200	14.5	146	12.3	1.20	0.64-2.25	.560
	C9D1	158	10.8	86	16.3	0.61	0.28-1.33	.223
	C19D1	67	10.4	24	4.2	4.50	0.28-72.12	.301
	C25D1	36	2.8	8	12.5	0.20	0.01-4.17	.276
Dyspnea								
	C5D1	200	28.0	146	24.0	1.18	0.72-1.93	.520
	C9D1	158	25.3	86	29.1	0.75	0.41-1.37	.352
	C19D1	67	10.4	24	20.8	0.48	0.12-1.94	.331
	C25D1	36	16.7	8	50.0	0.27	0.04-1.89	.198
Insomnia								
	C5D1	200	23.0	146	25.3	0.85	0.51-1.41	.529
	C9D1	158	20.9	86	25.6	0.75	0.40-1.40	.360
	C19D1	67	14.9	24	8.3	1.87	0.38-9.29	.445
	C25D1	36	5.6	8	25.0	0.13	0.01-1.28	.067
Appetite loss								
	C5D1	200	20.5	146	16.4	1.42	0.81-2.48	.213
	C9D1	158	22.2	86	20.9	1.09	0.58-2.05	.792
	C19D1	67	17.9	24	8.3	1.87	0.38-9.25	.446
	C25D1	36	8.3	8	12.5	0.32	0.02-4.74	.412
Constipation								

Domain	Visit	PVd		Vd		OR	95% CI	*P* value
		n	% Worsening	n	% Worsening			
	C5D1	200	32.5	146	28.8	1.13	0.71-1.81	.611
	C9D1	158	30.4	86	18.6	1.85	0.96-3.55	.066
	C19D1	67	26.9	24	12.5	2.44	0.59-10.16	.220
	C25D1	36	13.9	8	0.0	NE	NE-NE	.304
Diarrhea								
	C5D1	200	17.5	146	11.0	1.73	0.91-3.30	.095
	C9D1	158	22.2	86	20.9	1.04	0.54-2.00	.896
	C19D1	67	16.4	24	12.5	1.35	0.35-5.13	.648
	C25D1	36	8.3	8	12.5	0.44	0.03-5.71	.534
Financial difficulties								
	C5D1	200	15.5	146	11.6	1.30	0.68-2.48	.428
	C9D1	158	12.7	86	14.0	0.96	0.44-2.07	.916
	C19D1	67	7.5	24	16.7	0.26	0.05-1.26	.050
	C25D1	36	8.3	8	12.5	0.20	0.01-4.17	.276
Future perspective								
	C5D1	199	23.1	144	20.1	1.17	0.69-1.98	.563
	C9D1	158	22.8	84	20.2	1.21	0.61-2.40	.589
	C19D1	67	20.9	23	17.4	1.27	0.38-4.27	.699
	C25D1	35	20.0	8	12.5	0.60	0.05-7.00	.675
Body image								
	C5D1	199	27.1	144	20.1	1.44	0.87-2.39	.149
	C9D1	158	22.2	83	20.5	1.08	0.56-2.07	.825
	C19D1	67	20.9	23	39.1	0.31	0.11-0.91	.031
	C25D1	35	22.9	8	25.0	1.33	0.14-12.5	.802

C, cycle; D, day; NE, not evaluable; OR, odds ratio; PVd, pomalidomide in combination with bortezomib and low-dose dexamethasone; Vd, bortezomib and low-dose dexamethasone.

A ≥ 10-point worsening from baseline was considered clinically meaningful. ORs were estimated using the Cochran-Mantel-Haenszel test with modified ridit scores stratified by randomization stratification factors.

[a] A common OR at the C5D1 visit was reported, but the Breslow-Day test shows significant heterogeneity of ORs across stratification levels.

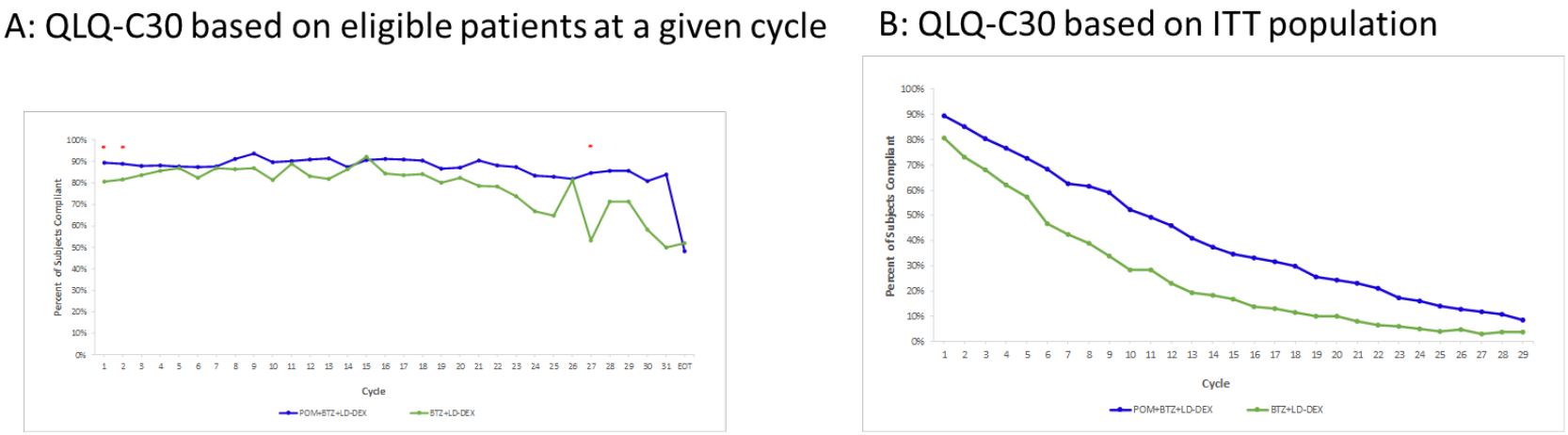
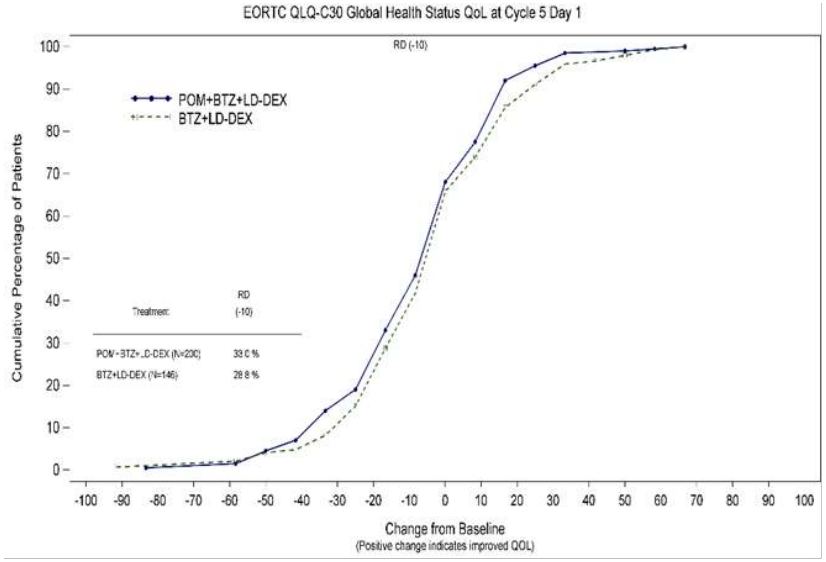


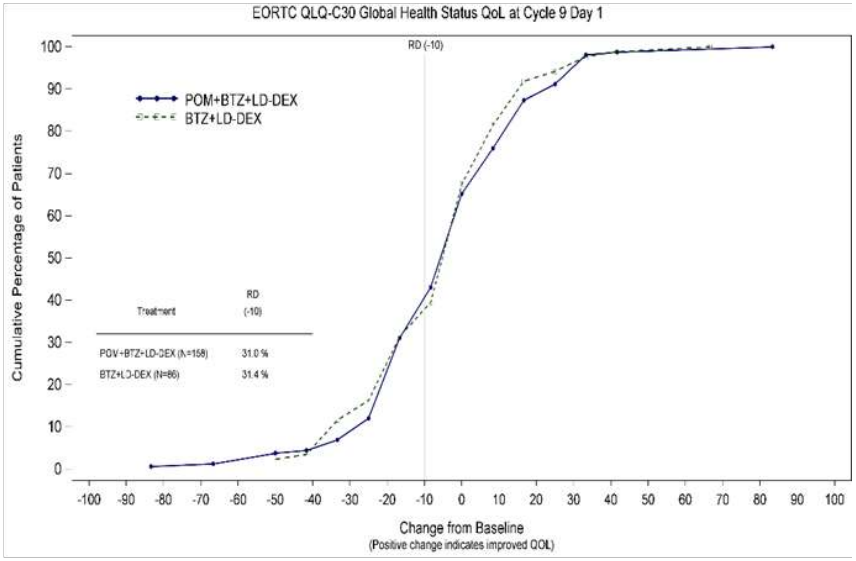
Figure S1

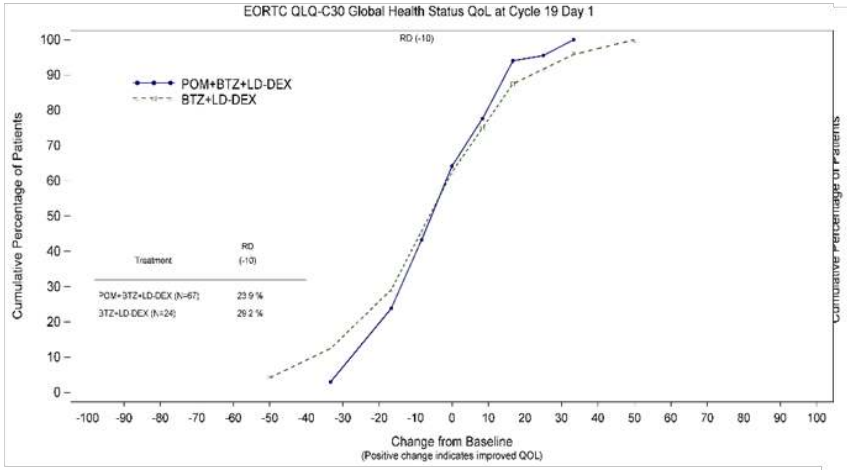
Adherence rates for European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 over time. A. Eligible patients at each cycle. B. Intent-to-treat population.

BTZ+LD-DEX, bortezomib and low-dose dexamethasone; EOT, end of treatment; POM+BTZ+LD-DEX, pomalidomide in combination with bortezomib and low-dose dexamethasone.

* Difference between treatments significant at $P < 0.05$ (Fisher exact test).


EORTC QLQ-C30 Global Health Status QoL at Cycle 5 Day 1
RD (-10)
POM+BTZ+LD-DEX
BTZ+LD-DEX
Cumulative Percentage of Patients
Change from Baseline
(Positive change indicates improved QOL)
Treatment
RD (-10)
POM+BTZ+LD-DEX (N=200) 33.0 %
BTZ+LD-DEX (N=146) 28.8 %


EORTC QLQ-C30 Global Health Status QoL at Cycle 9 Day 1
RD (-10)
POM+BTZ+LD-DEX
BTZ+LD-DEX
Cumulative Percentage of Patients
Change from Baseline
(Positive change indicates improved QOL)
Treatment
RD (-10)
POM+BTZ+LD-DEX (N=158) 31.0 %
BTZ+LD-DEX (N=86) 31.4 %


EORTC QLQ-C30 Global Health Status QoL at Cycle 19 Day 1
RD (-10)
POM+BTZ+LD-DEX
BTZ+LD-DEX
Cumulative Percentage of Patients
Change from Baseline
(Positive change indicates improved QOL)
Treatment
RD (-10)
POM+BTZ+LD-DEX (N=67) 23.9 %
BTZ+LD-DEX (N=24) 29.2 %

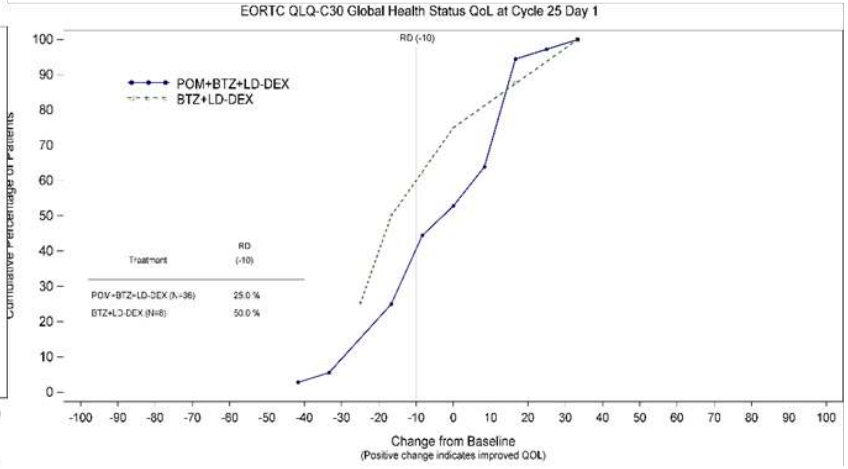

EORTC QLQ-C30 Global Health Status QoL at Cycle 25 Day 1
RD (-10)
POM+BTZ+LD-DEX
BTZ+LD-DEX
Change from Baseline
(Positive change indicates improved QOL)
Treatment
RD (-10)
POM+BTZ+LD-DEX (N=36) 25.0 %
BTZ+LD-DEX (N=8) 50.0 %

Figure S2

Cumulative distribution function curves for the global quality-of-life (QoL) domain of the QLQ-C30.

BTZ+LD-DEX, bortezomib and low-dose dexamethasone; POM+BTZ+LD-DEX, pomalidomide in combination with bortezomib and low-dose dexamethasone.

A: Functional domains

B: Symptom domains

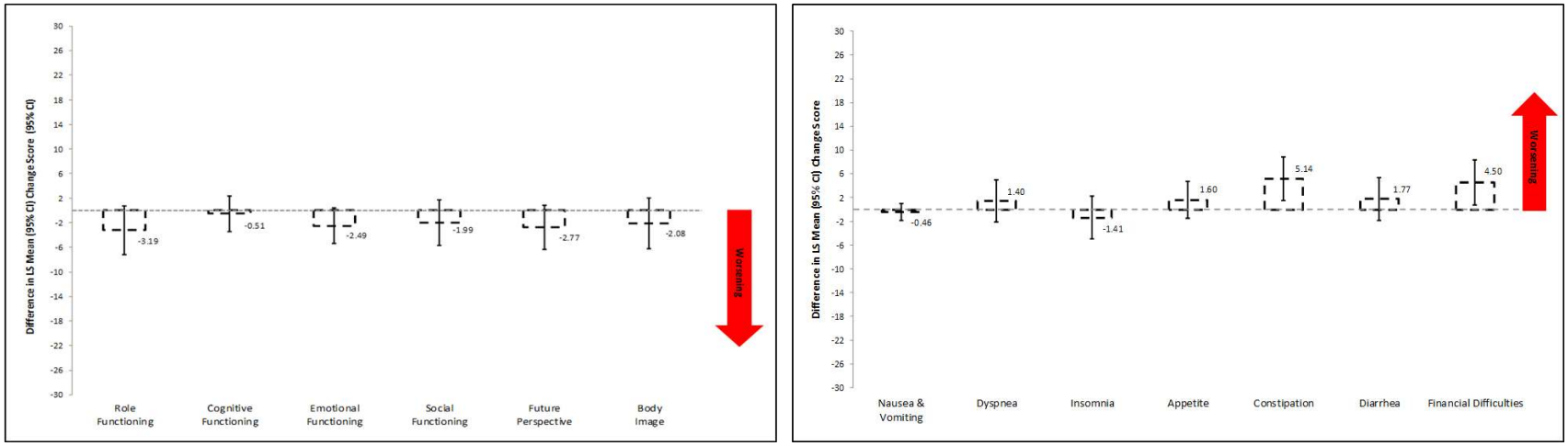


Figure S3

Differences in overall least-squares (LS) mean changes from baseline between pomalidomide in combination with bortezomib and low-dose dexamethasone and bortezomib and low-dose dexamethasone. A. Functional domains. B. Symptom domains.

Within-group LS mean changes and differences between groups were estimated based on a random intercept/slope model under the assumption of unstructured covariance and with the following covariates as fixed effects: baseline domain score, age, number of prior anti-myeloma regimens, β2-microglobulin, treatment, visit, treatment-by-visit interaction, and baseline domain score-by-visit interaction.