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Quality of life in patients with relapsed/refractory multiple myeloma during ixazomib-thalidomide-dexamethasone induction and ixazomib maintenance therapy and comparison to the general population

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ABSTRACT

This trial evaluated quality of life (QoL) using the EORTC QLQ-C30 and the EORTC QLQ-MY20 instruments in 90 patients with relapsed/refractory multiple myeloma during induction and maintenance therapy with eight cycles of ixazomib-thalidomide-dexamethasone, followed by 12 months of ixazomib maintenance therapy. When patient's baseline QoL was compared with data of the general population, a significant impairment in health-related QoL, physical, role, and social functioning and several other dimensions, as well as more pain and fatigue, was noted. Induction therapy resulted in significant improvement of pain and worsening of neuropathy, with no significant variation of other parameters. During maintenance treatment, scores for most dimensions including health-related QoL, physical functioning and pain, improved, while for neuropathy no improvement was observed. Time to deterioration (≥ 10 score points) of health-related QoL, physical functioning, pain, and neuropathy was distinctly shorter than time to progression. Health-related QoL and physical functioning at baseline correlated with overall survival.

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Introduction

The aim of multiple myeloma (MM) treatment is to control the disease, prolong survival, reduce disease-related symptoms, and improve quality of life (QoL) [1]. Several studies revealed that physicians often underestimate the impact of cancer associated symptoms such as nausea, fatigue, or pain on patient's

well-being [2]. Hence, patient-reported outcomes (PRO) have become the gold standard for the evaluation of the burden of disease and of the benefits and side effects of therapy [3]. Maintaining reasonable QoL is particularly important when treatments improve progression-free survival (PFS), but do not prolong the overall survival (OS), because in these instances,

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documentation of a substantial benefit in terms of QoL is required [4–6], otherwise the treatment would be of no or only questionable value. The impact of a specific treatment on QoL in patients with MM depends not only on the depth of response, but to a significant part on the tolerance and toxicity of individual drugs used for therapy, and also on the patient's individual biological robustness and possible morbidities. In this study, we aimed to evaluate changes in several predefined dimensions of QoL in patients with relapsed/refractory multiple myeloma (RRMM) treated with a triple combination employing ixazomib-thalidomide-dexamethasone, followed by ixazomib maintenance therapy. Dexamethasone is part of almost every myeloma treatment regimen, and after introduction of the low-dose regimen with once-weekly dosing, relatively well tolerated. Ixazomib, when combined with lenalidomide-dexamethasone (Rd), was found to prolong PFS in a large phase 3 trial with limited additional toxicity [7], and was well tolerated and did not result in impairment of QoL with the exception of a higher incidence of diarrhea, when compared to Rd alone [8].

Ixazomib maintenance therapy after autologous transplantation improved PFS by more than 5 months, was equally effective in patients with high- and standard risk cytogenetics, and was well tolerated with minimal increase in serious adverse events [9], but information on its impact on QoL is only limited until now. Thalidomide is still the most widely used immunomodulatory drug (IMiD) worldwide because it is simply the most affordable one, but is associated with several side effects, particularly neuropathy, which is the clinically most relevant. Side effects of thalidomide depend on dose, particularly cumulative dose, and on patient's individual susceptibility to thalidomide-induced toxicities [10]. In the Myeloma IX study, the combination of thalidomide with cyclophosphamide and dexamethasone (CTD) significantly reduced fatigue at 3 months and improved physical functioning at 12 months compared with the non-thalidomide containing combination of cyclophosphamide-vincristine-adriamycin-dexamethasone (CVAD), while in the non-intensive pathway attenuated cyclophosphamide-thalidomide-dexamethasone (CTD) was superior to melphalan-prednisone (MP) in terms of pain at 3 months. Thalidomide maintenance therapy improved pain at 12 months but decreased global health status/quality of life versus observation [11]. Unfortunately, results on polyneuropathy, the clinically most relevant side effect of thalidomide, were not reported. Here, we present the analysis of the clinically most relevant dimensions of QoL in patients with RRMM [12] during

planned treatment with eight cycles of ixazomib plus thalidomide and dexamethasone for relapsing/refractory disease followed by ixazomib maintenance therapy. In addition, as information regarding possible differences in QoL between myeloma patients and the general population is not available, we compared several dimensions of QoL between our patients with RRMM with that observed in the normal population of similar age from the same area.

Patients and controls from the general population

Ninety patients with relapsed/refractory MM had been enrolled (median age: 67 years, [International Staging Status (ISS) stage I: 41%, II: 33%, III: 26%, Eastern Cooperative Oncology Group (ECOG) performance status 0–1: 95%, 2: 5%]. Treatment consisted of eight cycles of ixazomib, 4 mg, d 1, 8, and 15, q 28 days; thalidomide, 100 mg/d; and dexamethasone: 40 mg, d 1, 8, and 15. Patients aged ≥ 75 years had a 50% dose reduction of thalidomide to 50 mg/d and of dexamethasone to 20 mg, and of ixazomib to 3 mg. Maintenance treatment consisted of ixazomib, 4 mg, days 1, 8, and 15 of a 28-day cycle, and was given for one year. Treatment results of this open-label multicenter single arm phase II study have been summarized and will be published in the British Journal of Cancer [13]. The trial protocol was approved by each study site's Independent Ethics Committee or Institutional Review Board, and the study was conducted in accordance with the Declaration of Helsinki. Two-thousand-three-hundred-thirty-seven individuals aged 60–69 years of the general population from 11 European-countries served as controls [14].

Methods

Health-related quality of life was assessed by the European Organization of Research and Treatment of Cancer (EORTC) questionnaires EORTC QLQ-C30 [15] and the Myeloma EORTC QLQ-MY20 module [16]. Comorbidity was assessed by the clinical care team using the activities of daily living (ADL) [17], and the instrumental activities of daily living (IADL) [18] instruments, and Charlson comorbidity index [19]. The questionnaires were distributed and filled out by patients in paper format prior to study treatment at baseline, and subsequently on day 1 of each treatment cycle, at end of induction therapy, at start of maintenance treatment, and monthly thereafter until the end of month 12, or at time of treatment discontinuation or progression. This study focused on nine pre-selected

and clinically relevant QoL domains: Three from the QLQ-MY20 (disease symptoms, side effects of treatment and neuropathy); and six from the QLQ-C30 (health-related QoL, physical, cognitive and social functioning, fatigue, and pain). QLQ-MY20 and QLQ-C30 scales were scored in accordance with their published guidelines [20]. Results were transformed to a standardized 0–100 final ‘scale score.’ For the functional scales (health-related QoL, physical, cognitive, and social functioning), higher scores indicate better QoL, whereas for the symptom scales (fatigue, pain, neuropathy, disease symptoms, and side effects of treatment), lower scores indicate less or no symptoms. As a guide for interpretation, an arbitrary difference of ≥ 10 points in a scale was considered as the minimal important difference (MID) required to suggest clinical relevance [21]. This cutoff is intended to produce robust results. In other recent myeloma trials (ASPIRE [22], ENDEAVOR [12]), a difference of ≥ 5 points has been used as cutoff, while in the FIRST study [23], differences from 5 to 12 points have been used for individual domains.

Compliance rates at each scheduled assessment were calculated as the number of compliant patients divided by the number of patients still on protocol treatment at that assessment. Analyses were performed on intention-to-treat patients; data cutoff was 31 March 2019. Due to the phase II design of the study, and HRQoL being only a secondary endpoint not reflected in the sample size calculation, all analyses and results have to be considered explorative. The constantly decreasing number of available observations is inevitable in a highly palliative setting, with missingness clearly not at random.

Therefore, no imputation or modeling of missing values was performed; all presented results were based on available data only. Differences were assessed by *t*-test (two-sample *t*-test for the comparison with the general population and paired *t*-test for the comparison within the course of therapy). Wilcoxon tests were used to evaluate differences in the QoL dimensions between patients who started maintenance therapy and those who discontinued earlier. For the comparison of time to progression (TTP) and time to deterioration of different HRQoL domains, and the assessment of the prognostic impact of QoL domains on long-term outcome, a Kaplan–Meier estimation [24] was used. For the comparison of PFS and OS, in patients with poorer or better health related QoL and physical functioning, patients were grouped according to lower or equal or above median scores at baseline and results were compared using Kaplan–Meier estimations [24] and log rank test [25] as appropriate. All *p*-values are two-sided without any adjusting for multiple testing. Thus, the corresponding term ‘significant’ in case of $p \leq .05$ has to be considered explorative without reference to pre-specified hypotheses. The selection of nine QoL domains as most relevant was fixed prospectively, based on the experience from the group’s previous trials, before any statistical analyses were performed.

Results

Patient population

Baseline patient characteristics and exposure to prior treatment in the intent-to-treat (ITT) group are shown

Table 1. Patient characteristics.

Parameter	Patients (<i>n</i> = 90)
Age, years (range)	67.3 (44–84)
Male/female	46 (51.1%)/44 (48.9%)
ISS stage: I/II/III	37 (41.1%)/30 (33.3%)/23 (25.5%)
ECOG Status 0–1/2	86 (95.6%)/4 (4.4%)
Charlson Comorbidity Index, median (range)	4 (0–9)
ADL Score, median (range)	20 (11–20)
IADL Score, median (range)	8 (2–8)
Type of MM	
IgG/IgA	47 (52.2%)/20 (22.2%)
Light chain only	23 (25.6%)
Cytogenetics	
t (4;14) and/or del (17p)	18 (29.5%)
Gain of 1q21	32 (52.5%)
None	22 (36.1%)
Prior treatment lines	
1–2/3–4/ ≥ 5	66 (73.3%)/15 (16.7%)/9 (10.0%)
Prior exposure to	
PI/IMiD/PI and IMiD	85 (94.4%)/54 (60.0%)/50 (55.5%)
Len exposed/Len refractory	42 (46.7%)/14 (15.6%)
Thal exposed/Thal refractory	12 (13.3%)/0 (0%)
Btz exposed/Btz refractory	79 (87.8%)/9 (10%)
Autologous stem cell transplantation	61 (67.8%)
Months since start of 1st line TX, median (IQR)	49 (31–87)

ISS: International Staging Status; ECOG: Eastern Cooperative Oncology Group; ADL: activities of daily living; IADL: instrumental activities of daily living; MM: multiple myeloma; PI: proteasome inhibitor; IMiD: immunomodulatory drugs.

in Table 1. QoL data were available in 89 of 90 ITT patients at baseline and in 41 of the 43 patients who started maintenance therapy and in 13 patients at the planned completion of maintenance treatment. Details of the patient flow during the study are shown in Supplementary Figure 1. Median follow-up was 19.1 months.

Comparison of QoL between patients and individuals from the general population

A significant impairment in several dimensions of QoL was noted when the baseline data of the patients were compared with the general population of similar age and same geographic region (Figure 1). Among those, physical (-12.4 , $p < .0001$), role (-26.6 , $p < .0001$), social function (-17 , $p < .0001$), fatigue ($+14.1$, $p < .0001$), and pain ($+18.5$, $p < .0001$) were all significantly worse in the patient cohort and exceeded the MID. Significant differences without meeting the threshold for clinical relevance were noted for global health status/QoL (-6.5 , $p = .0059$), emotional (-6.5 , $p = .0038$), cognitive function (-5.9 , $p = .0014$), dyspnea ($+7.2$, $p = .0085$), appetite loss ($+5.5$, $p = .0054$), constipation ($+7.8$, $p = .0005$), and diarrhea ($+3.6$,

$p = .0436$). No difference between patients and the general population was noted for nausea/vomiting, insomnia, and financial burden.

Compliance

Compliance rates were consistently high throughout the study period. At each predefined time point, more than 95% of patients still on therapy completed the questionnaires as requested.

Induction therapy with ixazomib-thalidomide-dexamethasone

Induction therapy was started in 90 patients and 43 completed all eight cycles. Thirty-three of 47 discontinued due to disease progression (70.2%), 5 due to investigator decision (10.6%), 3 developed unacceptable adverse events (6.4%), and 2 each (4.3%) stopped induction treatment due to death, patient's decision, and insufficient response, respectively. During induction therapy, most of the relevant dimensions in QoL, like global health-status/QoL, physical, cognitive, and social function, and fatigue remained stable, while a clinically relevant reduction in pain was noted during

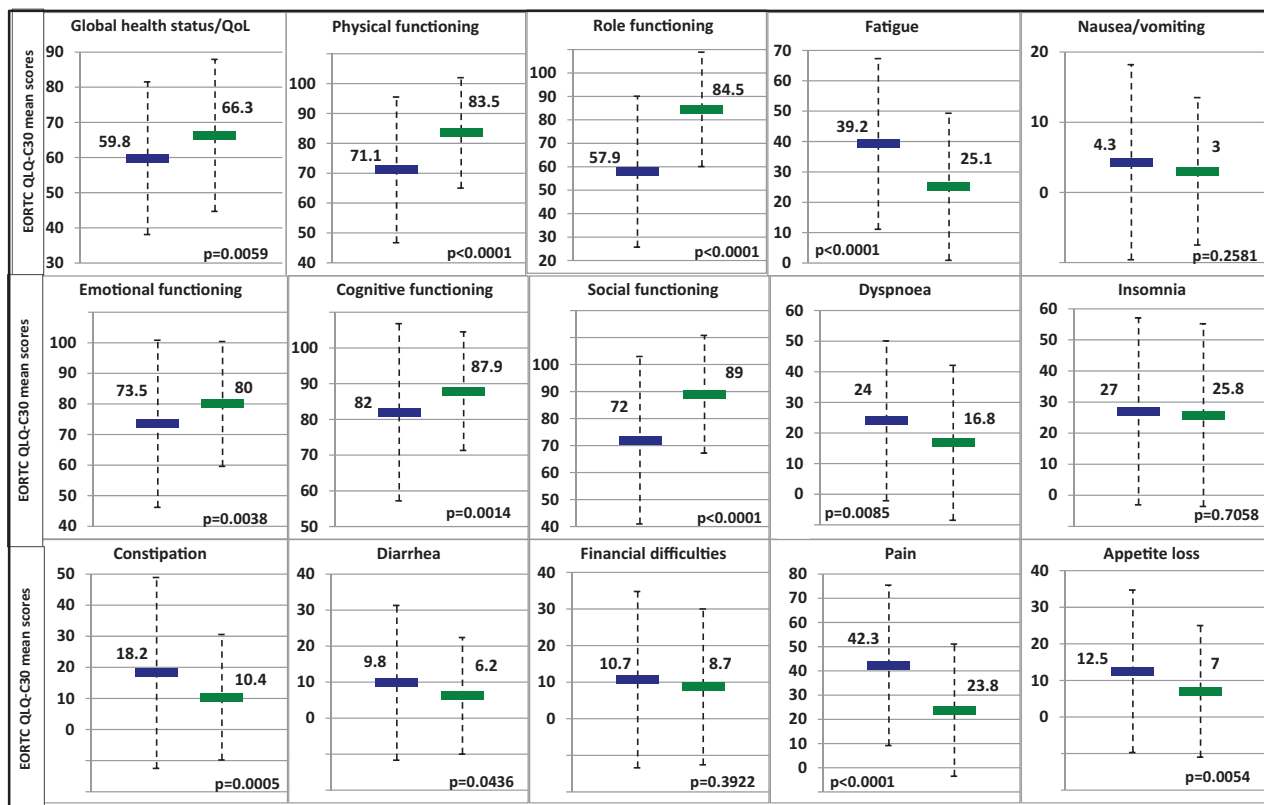


Figure 1. Comparison of several dimensions of QoL between patients of this study (blue) and individuals of the general population of similar age (green).

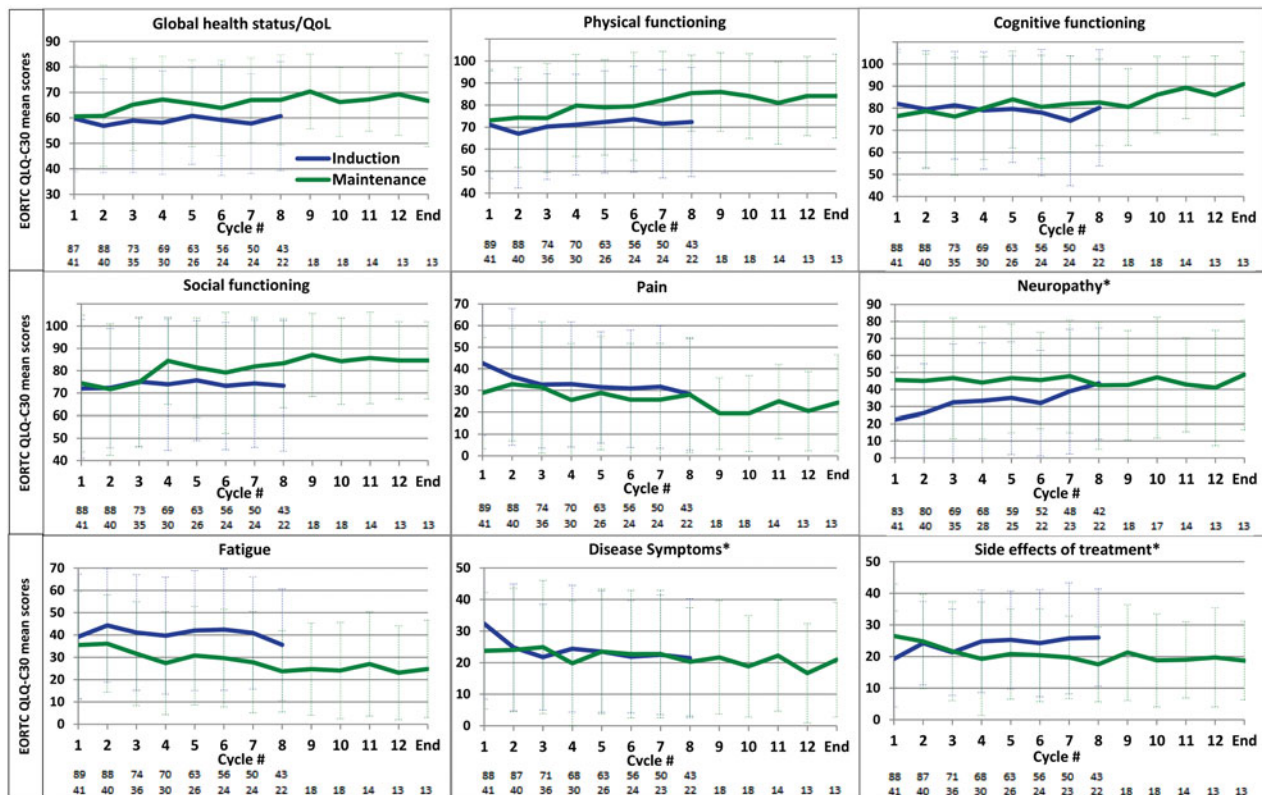


Figure 2. Mean scores of several dimensions of QoL during induction (blue) and maintenance therapy (green). A difference in the score of ≥ 10 is considered the threshold of a minimal important difference and of clinical relevance.

cycles 5–8, and at the end of induction therapy. The reduction was significant for cycle 5 (-10.8 , $p = .0124$) and cycle 8 (-14.0 , $p = .0331$). The mean score of disease symptoms reached the MID at cycle 3 (-10.7 , $p = .0001$), cycle 6 (-10.6 , $p = .0035$), and at cycle 8 (-10.9 , $p = .0852$). Patient-reported neuropathy was present in 41% of patients at time of enrollment into the trial (mean score 22.5). Polyneuropathy (PNP) worsened significantly and clinically meaningfully shortly after starting therapy at cycles 4, 5, 7, 8, and at end of induction treatment, where the highest difference was noted ($+23.0$, $p = .0094$) (Figure 2).

Maintenance therapy with ixazomib

Forty-three of the 76 eligible patients (56.6%) started maintenance therapy and 13 of them (17.1%) completed all 12 cycles. Reasons for discontinuation were disease progression in 26, PNP in 1, and patient's decision in 3 patients. Patients who started maintenance therapy did not differ at baseline in the scores of the important domains (health-related QoL, physical functioning, fatigue, pain, neuropathy, disease symptoms, and cognitive function; differences were not significant, and data not shown) from patients who stopped

therapy before the planned enrollment in the ixazomib maintenance phase. Patients who discontinued before the end of induction therapy in general scored lower at time of last QoL assessment compared to those who were started on maintenance (assessment at start of maintenance), but a clinical relevant significant difference was noted for fatigue (-15.7 , $p = .021$) and neuropathy ($+17.6$, $p = .019$), only (Table 2).

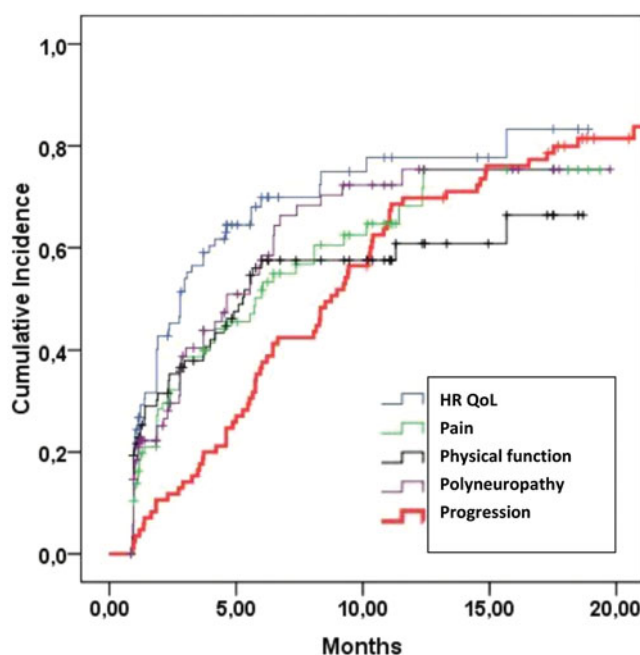
During maintenance treatment (Figure 2), scores improved for most dimensions assessed, specifically for health-related QoL and physical functioning (reaching the MID at cycles 8–10, cycle 12, and at end of maintenance and was significant for cycle 9 only ($+12.9$, $p = .0151$)). For cognitive functioning, a clinically relevant difference was observed at cycle 11 and end of maintenance ($+12.9$ and $+14.6$, not significant), while for social functioning scores ≥ 10 were noted at cycles 4, 9, 11, 12, and at end of maintenance, but differences were not significant. Regarding the symptom scales, clinically relevant improvement was observed for fatigue at cycles 8–10 and 12 and at end of maintenance [significant at cycle 8 only (-11.8 , $p = .0284$)], while scores for neuropathy, pain, disease symptoms, and side effects of treatment remained relatively stable during maintenance therapy (Figure 2).

Table 2. Mean scores and standard deviation of parameters of QoL in patients at start of maintenance therapy and in those who discontinued treatment earlier.

Parameter	Patients		Significance, $p =$
	No maintenance therapy due to earlier discontinuation ($n = 47$)	Enrolled in maintenance ($n = 43$)	
Assessment	at discontinuation	at cycle 1 of maintenance	
Health-related QoL	51.9 ± 23.7	59.8 ± 19.6	.07
Physical functioning	62.6 ± 27.8	72.7 ± 23.3	.13
Fatigue	51.9 ± 31	36.2 ± 23.9	.021
Pain	43.1 ± 34.6	29.1 ± 25.6	.091
Neuropathy	28.6 ± 31.5	46.2 ± 35.6	.019
Cognitive function	75.2 ± 29.1	73.6 ± 30.4	.90
Disease symptoms	30.3 ± 21.8	23.8 ± 18.4	.22
Side effects of treatment	26.3 ± 14.6	26.5 ± 16.4	.98

QoL: quality of life.

Bold represent the parameters which showed a significant difference between patients with early discontinuation and those who made it until enrollment in the maintenance part.

**Figure 3.** Time to progression (red) and time to deterioration (score $\Delta \geq 10$) of health-related QoL (blue), physical functioning (black), pain (green), and neuropathy (purple).

Time to deterioration of global health status/QoL, physical functioning, progressive disease, and to reduction in pain and disease symptoms

Time to deterioration of the health-related QoL and neuropathy by MID ≥ 10 was shorter (median 2.8 and 4.6 months, respectively) compared to time to objective signs of disease progression [median: 8.8 months (Figure 3), and time to deterioration of physical functioning and pain was also shorter than time to progression (median 5.3 and 5.8 months, respectively).

Variables associated with PFS and OS

Global health-status/QoL and physical functioning were associated with survival (Figure 4). PFS and OS were significantly longer in patients with a health-

status/QoL score of 66.7, which was the median value at baseline, or greater compared to those with lower scores (median: 10.2 vs 6.6 months, $p = .019$, and not reached vs 22.9 months, $p = .005$, respectively). Similarly, when the median score of 77.3 of physical functioning was used as cutoff, OS was found to be significantly longer in those with higher scores (not reached vs. 22.9 months, $p = .005$), but for PFS no difference between both groups was noted (median 8.5 vs 8.3 months, $p = .618$).

Discussion

Traditionally, physicians' primary treatment goal was improvement in response rate, quality of response, PFS, and OS. With patients living longer, increasing

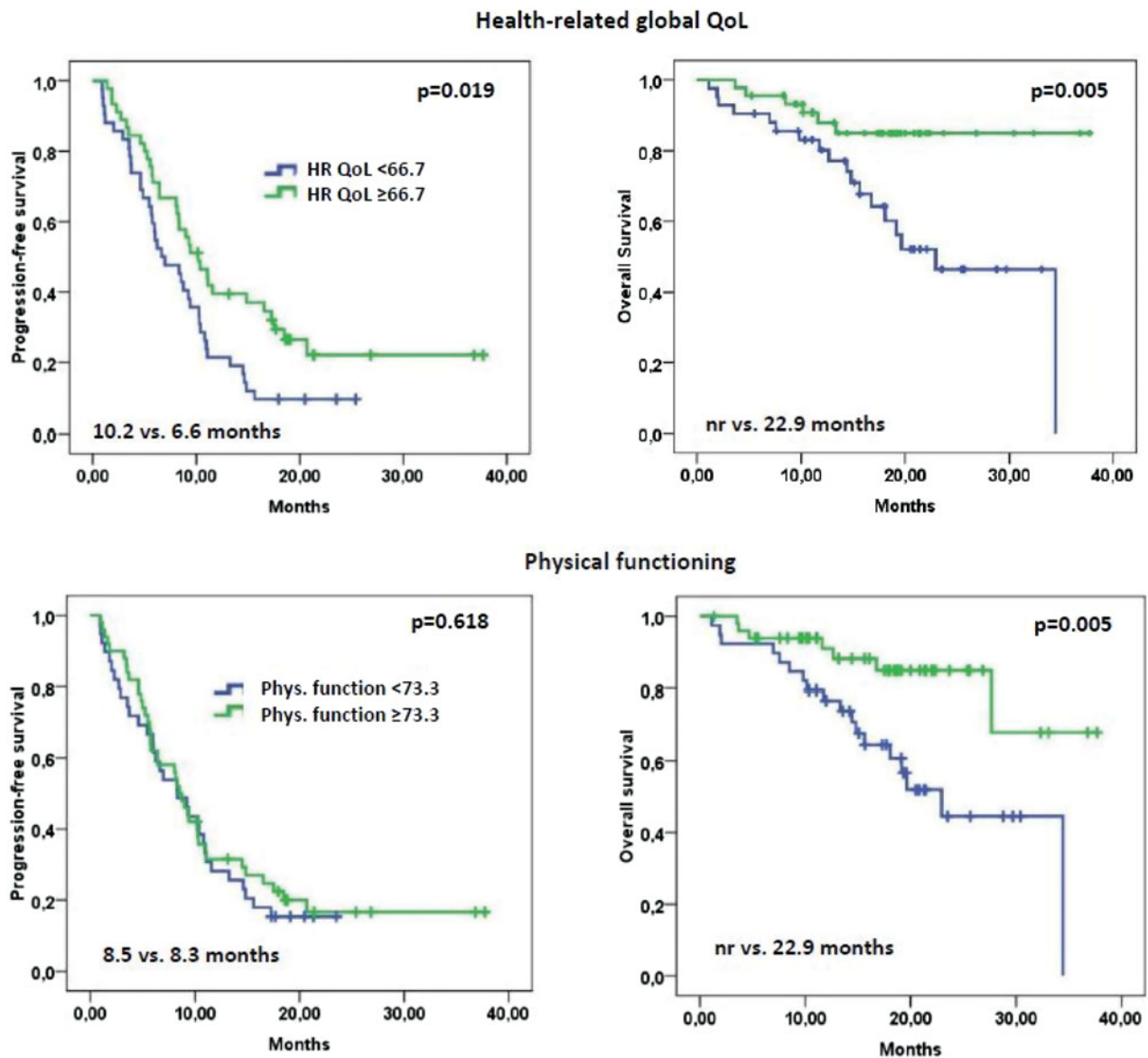


Figure 4. Health-related I QoL and physical functioning (grouped according to $<$ or \geq median baseline score) and PFS and OS.

patient involvement in decision-making, and increased focus on QoL data by regulatory authorities [26,27], patient-reported outcome data have become an essential source of information, both in clinical trials and in clinical practice [28]. This study highlights the significant impairment of most dimensions of QoL in our patients compared to the general population, shows improvement and deterioration of specific QoL items during treatment with IxaThalDex, improvement in almost all items during ixazomib maintenance therapy, and a decrease of specific QoL items already a few months before the criteria for progressive disease were met.

Although the impact of myeloma on QoL may vary greatly between individual patients depending on the stage, aggressiveness of the disease, treatment, and

the biologic fitness of the affected patients, many dimensions of physical QoL are severely impaired, particularly when compared to the general population. The greatest impairment was noted for role, social, and physical function, followed by fatigue and pain. Other dimensions, such as health-related QoL, emotional well-being, cognitive function, dyspnea, appetite loss, and constipation, were also markedly impaired, but differences did not reach the MID ($\Delta \geq 10$), indicating men's ability to adapt to difficult life situations. The baseline scores obtained in our patients are similar to those reported for the ENDEAVOR study comparing carfilzomib-dexamethasone with bortezomib-dexamethasone [12], the TOURMALINE MM-1 trial comparing ixazomib-lenalidomide-dexamethasone with lenalidomide-dexamethasone [8], the ASPIRE

study comparing carfilzomib-lenalidomide-dexamethasone with lenalidomide-dexamethasone [29], but more favorable compared to the patient populations enrolled in the first-line treatment studies FIRST [23] and VISTA [30]. It remains unclear whether this difference in baseline QoL scores between older and recent trials is a random observation, or the result of a more careful selection of study patients for the more recent studies, or differences in disease status.

Induction therapy with IxaThalDex resulted in the intended reduction of pain, but was associated with increasing neuropathy, while most other dimensions of QoL assessed, notably health-related QoL, physical functioning, and emotional well-being, remained rather stable during exposure to the treatment regimen. The 43 patients who started maintenance therapy had significantly less fatigue and somewhat less pain but significantly more neuropathy compared to those who discontinued treatment earlier. Other differences in terms of better health-related QoL, physical functioning, and fewer disease symptoms were noted, but these differences did not meet the required MID. Nevertheless, these results indicate that, like in most trials with a maintenance arm, patients must have responded to previous therapy, making them more likely to tolerate treatment longer and to benefit from prolonged therapy. Recognizing this phenomenon is important when interpreting the improvement in several dimensions of QoL at start of, and during maintenance therapy, which likely reflects a combination of both, the selection of patients with *a priori* better QoL, and the discontinuation of thalidomide and dexamethasone as side effects prone therapy. It also highlights excellent tolerance of ixazomib, particularly when given as single agent maintenance therapy, which was not associated with diarrhea or other relevant gastrointestinal toxicity.

The compliance rate was always above 95% as long as the patients were treated according to the protocol. Patient-reported assessments are the gold standard for QoL studies and results sometimes are discordant to physician's assessments, who often underrate the severity of symptoms such as pain; rarely, as noted in the Tourmaline-1 study, contrary findings are made, where patients did not report more nausea and vomiting during ixazomib maintenance but care givers did. Of note, assessments were no longer performed after patients discontinued therapy either because of progression of disease, or because of any other reason, which is one of the limitations of this study. Other limitations may be due to the open label design of the study which is inherent in phase II trials, and due to

the limited number of patients that completed maintenance therapy, which in part is unavoidable in patients with RRMM due to the increasing proportion of treatment failures during patient's course of their disease. For rating of neuropathy only question 43 of the QLQ MY-20 was used, which is less informative than a neuropathy-specific questionnaire and has not been validated as such. Also, one should keep in mind that the EORTC instruments do not specifically capture satisfaction with sexual function, an item which is of importance to a proportion of patients with excellent control of their disease [31,32]. Furthermore, other instruments such as the FACT-MM PRO [33] or the FACT-G could have been used, but we selected the EORTC QLQ C30 and QOL-MY20 questionnaire for this study as the latter tools have uniformly been used in all of the recent MM trials [9,12,13,28,29,23] with QoL assessments, a fact which facilitates comparison of results.

This study provides information on another important issue in MM, which may be informative for other cancers as well, namely on the presumed coupling between PFS and good QoL. Generally, physicians anticipate that patients enjoy a good QoL as long as they maintain their response status without meeting the criteria of progression. This dogma is not supported by the data obtained in this study, which show a clinically relevant deterioration in the scores of certain dimensions of quality of life such as global health-status/QoL, physical functioning, fatigue, and pain 2–3 months before progression of the underlying malignant disease (Figure 3). In our previous analysis of the QoL data of the ENDEAVOR trial [12], we observed similar findings indicating that this is a general phenomenon, which reduces the benefits of the time without progression by roughly 2–3 months. The most likely explanation is the rigidity of the criteria for myeloma progression, which do not include the clinical term 'symptomatic progression' [34], but instead require a 25% increase in paraprotein and/or meeting other parameters, which usually are observed with some delay from the time the malignant clone starts to regrow again. Obviously, evolving relapse may induce symptoms way before the arbitrarily defined criteria of progression are met. This discrepancy is more frequently seen in heavily pretreated patients with an increasing uncoupling between M-protein secretion and tumor proliferation, because of increasing downregulation of XBP-1 resulting in increasing de-differentiation of myeloma cells and impairment of their protein synthesis capacity [35]. Consequently, patient-reported outcomes need to be

assessed in parallel to clinical metrics in order to allow a more precise appreciation of the impact of any therapeutic regimen.

Lastly, our results support previous findings of an association between QoL at baseline and survival in myeloma [36,37] and in other cancers [38]. Better health-related QoL was associated with increased PFS, and both higher health-related QoL and physical functioning were associated with prolonged survival. Taken together, our results highlight that PRO assessments are an essential requirement for understanding patient's individual needs and impairments, for prognostication, and for elucidating the impact of therapy on the various dimensions of QoL.

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Author contributions

H. L., W. P., S. T. K., A. E., M. S., D. L., R. H., E. G., A. P., K. W., D. N., H. E., W. W., H. R., L. P., T. J., K. K., T. M., R. G., and N. Z. treated patients within the study, S. N. provided Clinical Lymphoma, Myeloma & Leukemia January 2019 data from individuals of the general population; A. H. provided statistical expertise. A. M. analyzed data. H. L. wrote a first draft of the manuscript. All authors participated in the manuscript development and approved the final version.

Disclosure statement

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