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Ixazomib, Daratumumab, and Low-Dose Dexamethasone in Frail Patients With Newly Diagnosed Multiple Myeloma: The Hovon 143 Study

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PURPOSE Frail patients with newly diagnosed multiple myeloma have an inferior outcome, mainly because of a high discontinuation rate due to toxicity. We designed a phase II trial specifically for frail patients, evaluating the efficacy and tolerability of ixazomib-daratumumab-low-dose-dexamethasone (Ixa-Dara-dex).

METHODS Sixty-five patients, who were frail according to the International Myeloma Working Group frailty index, were treated with nine induction cycles Ixa-Dara-dex followed by maintenance with Ixa-Dara for a maximum of 2 years.

RESULTS The overall response rate on induction therapy was 78%. After a median follow-up of 22.9 months, median progression-free survival (PFS) was 13.8 months and 12-month overall survival (OS) was 78%. Median PFS and 12-month OS were 21.6 months and 92% in patients who were frail based on age > 80 years alone, versus 13.8 months and 78%, and 10.1 months and 70% in patients who were frail based on additional frailty parameters either ≤ 80 or > 80 years of age, respectively. In 51% of patients, induction therapy had to be discontinued prematurely, of which 6% because of noncompliance to study treatment, 9% because of toxicity, and 9% because of death (8% within 2 months, of which 80% because of toxicity). Quality of life improved during induction treatment, being clinically meaningful already after three induction cycles.

CONCLUSION Ixa-Dara-dex lead to a high response rate and improved quality of life. However, treatment discontinuation because of toxicity and early mortality, negatively influencing PFS and OS, remains a concern in frail patients. The outcome was heterogeneous across frail subpopulations. This should be taken into account in the design and interpretation of future studies in frail patients, to pave the way for more precise treatment guidance.

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ASSOCIATED CONTENT

Appendix

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Multiple myeloma (MM) is a disease of older adults, reflected by a median age at diagnosis of 69 years.^{1,2} During recent years, the prognosis of older, non-transplant eligible (NTE) newly diagnosed multiple myeloma (NDMM) patients has improved significantly, mainly because of the addition of the anti-CD38 monoclonal antibody daratumumab to the standards-of-care bortezomib-melphalan-prednisone (dara-VMP) or lenalidomide-dexamethasone (dara-Rd).^{3,4} Interestingly, these regimens were found to be efficacious irrespective of age.^{3,4} However, in these clinical trials, frailty assessment was not incorporated. Palumbo and colleagues have shown in a large International

Myeloma Working Group (IMWG) trial that frailty, not only based on age, but also on comorbidities and dependency in (instrumental) activities of daily living (iADL), was associated with an inferior progression-free survival (PFS) and overall survival (OS) as well as higher rates of treatment discontinuation and non-hematological adverse events (AEs), which was confirmed by others.⁵⁻⁷ This indicates that study results in older NTE patients cannot be translated to frail patients with MM, highlighting the importance of clinical trials in frail patients. To the best of our knowledge, there are no published clinical trials yet that are specifically designed for frail patients. Besides the original IMWG-trial, there are only two published prospective trials

CONTEXT

Key Objective

Frailty as defined by the International Myeloma Working Group is associated with inferior clinical outcome. Prospective clinical trials in frail patients are lacking. To develop effective treatment regimens, we performed the first clinical trial specifically designed for frail patients. To this end, eligibility criteria were broad and drugs with presumed low toxicity were chosen.

Knowledge Generated

Ixazomib-daratumumab-low-dose-dexamethasone induced high response rates and improved quality of life. However, even low-grade toxicity led to treatment discontinuation and noncompliance, hampering efficacy. The study provides the first indication that the level of frailty, either based on age alone or based on geriatric impairments and/or comorbidities, is associated with outcome.

Relevance

Study results from nontransplant eligible patients cannot be translated to frail patients with multiple myeloma. This trial (1) provides a platform for the future design of trials for frail patients for more precise treatment guidance by proposing a frailty subclassification and (2) indicates that frail patients have different side-effect profiles and might need lower starting dose, only allowing dose increments in the absence of side effects.

describing post-hoc subanalyses of frail patients.^{8,9} In the phase II trial that evaluated three different low-dose bortezomib regimens, the outcome of frail was inferior as compared to intermediate-fit and fit patients. However, random assignment did not occur, so the feasibility and efficacy of the three different regimens could not be compared in the different frailty groups.⁸ In the randomized EMN01-study, post-hoc analysis showed that the addition of alkylators to lenalidomide-based treatment led to higher treatment discontinuation rates because of AEs without improvement in survival in frail patients, suggesting that in this patient group a gentler regimen is preferred.⁹ Therefore, we investigated the combination of ixazomib, daratumumab, and low-dose dexamethasone in a population of frail patients, as defined by the IMWG-frailty index. Ixazomib and daratumumab were chosen because of their favorable safety profile.^{3,4,10-17} Dexamethasone dose was significantly reduced as compared to other studies in NTE patients, as an excess mortality has been reported with high doses of dexamethasone.¹⁸

METHODS

Patients

Patients were eligible if they had a previously untreated symptomatic MM. Patients had to be frail according to the IMWG-frailty index (Data Supplement, online only).⁷ Sufficient bone marrow capacity (absolute neutrophil count $\geq 1.0 \times 10^9/L$; platelet count $\geq 75 \times 10^9/L$) was required. Exclusion criteria were liberal; only patients with severe organ dysfunction, defined as New York Heart Association class III and IV, creatinine clearance < 20 mL/min, and transaminases ≥ 5 normal level, were excluded. Only patients with an active malignancy requiring treatment were excluded. In addition, neuropathy grade 1 with pain or

grade ≥ 2 and active or uncontrolled infections excluded participation in the trial (for complete inclusion and exclusion criteria, see the Data Supplement). The study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice and approved by the institutional review board and ethics committees before study initiation. All patients provided written informed consent.

Study Design and Treatment

The HOVON-143 trial (NTR6297) is a prospective, multi-center phase II trial conducted in 39 hospitals throughout the Netherlands and Belgium. Study treatment consisted of nine 28-day induction cycles consisting of ixazomib 4 mg (days 1, 8, and 15), daratumumab 16 mg/kg intravenously (cycles 1-2: days 1, 8, 15, and 22; cycles 3-6: days 1 and 15; cycles 7-9: day 1), and dexamethasone (on the days that daratumumab was administered; cycle 1-2: 20 mg; subsequent cycles 10 mg), followed by maintenance therapy, consisting of 8-week cycles with ixazomib (days 1, 8, 15, 29, 36, and 43) and daratumumab (day 1) until progression for a maximum of 2 years. The protocol recommended antibiotic and antiviral prophylaxis. Vaccinations were advised according to national guidelines, and myeloid growth factor use was permitted according to institutional practice.

Outcomes

The primary end point was the overall response rate (ORR) on induction treatment, defined as a partial response (PR) or better.¹⁹ Key secondary end points are described in the Data Supplement.

Statistical Analysis

For sample size calculation, the optimal Simon's two-stage design was used. An ORR of 50% was considered to be

insufficient and an ORR of 65% sufficient. With an α of .1 and a power of 80%, 60 patients were needed. Taking into account a 10% ineligibility rate, 66 frail patients had to be included (Data Supplement). Since 65 eligible patients were included finally, we computed the point estimate for ORR, 95% CI, and *P* value for overrunning Simon's two-stage design (Data Supplement).^{20,21} Efficacy end points were determined based on outcome of all eligible patients. Time-to-event end points were estimated using the Kaplan-Meier method and 95% CI. Post-hoc analyses of survival in frail subgroups (Data Supplement) were performed using Cox proportional hazard models. Mortality was annotated early (within 60 days of registration) versus late (> 60 days after registration).

Global health status or quality of life (GHS or QOL), evaluated with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, was assessed at baseline, after induction cycles 3 and 9 for patients still receiving protocol treatment.²² Change in GHS or QOL over time was assessed by a linear mixed-effects model, and clinically meaningful health-related quality of life (HRQOL) change from baseline was evaluated using minimal important difference (Data Supplement).²³ Two preplanned interim analyses were conducted, reviewed, and approved by the independent data and safety monitoring board (Data Supplement).^{24,25}

Observations were censored on August 24, 2020. Statistical analyses were performed by Stata version 15.1 and R version 3.6.1. No correction for multiple testing was applied.

RESULTS

From September 2017 to December 2018, a total of 67 patients were enrolled of which two were excluded because of ineligibility (Fig 1). The demographics of the 65 eligible frail patients are described in Table 1. Median age was 81 years (range, 70-92 years). Fifty-one percent of patients had a Charlson Comorbidity Index of ≥ 2 , 25% were ADL-dependent and 57% iADL-dependent. Details about comorbidities and (i)ADL dependencies are described in the Data Supplement. Thirteen (20%) patients were frail based on age > 80 years alone, 32 (49%) were frail based on the frailty parameters ADL, iADL, and/or Charlson Comorbidity Index, but not on age (age ≤ 80 years), and the remaining 20 (31%) were > 80 years of age with

FIG 1. Diagram of the number of frail patients participating in the HOVON 143 study, flow through the induction phase and timing and reason for treatment discontinuation. ^aRepresents two patients who were excluded because of a second malignancy and infection at the time of registration. Ind, induction cycle.

TABLE 1. Demographics at Registration of Eligible Frail Patients

Ixa-Dara-dex	Frail (N = 65)
Median age, years (range)	81 (70-92)
> 80 years (%)	33 (51)
Frail based on age alone (%)	13 (20)
Frail based on only other frailty parameters (%)	32 (49)
Frail based on both age > 80 and other frailty parameters (%)	20 (31)
WHO performance (%)	
0	9 (14)
1	29 (45)
2	20 (31)
≥ 3	5 (8)
Unknown	2 (3)
CCI, median (SD)	2 (1.5)
≤ 1 (%)	32 (49)
≥ 2 (%)	33 (51)
ADL, median (SD)	6 (1.6)
≥ 5 (%)	49 (75)
≤ 4 (%)	16 (25)
(i)ADL, median (SD)	5 (2.5)
≥ 6 (%)	28 (43)
≤ 5 (%)	37 (57)
Total frailty score (%)	
2	32 (49)
3	19 (29)
4	13 (20)
5	1 (2)
ISS disease stage (%)	
I	10 (15)
II	25 (38)
III	29 (45)
Unknown	1 (2)
LDH (%)	
Normal	52 (80)
Elevated	12 (18)
Unknown	1 (2)
Cytogenetic results by FISH/array (%)	
t(4;14)	3 out of 55 (5)
del(17p)	6 out of 59 (10)
t(14;16)	2 out of 55 (4)
High-risk cytogenetic disease ^a	11 out of 56 (20)
R-ISS disease stage (%)	
I	10 (15)
II	25 (38)

(continued in next column)

TABLE 1. Demographics at Registration of Eligible Frail Patients (continued)

Ixa-Dara-dex	Frail (N = 65)
III	12 (18)
Unknown	12 (18)
Type of measurable disease (%)	
IgG	39 (60)
IgA	15 (23)
FLC	9 (14)
Other	2 (3)
Median creatinine clearance (mL/min) (range)	56 (20-90)
Median hemoglobin (mmol/L) (range)	6.2 (4.4-9.5)

Abbreviations: ADL, activities of daily living; CCI, Charlson Comorbidity Index; FISH, fluorescent in situ hybridization; FLC, free light chain; (i)ADL, (instrumental) activities of daily living; ISS, International Staging System; Ixa-Dara-dex, ixazomib-daratumumab-low-dose-dexamethasone; LDH, lactate dehydrogenase; R-ISS, Revised International Staging System; SD, standard deviation; WHO, World Health Organization.

^aHigh-risk cytogenetic disease: presence of t(4;14) and/or t(14;16) and/or del17p13.^{41,42}

additional frailty parameters (Data Supplement). Patients who were frail based on age alone had less often Revised International Staging System 3 (8% v 19% in patients ≤ 80 years with other frailty parameters and 25% in patients > 80 years and other frailty parameters) and better performance (WHO ≥ 2 in 8% v 50% in patients ≤ 80 years with other frailty parameters and 40% in patients > 80 years and other frailty parameters; Data Supplement).

Efficacy

The ORR during induction was 78% (95% CI, 0.73 to 0.82), including 5 (8%) patients with a (stringent) complete response (CR), 18 (28%) with a very good partial response, and 28 (43%) patients with a PR (Table 2). Of the five patients who achieved (s)CR, minimal residual disease analysis was performed in four (80%) and all were minimal residual disease-negative.

After a median follow-up of 22.9 months (range, 12.7-31.0 months), 43 (66%) patients had progressed or died. The median PFS was 13.8 months (Fig 2A). In patients who were frail based on age alone, median PFS was 21.6 months (95% CI, 9.2 to not reached [NR]). Median PFS was 13.8 months (95% CI, 7.8 to NR) in patients who were frail based on other frailty parameters ≤ 80 years of age, and 10.1 months (95% CI, 3.3 to 21.4) in patients who were frail based on both age > 80 years and other frailty parameters (Fig 2B).

After a median follow-up of 22.9 months, 25 out of 65 (38%) patients had died. The median OS was not reached. OS at 12 months was 78% (95% CI, 66 to 87) (Fig 2C).

TABLE 2. Best Response on Induction Treatment With Ixa-Dara-dex
Response Status¹⁹

	All (N = 65)
ORR (≥ PR), No. (%)	51 (78) ^a
(s)CR	5 (8)
VGPR	18 (28)
PR	28 (43)
MR, No. (%)	7 (11)
SD, No. (%)	2 (3)
PD, No. (%)	1 (2)
NE, No. (%)	4 (6)
Median time to first response (range)	1 (1-6)
Median duration of response (range)	11 (1-26)

Abbreviations: MR, minimal response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; (s)CR, (stringent) complete response; SD, stable disease; VGPR, very good partial response.

^aFour patients were not evaluable for response because of early death within 1 month (three patients) and one because of missing parameters.

Twelve-month OS was 92% (95% CI, 57 to 99) in patients who were frail based on age alone, 78% (95% CI, 59 to 89) in patients who were frail based on only other frailty parameters and ≤ 80 years of age, and 70% (95% CI, 44 to 85) in patients who were frail based on both age > 80 years and other frailty parameters (Fig 2D). Thirteen patients died on protocol: three because of progression (relapse mortality 3 out of 65 [5%]) and 10 because of other reasons (nonrelapse mortality 10 out of 65 [15%]). Causes for nonrelapse mortality were infections (4 out of 10), organ dysfunction (3 out of 10), sudden death (2 out of 10), and bleeding because of thrombocytopenia (1 out of 10). Five patients died within 60 days from treatment initiation (early mortality 5 out of 65 [8%]), all but one because of toxicity. Among the five patients who died early, three were frail based on both age > 80 years and other frailty parameters, one based on age > 80 years alone, and one on only other frailty parameters ≤ 80 years of age (Data Supplement). Patients who died early were older (> 80 years; 80% v 40%), more often had Revised International Staging System 3 (60% v 24%), and an elevated lactate dehydrogenase (40% v 16%) as compared to patients who died after 60 days, respectively (Data Supplement).

Tolerability

The patient flow through the study is summarized in the CONSORT diagram (Fig 1). Thirty-three out of 65 (51%) patients discontinued treatment with ixazomib-daratumumab-low-dose-dexamethasone (Ixa-Dara-dex) before initiation of maintenance. This was because of progression in 12 (19%), intercurrent death in 6 (9%: three infections, one acute renal failure, and two sudden unexplained deaths), toxicity in six (9%; for details, see Fig 1), noncompliance to

the study treatment in four (6%), and other reasons in five (8%; for details, see Fig 1). Discontinuation because of an infection occurred in four patients (6%). Patients > 80 years, either with or without other frailty parameters, discontinued treatment more often because of reasons other than progressive disease (PD) or death as compared to younger patients: 30% and 38% versus 13%, respectively (Data Supplement). An additional 12 patients (18%) discontinued ixazomib only, which was related to peripheral neuropathy (PNP) in 10 out of 12 patients (grade 1 in three, grade 2 in four, and grade 3 in three patients) (Data Supplement).

The median relative dose intensity and interquartile range (IQR) on induction treatment for ixazomib was 0.91 (0.75-1.00), for daratumumab 0.97 (0.90-1.00), and for dexamethasone 0.98 (0.94-1.00) (Data Supplement). In 14 patients (22%) ixazomib dose was reduced, including one patient with two dose-level reductions, and in 14 (22%) ixazomib had to be withheld (one dose in 12 and two doses in two patients), of which three in combination with dose-level reductions (Data Supplement). Dose withholds of daratumumab and dexamethasone were observed infrequently (Data Supplement).

Thirty-two patients (49%) started maintenance treatment, of whom 10 (15%) with daratumumab monotherapy. After a median follow-up of 13.6 months (7.4-21.2) from the start of maintenance, 15 patients (47%) discontinued therapy, because of PD (12 patients) or other reasons (three patients; for details, see Fig 1).

Of the patients who discontinued protocol treatment because of progression, 20 out of 24 (83%) started with second-line treatment. This was only 28% (5 out of 18) in those patients who discontinued therapy for other reasons than PD (toxicity, noncompliance, or other reasons). After a median follow-up of 22.9 months, median PFS2 was 23.5 months (95% CI, 18.3 to NR), which was 31.9 months in those being frail based on age alone.

Safety

Cumulative hematological and nonhematological toxicity grade ≥ 3 during induction was reported in 20 out of 65 (31%) and 48 out of 65 (74%) patients, respectively (Table 3). AE incidences were comparable in the three frail subgroups (Data Supplement). Nonhematological toxicity grade ≥ 3 included neuropathy (6%), cardiac (11%), GI (13%), and infectious (25%) AEs. Antibiotic and antiviral prophylaxis was started in 92% and 95% of patients, respectively. Antibiotic prophylaxis consisted of co-trimoxazole in the majority of patients (95%, only 5% received levofloxacin instead).

After a median follow-up of 22.9 months (12.7-31.0), 53 out of 65 (81.5%) patients experienced serious adverse events (SAEs), mainly because of (prolongation of) hospitalization, without differences in SAE incidences between

FIG 2. Survival outcomes. PFS from registration for (A) all eligible frail patients and (B) stratified by frail subgroups. OS from registration for (C) all eligible frail patients and (D) stratified by frail subgroups. Frail subgroups are divided by patients who are frail based on age > 80 years alone ($n = 13$), based on only other frailty parameters and ≤ 80 years of age ($n = 32$), or based on both age > 80 years and additional frailty parameters ($n = 20$). OS, overall survival; PFS, progression-free survival.

frail subgroups. Of 13 SAEs resulting in death, none of them were considered to be treatment-related.

HRQOL

All patients completed a baseline HRQOL questionnaire (compliance 100%). Compliance after three induction

cycles was 56 out of 58 (96.6%) and after nine cycles 38 out of 41 (92.7%) (Data Supplement). The baseline GHS or QOL score was 54.1 (standard deviation [SD], 26.2), and increased after three and nine cycles to 65.8 (IQR, 50.0–83.3) (+11.7 from baseline) and 71.5 (IQR, 58.3–83.3) (+17.4 from baseline), respectively. Improvement in GHS or

TABLE 3. AE Grade 2-4 During Induction Treatment

CTCAE Grade	2	3	4
Any hematological AE, No. (%)	12 (18)	12 (18)	8 (12)
Anemia	4 (6)	1 (2)	1 (2)
Thrombocytopenia	6 (9)	12 (19)	3 (5)
Neutropenia	7 (11)	2 (3)	4 (6)
Any nonhematological AE, No. (%)	13 (20)	36 (55)	12 (18) ^a
Cardiac	3 (5)	5 (8)	2 (3)
CNS	11 (17)	4 (6)	1 (2) ^b
Edema	14 (22)	—	—
GI	16 (25)	7 (11)	1 (2)
Infections	11 (17)	12 (19)	4 (6) ^b
Infusion-related reactions	5 (8)	1 (2)	—
Pain	15 (23)	5 (8)	—
PNP ^c	10 (16)	4 (6)	—
Psychiatry	7 (11)	5 (8)	—
Skin	11 (17)	4 (6)	—

NOTE. AEs of grade ≥ 3 that occurred in at least 5% of patients and AEs of special interest are reported.

Abbreviations: AE, adverse event; CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0⁴³; PNP, peripheral neuropathy.

^aIncluding four patients with grade 5 nonhematological AE.

^bIncluding one patient with grade 5 AE.

^cGrade 1 PNP was observed in 11 patients (17%).

QOL during induction treatment was statistically significant and clinically relevant already after induction cycle 3, further increasing over time during induction (Fig 3 and the Data Supplement).

DISCUSSION

The results of this first prospective study, which was specifically designed for frail NTE NDMM patients, showed that treatment with ixazomib, daratumumab, and low-dose dexamethasone resulted in a rapid and high overall response of 78%. Importantly, treatment of this pronounced frail population led to a clinically relevant improvement in GHS or QOL already after 3 months, which further increased during induction therapy. The increase seems even more pronounced than with dara-VMP and dara-Rd in NTE NDMM patients.^{26,27} This is critical, since there is evidence that patients with advanced cancer and older age are more likely to prefer quality over length of life, aiming to remain independent in daily life and accepting less serious side effects.²⁸⁻³¹

Notwithstanding high response rates, the median PFS was limited with 13.8 months. At 12 months, 78% of patients were alive. Importantly, we showed that even within this strictly defined frail patient population, based on the IMWG-frailty index, clinical outcome was heterogeneous. Of the

patients who were defined frail based on age alone, the median PFS was 21.6 months and 92% were still alive at 12 months. However, the majority of frail patients (80%) had geriatric impairments and/or comorbidities. From those, the patients > 80 years of age had a median PFS of only 10.1 months and 30% died within the first year from treatment initiation. Early death and treatment discontinuation because of reasons other than progression or death are important reasons for concern in this vulnerable population.

To put our findings in context, comparisons of studies in frail patients, according to the IMWG-frailty index, are needed. This is challenging, as our trial is the first prospective trial including frail NDMM patients only, whereas other trials incorporated also nonfrail patients and performed post-hoc subanalyses only. These analyses show a PFS ranging from 13.8 to 21.5 months with low-dose bortezomib and lenalidomide-based regimens.^{8,9} Such a range can well be explained by differences in the level of frailty, either based solely on age or with additional geriatric impairments. However, we cannot exclude that the difference in outcome are partly treatment-related. Indeed, in a preliminary analysis in frail patients treated with ixazomib-based regimens (although without daratumumab), the median PFS was 12.2 months only.³² In addition, although we aimed for a combination of ixazomib and daratumumab maintenance therapy, 31% were treated with daratumumab monotherapy because of premature discontinuation of ixazomib.

This highlights the need to further reduce toxicity in this vulnerable population. This especially is important for nonhematological AEs, as those were observed more frequently compared with the EMN01 and IMWG-trials: 74% versus 39%-45% and 34%, respectively.^{7,9} PNP deserves special attention, as unexpectedly, we found that low-grade PNP was the main cause of discontinuation of ixazomib. The impairment in walking and balance and worse HRQOL caused by PNP may have contributed to early discontinuation of ixazomib.^{33,34} Another possibility is to decrease infections by expanding antibacterial prophylaxis. The addition of levofloxacin, either with or without cotrimoxazole, for the first 3 months of treatment has recently been shown to reduce febrile episodes or death by 34%.³⁵ Furthermore, as we observed side effects (eg, psychiatric) that could have been provoked by even the low dose of dexamethasone we used, dexamethasone-free regimens should be explored, which is currently investigated by the Intergrroupe Francophone du Myelome-study group (ClinicalTrials.gov identifier: [NCT03993912](https://clinicaltrials.gov/ct2/show/study?term=NCT03993912)).^{18,36}

Another concern is the 8% early mortality rate, of which 80% was because of toxicity, as is also reported in other studies including frail patients.^{7,8,37} Of the patients who died early, 4 out of 5 patients were frail based on at least other frailty parameters than age, comparable with preliminary post-hoc analysis of the original IMWG-trial.³⁸ Unfortunately, the limited number of frail patients included in this

FIG 3. HRQOL during induction. Estimated statistically significant change in GHS or QOL over time from baseline through the end of induction cycle 3 until the end of induction cycle 9 in patients who completed nine induction cycles. The dotted horizontal lines represent the calculated threshold for minimal important difference (Δ 11.3). A positive score represents an improvement in GHS or QOL, and a negative score represents deterioration in GHS or QOL. The *P* value represents the significance level of change in GHS or QOL over time. For further details, please refer to the Data Supplement. GHS or QOL, global health status or quality of life; HRQOL, health-related quality of life.

study restricted multivariate analyses to explore independent prognostic markers for adverse clinical outcome. This is urgently needed, as the discriminative power of the currently available frailty indexes such as the IMWG-frailty index and the R-MCI is still insufficient to select patients who are suitable for therapy or in whom benefit will be negligible, leading to the decision not to start treatment.^{5,7} In addition to refinement of the IMWG-frailty index by subclassification we here describe, we are currently

investigating the added value of functional frailty assessments and sarcopenia. This will hopefully allow the identification of a smaller but more vulnerable frail population with inferior outcome, for whom the need for treatment modification is most pronounced.

One might argue we should compare our study with dara-VMP (median PFS, 36.4 months) and dara-Rd (median PFS projected to be > 50 months); however, we feel this is not reasonable. Pronouncedly fitter patients were included in these studies as compared to our study, although age and performance status were comparable.^{4,9,39,3,4,17} This is exemplified by a higher incidence of SAEs in our study; 81.5% versus 41.6% and 62.9% with dara-VMP and dara-Rd, respectively.^{3,4} Moreover, we observed higher discontinuation rates because of AEs; 6% versus < 1%.^{3,4} Furthermore, patients $\geq$ 75 years of age who were treated with Rd in the control arm of the dara-Rd study had a median PFS of 31.9 months, whereas in frail patients who were treated with a similar Rd regimen in the EMN01 and FIRST trials, the median PFS was only 18.2 and 19.4 months, respectively.

In conclusion, with this first study, specifically designed for frail patients, we show that a presumably nontoxic regimen, such as Ixa-Dara-dex, leading to high response rates and improvement in HRQOL indeed, needs modification to limit not only high-grade but also low-grade toxicity and early mortality. Our study may serve as prototype for forthcoming trials in frail patients. First, using liberal inclusion and exclusion criteria is a prerequisite, supporting not only the feasibility of such trials but also providing insight into the outcome of treatment of severe frail patients with comorbidities and impaired functional performance.⁴⁰ Second, our data indicate to improve supportive care and to investigate other treatment regimes, either with a different side-effect profile or with a much lower starting dose, only allowing dose increments in absence of side effects. Finally, we propose to design studies that are sufficiently powered to determine the outcome in different frailty subcategories based on age-only versus with geriatric impairments and/or comorbidities. This will allow a straight comparison of the outcome of frail patients within and across studies, which will pave the way for more precise treatment guidance.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Ixazomib, Daratumumab, and Low-Dose Dexamethasone in Frail Patients With Newly Diagnosed Multiple Myeloma: The Hovon 143 Study**

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