Ixazomib-thalidomide-low dose dexamethasone induction followed by maintenance therapy with ixazomib or placebo in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplantation; results from the randomized phase II HOVON-126/NMSG 21.13 trial

The prognosis of older patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for stem cell transplantation has greatly improved as a result of treatment with either a combination of bortezomib with lenalidomide, or the addition of daratumumab to bortezomib or to lenalidomide.[1-3] Although not compared head-to-head, progression-free survival (PFS) was longer with lenalidomide used continuously as compared to bortezomib for a limited number of cycles only.[4,5] Continuous treatment with the oral proteasome inhibitor, ixazomib, in combination with lenalidomide and dexamethasone (IRd) did not increase the incidence of grade ≥3 neuropathy as compared to lenalidomide and dexamethasone (Rd) only.[6] A possible additional advantage of continuous therapy with this proteasome inhibitor is that it may overcome the negative impact of high-risk cytogenetic abnormalities.[7] Furthermore, there was no need for discontinuation of ixazomib due to toxicity during the maintenance phase, whereas approximately 25% of patients discontinued lenalidomide treatment.[8,9] Therefore, in this randomized phase II trial (registered at *www.trialregister.nl as NTR4910*), we investigated the efficacy and feasibility of ixazomib *versus* placebo maintenance in transplant-ineligible patients with NDMM, after nine cycles of induction with ixazomib, thalidomide and dexamethasone (ITd) (protocol details in the *Online Supplementary Appendix*). To improve knowledge about unfit and frail patients, we investigated the outcome in such patients, using a simplified frailty score.[10] We did not observe an improvement in PFS with maintenance treatment with ixazomib compared to placebo. However, in the elderly population, including 44% of frail patients, only 55% of patients could be randomized after induction therapy. Importantly, for those patients who were randomized, ixazomib maintenance was very well tolerated and the PFS was comparable in patients >75 *versus* ≤75 years and in frail *versus* unfit or fit patients.

The characteristics of the 143 eligible patients are presented in Table 1. According to the simplified frailty score, using World Health Organization (WHO) performance status as a replacement for (instrumental) activities of daily living, 33 (23%) of patients were classified as fit, 38 (27%) as unfit and 63 (44%) as frail; the frailty score was unknown for 6%. A total of 78/143 (55%) patients were randomized to maintenance treatment with either

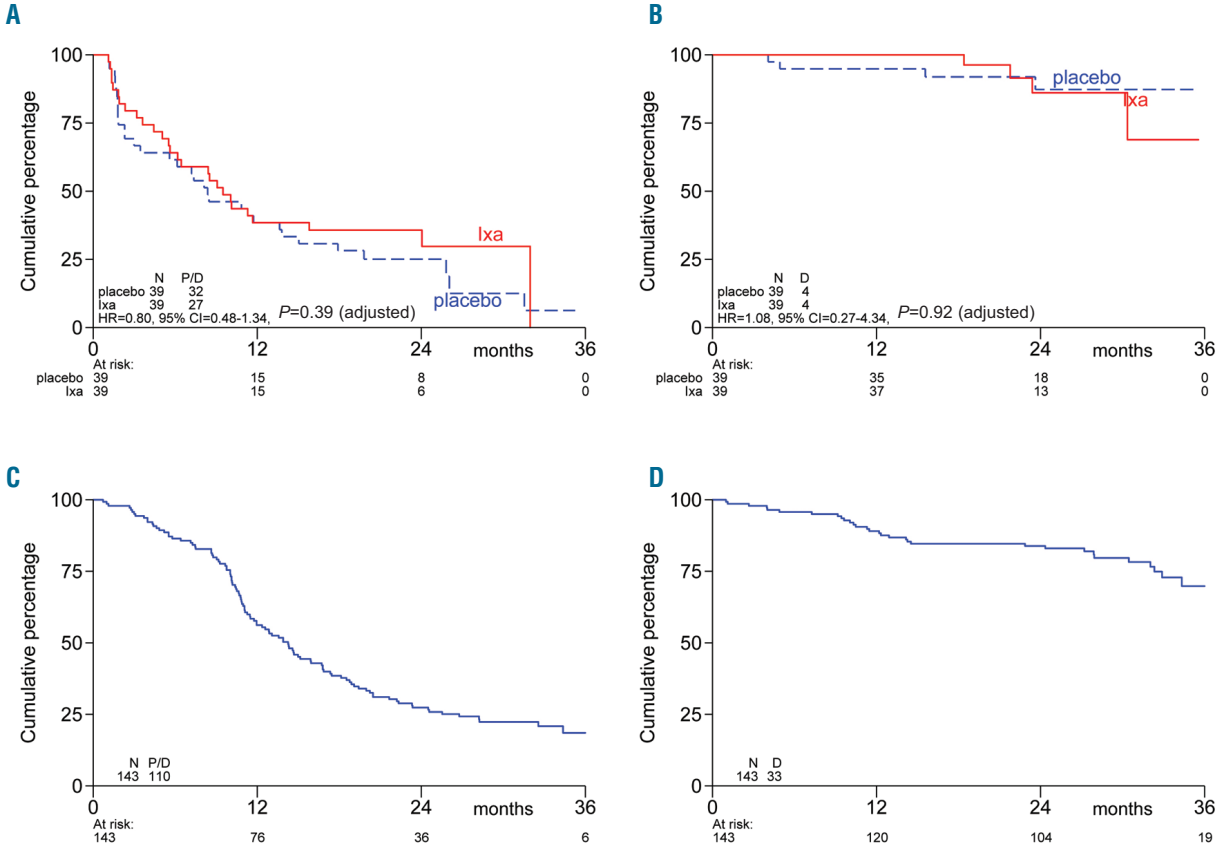

Figure 1. Survival from randomization and registration. (A, B) Progression-free survival (A) and overall survival (B) after randomization (PFS-R and OS-R, respectively). With a median follow-up of 23.4 months after randomization (range, 6.9-35.5), the median PFS-R for patients treated with ixazomib was 9.5 months (95% confidence interval [95% CI]: 5.5-24.0) *versus* 8.4 months (95% CI: 3.0-13.8) for those given the placebo. The OS-R at 18 months for all patients was 96% (88-99%), with the value being comparable for patients treated with ixazomib (ixa, 100%) or placebo (92% [95% CI: 77-97%], *P*=1.00). (C, D) Progression-free survival (C) and overall survival (D) after registration (PFS and OS, respectively). With a median follow-up of 28.5 months (range, 0.9-44.1), the median PFS from registration for all patients was 14.3 months (95% CI: 11.5-16.8). The median OS from registration for all patients has not yet been reached.

Table 1. Demographics of patients at registration and at randomization.

	Induction	Maintenance		% randomized
	ITd	Placebo	Ixazomib	
Total, n (%)	143	39	39	78/143 (55)
Median age (range), years	73 (64-90)	73 (67-82)	72 (66-80)	73 (66-82)
> 75 years n (%)	52 (36)	12 (31)	9 (23)	21/52 (40)
> 80 years n (%)	11 (8)	1 (3)	–	1/11 (9)
WHO performance months, n (%)				
0	51 (36)	20 (51)	15 (38)	35/51 (68)
1	59 (41)	13 (33)	15 (38)	28/59 (47)
2	32 (22)	6 (15)	8 (21)	14/32 (44)
3	1 (1)	–	1 (3)	1/1 (100)
Frailty score, n (%)				
Fit	33 (23)	13 (33)	12 (31)	25/33 (76)
Unfit	38 (27)	14 (36)	9 (23)	23/38 (61)
Frail	63 (44)	12 (31)	14 (36)	26/63 (41)
Unknown	9 (6)	–	4 (10)	4/9 (44)
International Staging System, n (%)				
I	28 (20)	9 (23)	10 (26)	19/28 (68)
II	72 (50)	19 (49)	21 (54)	40/72 (56)
III	42 (29)	11 (28)	8 (21)	19/42 (45)
Unknown	1 (1)	–	–	0/1 (0)
LDH level, n (%)				
Normal	121 (85)	35 (90)	31 (79)	66/121 (55)
Elevated	18 (13)	3 (8)	6 (15)	9/18 (50)
Unknown	4 (3)	1 (3)	2 (5)	3/4 (75)
FISH analysis done, n (%)	132 (92)	34 (87)	36 (92)	70/132 (53)
t(4;14)	12/128 (9)	5/34 (15)	1/3 (3)	6/12 (50)
del(17p)	17/127 (13)	2/34 (6)	5/35 (14)	7/17 (41)
High-risk cytogenetics	27/123 (22)	6/34 (18)	6/33 (18)	12/27 (44)
Standard-risk cytogenetics	96/123 (78)	28/34 (82)	27/34 (79)	55/96 (57)

ITd: ixazomib, thalidomide and dexamethasone; n: number; WHO: World Health Organization; LDH: lactate dehydrogenase; FISH: fluorescence *in situ* hybridization. *Frailty score: based on age, WHO performance status and comorbidities as defined by the Charlson Comorbidity Index;

ixazomib (n=39) or placebo (n=39). Patients who were randomized were younger and less frail at registration (Table 1). The median PFS from randomization (PFS-R) was 9.5 months (95% confidence interval [95% CI]: 5.5-24.0) for ixazomib-treated patients *versus* 8.4 months (95% CI: 3.0-13.8) for those given placebo (Figure 1A). The lack of difference in PFS-R between arms was independent of age, frailty, cytogenetics and best response on ITd induction (*Online Supplementary Figure S1A*). Importantly, although patients who were older, frail or had high-risk cytogenetics were less likely to reach randomization, those patients who were randomized for maintenance therapy experienced a similar outcome compared to younger, non-frail and standard-risk patients (*Online Supplementary Figure S1B-D*). The median overall survival (OS) from randomization has not been reached in either arm and was comparable in the two arms (Figure 1B). The median second progression-free survival (PFS2) from randomization has not been reached yet, since the PFS2 rate was 83% at 18 months, and was comparable in the two arms (*Online Supplementary Figure S2*).

The median PFS from registration for all patients was 14.3 months (95% CI: 11.5-16.8) (Figure 1C). Subgroup analyses showed a comparable PFS in patients with high *versus* standard cytogenetic risk (median 12.0 *vs.* 14.6 months, respectively; *P*=0.11), patients aged ≤75 *versus* >75 years (14.3 *vs.* 13.9 months, respectively; *P*=0.96) and fit *versus* unfit *versus* frail patients (15.9 months *vs.* 13.6 months *vs.* 12.9 months, respectively; *P*=0.26). The median OS from registration has not yet been reached (Figure 1D). OS was independent of cytogenetic risk. Age >75 and frailty were associated with inferior OS rates at 2 years (73% *vs.* 90% in patients ≤75 years, *P*=0.002, and 74% *vs.* 89% in unfit and 90% in fit patients at 2 years, *P*=0.08).

Response rates are presented in Table 2. The ITd induction regimen was effective with an overall response rate of 81%, including 47% of patients who achieved at least a very good partial remission, which is comparable to the rate obtained with bortezomib, lenalidomide, dexamethasone (VRd).[1] Response was not affected by cytogenetic risk status, age or frailty.

The flow of patients through the study is shown in CONSORT diagrams (*Online Supplementary Figure S3A, B*). Sixty-five of 143 patients (45%) discontinued the study prematurely, during or after induction treatment, and were not randomized. Reasons for discontinuation of induction treatment were toxicity (17%), progressive disease (15%), death (3%) and other reasons (10%) (*Online*

Table 2. Response rates during induction and on protocol.

Response rate (%)	ITd induction N=143	On protocol placebo N=39	On protocol ixazomib N=39
Overall response	81	97	100
(s)CR	9	28	23
VGPR	38	44	38
PR	34	26	38
< PR	19	3	–
≥ VGPR	47	72	62
Improvement in response during maintenance		13	13
Median time to response (months)	1.1		
Median time to maximum response (months)	2.9		

ITd: ixazomib-thalidomide-dexamethasone; N: number; (s)CR: (stringent) complete response; VGPR: very good partial response; PR: partial response..

Supplementary Figure S4A). The main toxicity was neurotoxicity attributed to thalidomide (46%) (*Online Supplementary Figure S4B*). Patients >75 years had to discontinue induction treatment more often compared to patients ≤75 years (60% *vs.* 38%; *P*=0.023) (*Online Supplementary Figure S4C*). The early mortality was 8% in patients >75 years old compared to only 1% in patients ≤75 years of age. Similarly, more frail patients had to discontinue induction treatment than unfit and fit patients (59%, 39% and 27%, respectively; *P*=0.008). The main reasons for discontinuation were progressive disease (21% in frail, 13% in unfit and 9% in fit patients; *P*=0.34) and toxicity (17% in frail, 16% in unfit and 9% in fit patients; *P*=0.60) (*Online Supplementary Figure S4D*). Hematologic toxicity was limited (*Online Supplementary Table S1*). The main non-hematologic toxicities were infections and cardiac events. The incidence of grade 3 neuropathy was low (5%).

Seventy-eight patients proceeded to randomization of maintenance treatment (*Online Supplementary Figure S3B*). During maintenance, 84% of patients discontinued treatment, mainly due to progressive disease (61%), which was comparable between the arms (59% with ixazomib, 63% with placebo). In both arms four patients had to discontinue therapy because of toxicity, of whom three because of neurotoxicity. This was ascribed to thalidomide use, as there was no new-onset neurotoxicity during maintenance therapy and the incidence of neurotoxicity was similar in the two arms. Older age did not negatively affect discontinuation of maintenance therapy, with the rates being 71% in patients >75 years *versus* 89% in patients ≤75 years, and toxicity accounting for 5% and 13% of the cases, respectively. The same was true for frailty, with the discontinuation rates being 73% in frail patients *versus* 87% in fit patients, with the discontinuation being due to toxicity in only one frail patient. The median relative dose intensity of both ixazomib and placebo maintenance was 100% (range, 58-100% and 65-100%, respectively). The incidence of grade ≥3 adverse events with ixazomib maintenance therapy was comparable to that with placebo maintenance therapy.

The lack of improvement in PFS with ixazomib was an unexpected finding as the TOURMALINE-MM3 study had shown an improvement in PFS of 5.2 months with ixazomib maintenance therapy compared to placebo following stem cell transplantation.[11] A relevant, yet unexplained, observation is that a sub-analysis of the TOURMALINE-MM3 study showed that in the patients who were treated with induction therapy consisting of both a proteasome inhibitor and an immunomodulatory drug (mainly thalidomide), as being used in our study, there was no improvement in PFS with ixazomib maintenance. However, most importantly, the small sample size in our phase II study, which was calculated hypothesizing a pronounced hazard ratio of 0.39 for PFS following randomization, might have caused a type II error. Therefore, the results of the TOURMALINE-MM4 study comparing ixazomib with placebo maintenance in patients with NDMM not eligible for transplantation, which is reported to have met its primary endpoint, will hopefully clarify the role of ixazomib maintenance in the non-transplant-eligible population. Importantly, based on preclinical data it may be that the standard maximum dose of ixazomib is suboptimal. We and others have shown sensitivity of the myeloma cell line RPMI 8226 to ixazomib in the nanomolar range; however, as compared to bortezomib, 10-fold higher concentrations of ixazomib were required for the inhibition of cell growth (*Online Supplementary Figure S5*).[12] In this respect, current studies investigating higher doses of ixazomib are of great interest.[13,14]

Importantly, we found that the PFS in patients with high cytogenetic risk was comparable to that in patients with standard-risk cytogenetics, suggesting that ixazomib overcomes the negative impact of high-risk cytogenetics, which is in accordance with the results of the TOURMALINE-MM1 study.[6]

The shorter than expected PFS of 14.3 months might well be explained by different levels of frailty of the patients who were included in the different studies. That fitness level may indeed affect treatment efficacy was recently shown by Larocca *et al.*, who observed a PFS of only 14 months with Rd in an unfit, not even a frail, population *versus* 25.5 months in the original FIRST trial.[15] This is in accordance with the findings of a *post-hoc* analysis of the outcome of patients in the FIRST trial, showing a PFS of only 19.4 months with Rd in frail patients *versus* 31.3 months in the non-frail patients.[10]

In conclusion, in this phase II randomized trial we could not show an improvement in PFS with maintenance treatment with ixazomib as compared to placebo. However, the sample size was small, partly due to toxicity of the combination with thalidomide during induction therapy, only allowing randomization of 55% of all patients and 40% of the oldest and frail patients. Importantly, for those patients who were randomized, ixazomib maintenance was very well tolerated, irrespective of age and frailty. Therefore, the results of the randomized phase III trial comparing ixazomib *versus* placebo maintenance in transplant-ineligible patients are eagerly awaited, as the mild toxicity profile even in frail

patients and the efficacy independent of high-risk disease would pave the way for a new therapy in those categories of patients with an unmet need for novel treatment options.

Sonja Zweegman,[1] Claudia A.M. Stege,[1] Einar Haukas,[2] Fredrik H. Schjesvold,[3] Mark-David Levin,[4] Anders Waage,[5] Rineke B.L. Leys,[6] Saskia K. Klein,[7] Damian Szatkowski,[8] Per Axelsson,[9] Trung Hieu Do,[10] Dorota Knut-Bojanowska,[11] Ellen van der Spek,[12] Asta Svirskaite,[13] Anja Klostergaard,[14] Morten Salomo,[15] Celine Blimark,[16] Paula F. Ypma,[17] Ulf-Hendrik Mellqvist,[18] Pino J. Poddighe,[1] Marian Stevens-Kroef,[19] Niels W.C.J. van de Donk,[1] Pieter Sonneveld,[20] Markus Hansson,[9] Bronno van der Holt[20] and Niels Abildgaard[21]

[1]Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; [2]Stavanger University Hospital-Rogaland Hospital, Stavanger, Norway; [3]Oslo Myeloma Center, Oslo, Norway; [4]Albert Schweitzer Hospital, Dordrecht, the Netherlands; [5]St Olavs Hospital and Norwegian University of Science, Trondheim, Norway; [6]Maasstad Hospital, Rotterdam, the Netherlands; [7]Meander Medical Center, Amersfoort, the Netherlands; [8]Førde Central Hospital, Førde, Norway; [9]Skanes University Hospital Lund, Scania, Sweden; [10]Herlev Hospital, Herlev, Denmark; [11]NU-Hospital, Uddevalla Hospital, Uddevalla, Sweden; [12]Rijnstate Hospital, Arnhem, the Netherlands; [13]Aalborg Hospital, Aalborg, Denmark; [14]Aarhus University Hospital, Aarhus, Denmark; [15]Rigshospitalet Copenhagen, Copenhagen, Denmark; [16]Sahlgrenska University Hospital, Gothenburg, Sweden; [17]Haga Hospital, Den Haag, the Netherlands; [18]Sodra Alvsborgs Sjukhus Boras, Boras, Sweden; [19]Radboud Medical Center, Nijmegen, the Netherlands; [20]Erasmus Medical Center Cancer Institute, Rotterdam, the Netherlands and [21]Hematology Research Unit and Academy of Geriatric Cancer Research, Odense University Hospital and University of Southern Denmark, Denmark

Correspondence:
SONJA ZWEEGMAN - s.zweegman@amsterdamumc.nl

doi:10.3324/haematol.2019.240374

References

1. 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(10068):519-527.
2. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med. 2018;378(6):518-528.
3. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019; 380(22):2104-2115.
4. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008;359(9):906-917.
5. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.
6. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016; 374(17):1621-1634.
7. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood. 2016;127(24):2955-2962.
8. Kumar SK, Berdeja JG, Niesvizky R, et al. Ixazomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up including ixazomib maintenance. Leukemia. 2019;33(7):1736-1746.
9. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-1791.
10. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2019;34(1):224-233.
11. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2019;393(10168):253-264.
12. Brunnert D, Kraus M, Stuhmer T, et al. Novel cell line models to study mechanisms and overcoming strategies of proteasome inhibitor resistance in multiple myeloma. Biophys Acta Mol Basis Dis. 2019;1865(6):1666-1676.
13. Kumar SK, LaPlant BR, Reeder CB, et al. Randomized phase 2 trial of ixazomib and dexamethasone in relapsed multiple myeloma not refractory to bortezomib. Blood. 2016;128(20):2415-2422.
14. Richardson PG, Hofmeister CC, Rosenbaum CA, et al. Twice-weekly ixazomib in combination with lenalidomide-dexamethasone in patients with newly diagnosed multiple myeloma. Br J Haematol. 2018;182(2):231-244.
15. Larocca A, Salvini M, De Paoli L, et al. Efficacy and feasibility of dose/schedule-adjusted Rd-R vs. continuous Rd in elderly and intermediate-fit newly diagnosed multiple myeloma (NDMM) patients: RV-MM-PI-0752 phase III randomized study. Blood. 2018; 132(Suppl 1):305.