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

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

Supplemental data

S1 Patients and study design

Patients

Patients with symptomatic newly diagnosed multiple myeloma (NDMM), with measurable disease according to the International Myeloma Working Group (IMWG) criteria, who were not candidates for high-dose therapy plus stem-cell transplantation, because of age (≥65 years) or because of coexisting conditions, were eligible for the trial.[1] For patients <75 years a World Health Organisation (WHO) 0-3 was allowed, for patients ≥75 a WHO 0-2 was required. Main exclusion criteria were AL-amyloidosis, creatinine clearance <30 ml/min, uncontrolled cardiovascular conditions, severe pulmonary dysfunction and neuropathy grade 2 with pain or grade 3. In order to be randomized for maintenance therapy, patients either had to complete 9 induction cycles or receive at least 6 cycles without non-hematological toxicity related to ixazomib as the cause for early discontinuation of induction. In addition, at least a partial response (PR) and hematological recovery (defined as absolute neutrophil count (ANC) ≥ 1.0 x 10^9/l and platelet count ≥ 75 x 10^9/l) after induction treatment were required.

Study design and procedures

This prospective multicenter phase II trial was a collaboration between the Dutch-Belgium Cooperative Trial Group for Hematology Oncology (HOVON) and the Nordic Myeloma Study Group (NMSG), including joint registration, randomization, data management and analysis. Eligible patients were treated with nine 28 day induction cycles consisting of ixazomib 4 mg on day 1, 8 and 15, thalidomide 100 mg on day 1-28 and dexamethasone 40 mg on day 1, 8, 15, 22. In patients with at least a PR, this was followed by a randomization between maintenance treatment with ixazomib 4 mg or placebo, both administered on day 1, 8 and 15 of a 28-day cycle, until progression or occurrence of a medical event that required treatment discontinuation. Dose levels and - reductions for ixazomib, thalidomide and dexamethasone can be found at the end of this paragraph. All patients received supportive care, consisting of thrombosis prophylaxis with acetylsalicylic acid or low molecular weight heparin in case of a previous thrombotic event, herpes zoster prophylaxis with valaciclovir, antibiotic prophylaxis according to local protocols, and bisphosphonates. Cytogenetic analysis was centrally performed by Fluorescence In Situ Hybridization (FISH) on isolated CD38-positive plasma cells according to the European Myeloma Network guidelines[2], investigating del1p, gain1q, t(4;14)(p16;q32), t(14;16)(q32;q23), t(11;14)(q13;q32), del13q/13-, del17p and hyperdiploidy.

Dose levels for ixazomib, thalidomide and dexamethasone

Dose levels ixazomib during induction and maintenance therapy

Starting Dose 4 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -1 3 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -2 2,3 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -3 discontinue ixazomib (off protocol treatment)

Dose Levels for Thalidomide during induction therapy

Starting Dose 100 mg every day

Dose Level -1 50 mg every day

Dose Level -2 no thalidomide

Dose Levels for Dexamethasone during induction therapy

Starting Dose 40 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -1 20 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -2 8 mg once weekly on days 1,8 and 15 every 28 days

Dose Level -3 discontinue dexamethasone

S2 Statistical analysis

The primary objectives were to assess whether maintenance therapy with ixazomib improved progression free survival (PFS), calculated from the date of randomization (PFS-R) and to determine overall response rate (ORR) of induction therapy with ixazomib-thalidomide-dexamethasone (ITd). The expected median PFS-R following induction therapy with ITd was unknown, but in the placebo arm it was hypothesized to be 10 months based on the PFS of 7 months following randomization after 9 cycles of melphalan-prednisone-lenalidomide (MPR) in the GIMEMA trial.[3] We calculated that 94 randomized patients (47 per arm) would provide 90% power (2-sided significance level $\alpha = 0.05$) to detect a 61% reduction in progression or death following randomization (hazard ratio (HR) = 0.39), corresponding with a median PFS of 26 months in the ixazomib arm, which was the median PFS following randomization in the lenalidomide arm in the GIMEMA trial.[3] Assuming that 66% (based on the 34% discontinuation rate in the VISTA trial[4]) of the patients would be randomized, 142 patients should be enrolled. These 142 patients would also enable to estimate the response rate with a standard error of about 3%. Secondary objectives were determination of overall survival (OS), both from registration and from randomization, comparison of toxicity and discontinuation due to toxicity and response improvement of maintenance treatment.

Preplanned exploratory subgroup analyses were performed, with subgroups based on International Staging System (ISS), cytogenetic risk (high risk disease defined as the presence of a del(17p13), t(4;14)

and/or t(14;16); and standard risk if all of the three abnormalities were absent), age and frailty. Frailty was assessed by a modification of the IMWG frailty index based on age (<76 years: 0 points; 76-80 years: 1 point; >80 years: 2 points), the Charlson Comorbidity Index (CCI; ≤1: 0 points; ≥2: 1 point) and the WHO performance as a proxy for (instrumental) Activities of Daily Living ((i)ADL) (WHO 0: 0 points; WHO 1: 1 point; WHO 2-3: 2 points). The WHO performance was prospectively assessed by the treating physician and the CCI was retrospectively retreived from patient data. Patients with a total score of 0 points were defined fit, with 1 point unfit and with ≥2 points frail. In non-transplant eligible (NTE) NDMM patients, frailty based on this revised frailty index proved to be associated with inferior clinical outcome.[5,6]

All analyses were performed according the intention to treat (ITT) principle. However, patients initially registered but considered ineligible afterwards based on information that should have been available before randomization, were regarded as screen failures and excluded from the respective analyses (modified-ITT). The primary analysis of PFS-R was done with a multivariate Cox regression with adjustment for ISS (ISS, I vs II and III), age (<75 vs ≥75 years) and response after induction treatment ((stringent) complete response ((s)CR), very good partial response (VGPR) and PR), and at least 55 events had to be reported.

References

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 2014; **15**(12): e538-e48.
2. Ross FM, Avet-Loiseau H, Ameye G, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. *Haematologica* 2012; **97**(8): 1272-7.
3. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007; **25**(28): 4459-65.
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): 906-17.
5. Stege CAM, van der Holt B, Mellqvist U, et al. Frailty predicts survival and toxicity in newly diagnosed multiple myeloma patients ineligible for autologous stem cell transplantation; report of the HOVON-87/NMSG-18 study group. *Blood* 2017; **130**.
6. 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.

TABLE S1 Adverse events according to CTCAE version 4.0

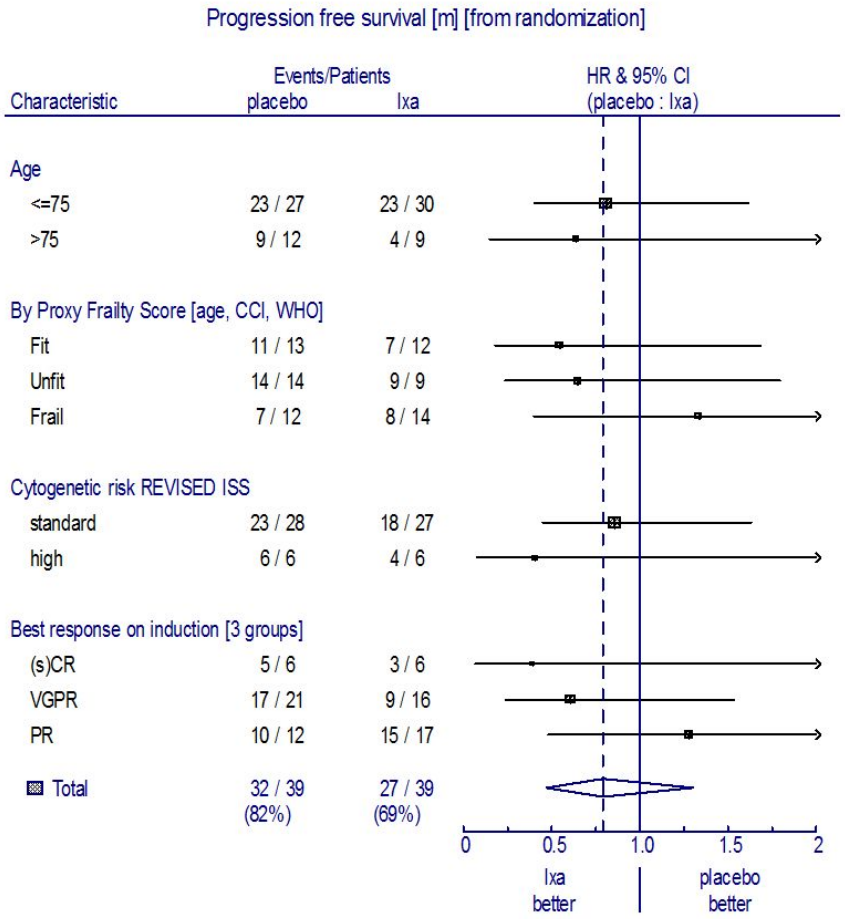
	Induction ITd (n=143)		Maintenance Placebo (n=38)		Maintenance Ixazomib (n=39)	
CTCAE grade (%)	**3**	**4**	**3**	**4**	**3**	**4**
Any	51	10	18	5	23	-
Anemia	3	1	-	-	3	-
Thrombocytopenia	3	1	-	-	-	-
Neutropenia	1	1	-	-	-	-
Infections	11	2	-	-	3	-
Neuropathy	5	-	5	-	5	-
VTE any grade*	2		3		-	

* including both deep venous thrombosis and pulmonary embolism

CTCAE: Common Terminology Criteria for Adverse Events; ITd: ixazomib-thalidomide-dexamethasone; mo: months; n: number; VTE: venous thromboembolic event

Figure S1

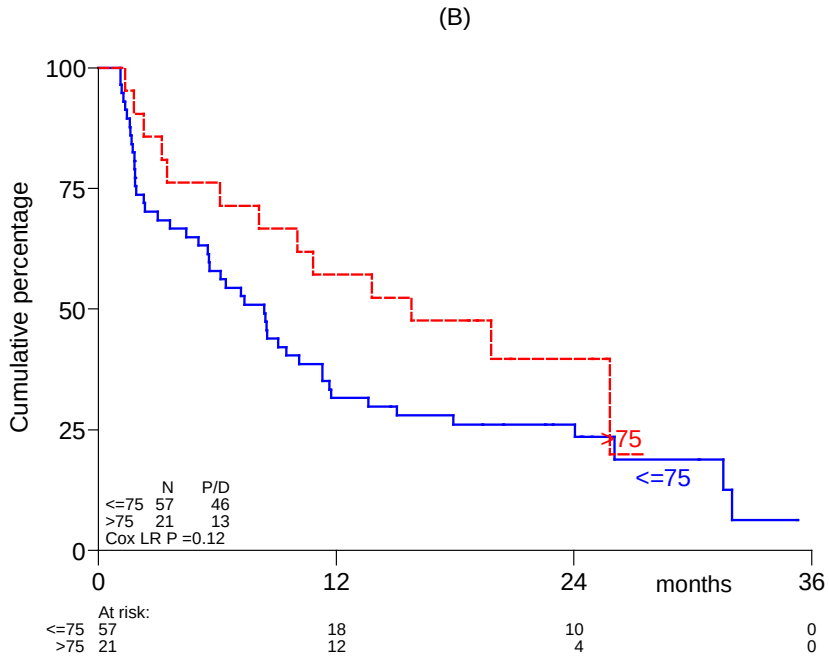
A Subgroup analysis of Progression Free Survival from randomization (PFS-R)



The progression free survival from randomization (PFS-R) among subgroups of patients, as defined according to base line demographic and disease characteristics and response following induction, showed no advantage of ixazomib maintenance compared to placebo. P-values for test for interaction: age, p=0.78; by proxy frailty score, p=0.56; cytogenetic risk, p=0.40; best response, p=0.39.

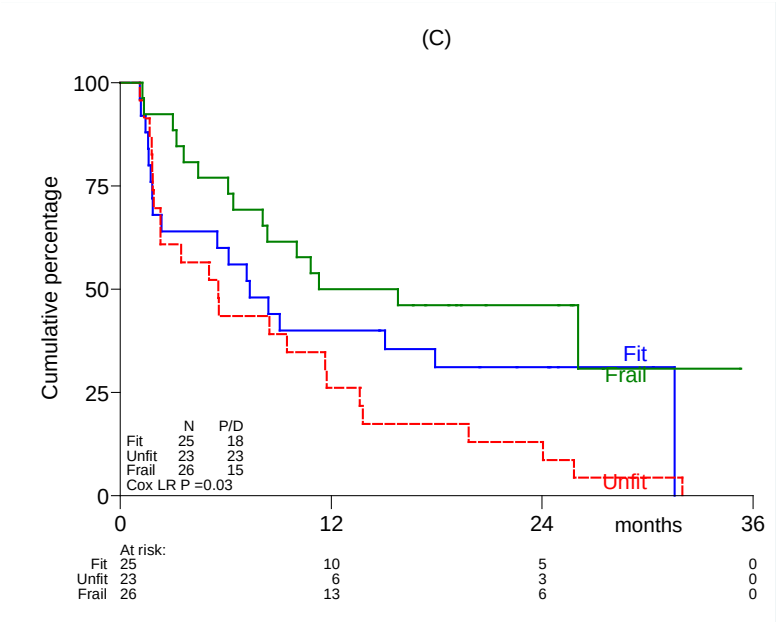
CCI: Charlson Comorbidity Index; CI: confidence interval; High risk cytogenetics: presence of either del(17p13), t(4;14) and/or t(14;16)HR: hazard ratio; ixa: ixazomib; PR: partial response; (s)CR: (stringent) complete response; VGPR: very good partial response; WHO: World Health Organization performance

B PFS-R by age



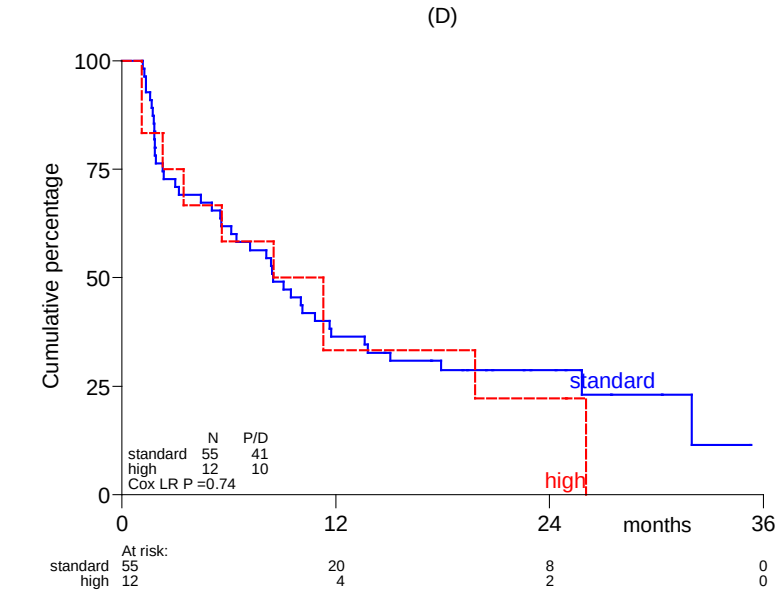
After a median follow-up of 23.4 months after randomization (range 6.9-35.5), the median PFS from randomization (PFS-R) is 8.4 months (95% Confidence Interval (CI) 5.1-11.3) for patients ≤75 years versus 15.8 months (95% CI 6.1-∞) for patients >75 years of age.

C PFS-R by frailty



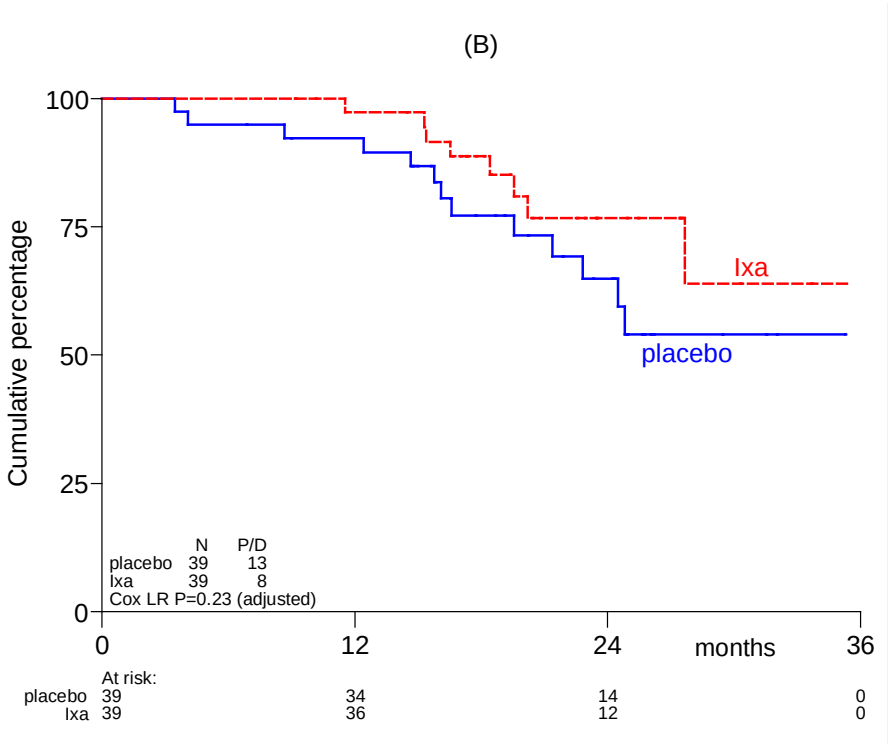
After a median follow-up of 23.4 months after randomization (range 6.9-35.5), the median PFS from randomization (PFS-R) is 7.4 months (95% Confidence Interval (CI) 1.8-17.9) for fit patients versus 5.6 months (95% CI 1.9-11.7) for unfit patients versus 11.3 months (95% CI 6.4-∞) for frail patients.

D PFS-R by cytogenetic risk



After a median follow-up of 23.4 months after randomization (range 6.9-35.5), the median PFS from randomization (PFS-R) is 8.5 months (95% Confidence Interval (CI) 5.5-11.7) for patients with standard cytogenetic risk versus 8.5 months (95% CI 1.1-19.8) for patients with high cytogenetic risk.

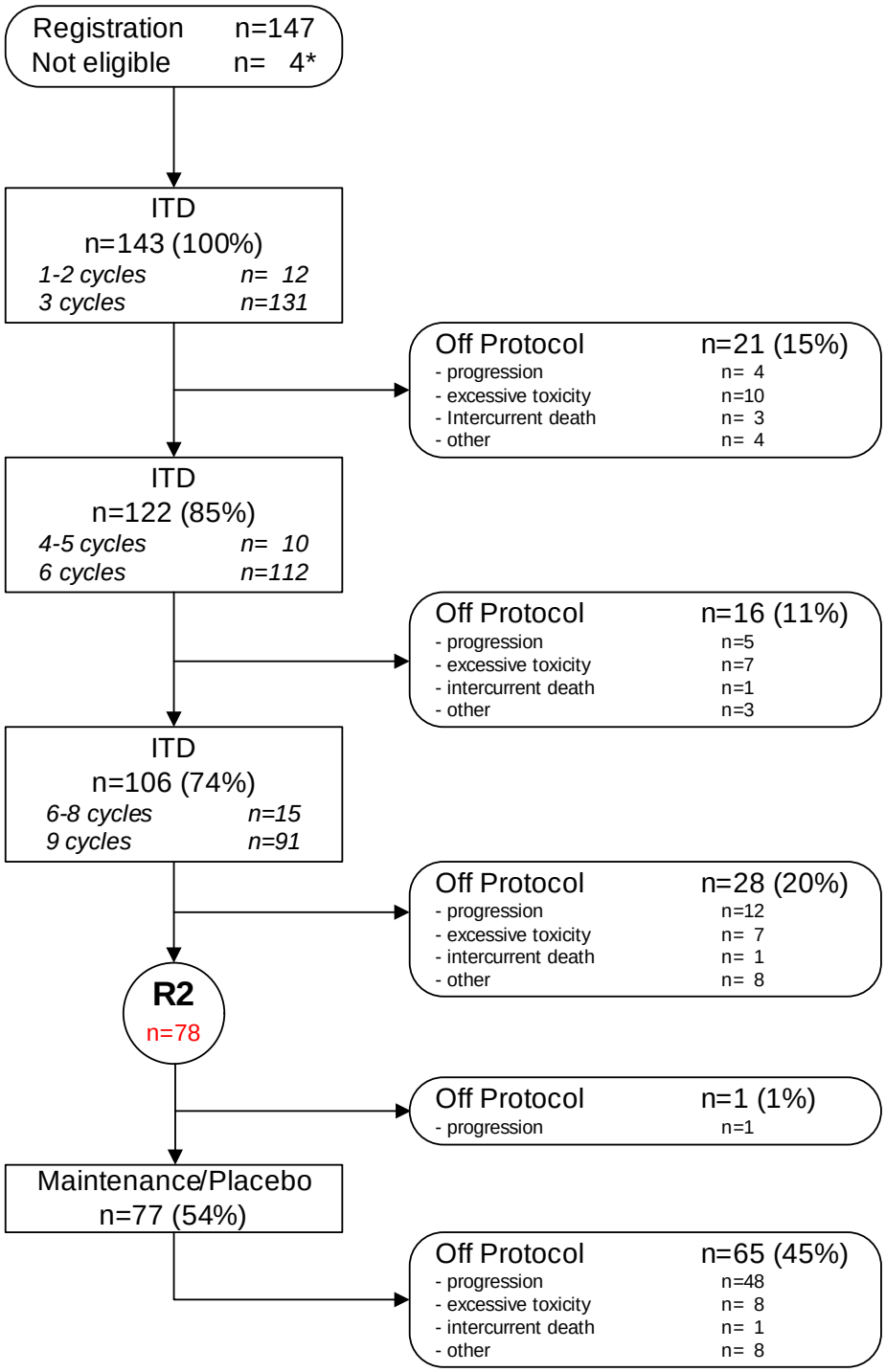
Figure S2 PFS2 from randomization by arm



After a median follow-up of 23.4 months after randomization (range 6.9-35.5), the median PFS2 from randomization has not yet been reached for all patients (either treated with ixazomib or placebo maintenance).

Figure S3

A CONSORT diagram

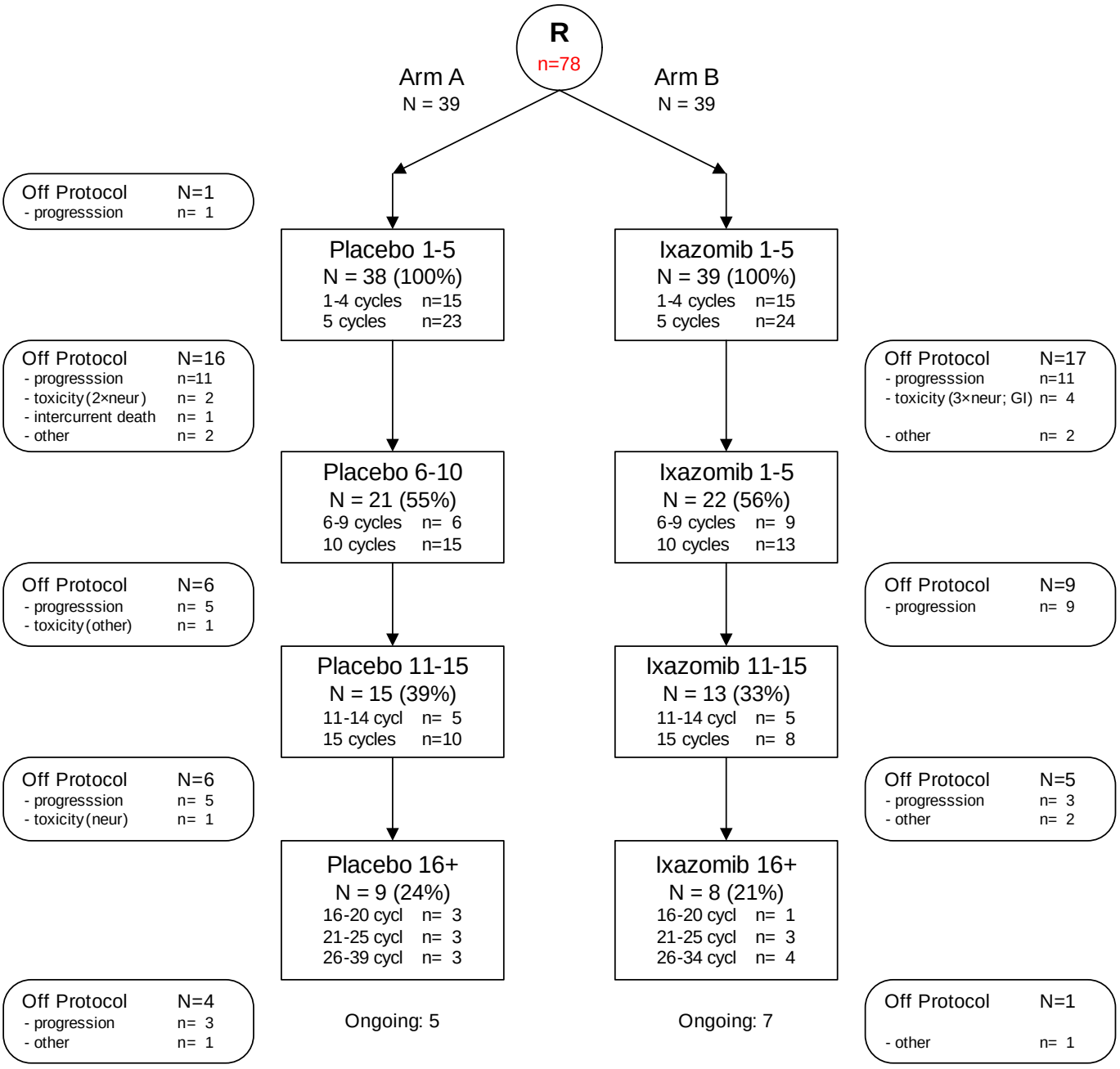


Consort diagram of the patient flow through the study (induction and maintenance), the number of patients off protocol and reason for treatment discontinuation

* 2 due to previous malignancy, 1 treated with thal/dex prior to start treatment; 1 not meeting criteria for symptomatic MM

ITD: ixazomib-thalidomide-dexamethasone; n: number; R2: randomization

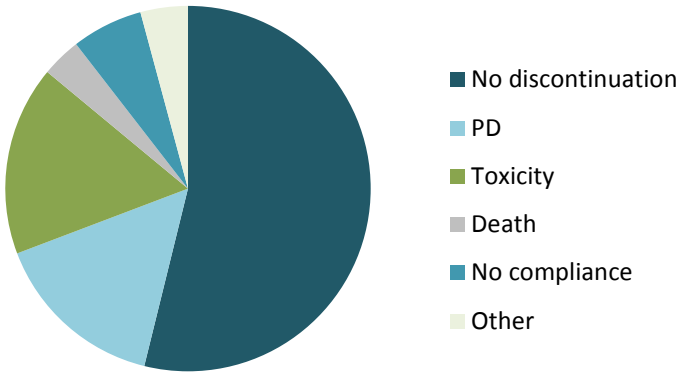
B CONSORT diagram of patients randomized between maintenance treatment with placebo (arm A) or ixazomib (arm B)



Consort diagram of the patient flow through the maintenance treatment phase, the number of patients off protocol and reason for treatment discontinuation

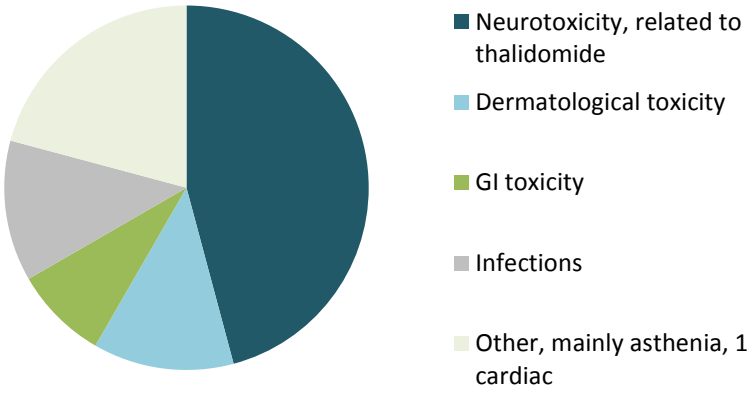
n: number; R: randomization

Figure S4A Reasons for discontinuation of induction therapy with ITd – all patients



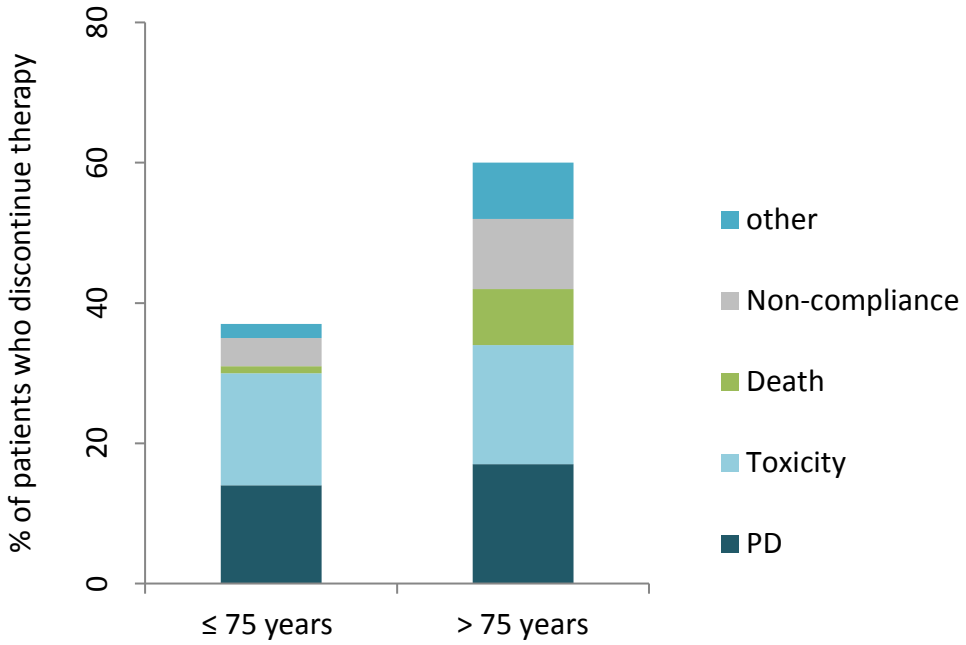
Reasons for discontinuation of induction treatment with ixazomib-thalidomide-dexamethasone (ITd) for all patients (n=143): progressive disease (PD, 15%), toxicity (17%), intercurrent death (3%), no compliance (6%) and other reasons (4%). A total of 78 (55%) patients were able to complete induction treatment.

Figure S4B Reasons for toxicity leading to discontinuation of induction therapy with ITd – all ages



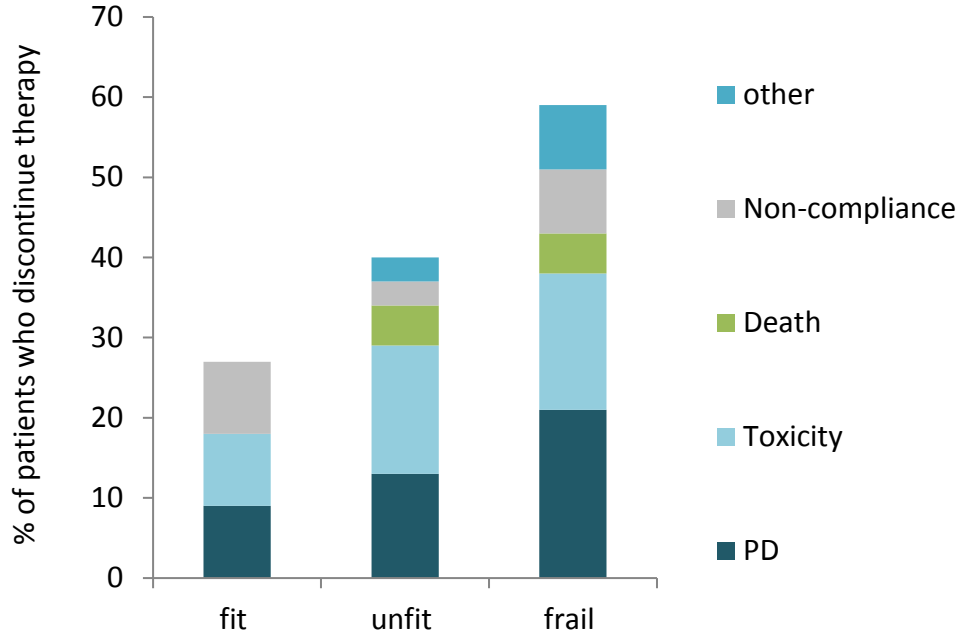
Reasons for discontinuation of induction treatment with ixazomib-thalidomide-dexamethasone (ITd) due to toxicity (n=24): neurotoxicity (46%), dermatological toxicity (13%), infections (13%), gastro-intestinal (GI) toxicity (8%) and other toxicity (21%).

Figure S4C Discontinuation of induction therapy with ITd according to age



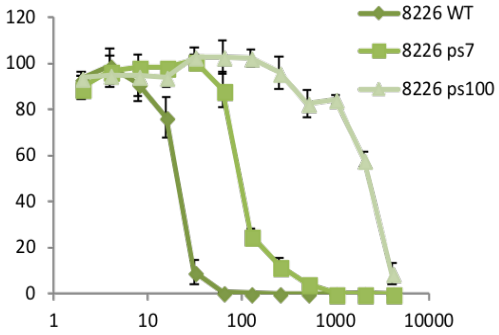
Reasons for discontinuation of induction treatment with ixazomib-thalidomide-dexamethasone (ITd) according to age ≤75 (38%) versus >75 years (60%): progressive disease (14 vs 17%), toxicity (16 vs 17%), intercurrent death (1 vs 8%), non-compliance (4 vs 10%) and other reasons (1 vs 8%).

Figure S4D Discontinuation of induction therapy with ITd according to frailty



Reasons for discontinuation of induction treatment with ixazomib-thalidomide-dexamethasone (ITd) according to frailty (fit (27%) versus unfit (39%) versus frail (59%)): progressive disease (9 vs 13 vs 21%), toxicity (9 vs 16 vs 17%), intercurrent death (0 vs 5 vs 5%), non-compliance (9 vs 3 vs 8%) and other reasons (0 vs 3 vs 8%).

Figure S5 Cell growth inhibition dose-response to Ixazomib- or bortezomib-sensitive and resistant cells.



	IC_{50} IXA ± SD nM (RF)	IC_{50} BTZ ± SD nM (RF)*
8226 WT	22±2	2.9±0.3
8226 BTZ7	100±1(5)	-
8226 BTZ100	2332±105(106)	120±17(41)

Cell growth inhibition dose-response to ixazomib (IXA) of bortezomib (BTZ)-sensitive (8226 wild type (WT)) and resistant (8226 BTZ7; resistant to 7 nM of BTZ and 8226 BTZ100; resistant to 100 nM BTZ) cells. A) Sensitivity of 8226 cells and the BTZ-resistant sublines, as determined by 4-day MTT cytotoxicity assay. The mean ± SD of 3 individual experiments performed in triplicate is depicted. B) Concentration required to inhibit 50% of control untreated cell growth (IC50) is given as mean ± standard deviation (SD). Between brackets the resistance factor (RF) compared to WT is given.