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


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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

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This trial was registered at www.trialregister.nl as NTR4910.
To the editor,

The prognosis of older newly diagnosed patients with multiple myeloma (NDMM), who are not stem cell transplantation eligible (NTE), has greatly improved, either by the combination of bortezomib with lenalidomide, or the addition of daratumumab to bortezomib or to lenalidomide.\textsuperscript{1-3} Although not head-to-head compared, progression free survival (PFS) was longer with lenalidomide used continuously as compared to bortezomib for a limited number of cycles only.\textsuperscript{4,5} Continuous treatment with the oral proteasome inhibitor (PI), ixazomib, in combination with lenalidomide and dexamethasone (IRd) did not increase the incidence of grade ≥3 neuropathy as compared to Rd only.\textsuperscript{6} A possible additional advantage of continuous therapy with PI is that it may overcome the negative impact of high risk cytogenetic abnormalities.\textsuperscript{7} Furthermore, there was no need for discontinuation of ixazomib due to toxicity during the maintenance phase, compared to approximately 25% with lenalidomide.\textsuperscript{8,9} Therefore, in this randomized phase 2 trial, we investigated the efficacy and feasibility of ixazomib versus placebo maintenance in NTE-NDMM, following 9 cycles of induction with ixazomib, thalidomide and dexamethasone (ITd) (protocol details in the Supplementary Appendix). To improve knowledge about unfit and frail patients, we investigated the outcome in those patients, using a simplified frailty score.\textsuperscript{10} We could not observe an improvement in PFS with maintenance treatment with ixazomib compared to placebo. However, in this 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 with a PFS that was comparable in patients >75 versus ≤75 years and in frail versus unfit or fit patients.

Characteristics of the 143 eligible patients are presented in Table 1. According to the simplified frailty score, using World Health Organization (WHO) performance as replacement for (instrumental) activities of daily living ((i)ADL), 33 (23%) of patients were fit, 38 (27%) unfit and 63 (44%) frail (6% unknown). A total of 78 out of 143 (55%) patients were randomized between maintenance treatment with ixazomib (n=39) and 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 (CI) 5.5-24.0) for ixazomib versus 8.4 months (95%CI 3.0-13.8) for placebo (Figure 1A). The lack of difference in PFS-R between arms was independent from age, frailty, cytogenetics and best response on ITd induction (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 (Figure S1B-D). Median Overall Survival (OS) from randomization has not
been reached in both arms and was comparable (Figure 1B). Median PFS2 from randomization has not been reached, being 83% at 18 months, comparable between the 2 arms (Figure S2).

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 versus 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). Median OS from registration had not yet been reached (Figure 1D). OS was independent of cytogenetic risk. Age >75 and frailty were associated with inferior OS at 2 years (73%, versus 90% in patients ≤75, p=0.002, and 74%, versus 89% in unfit and 90% in fit at 2 years, p=0.08).

Response rates are described in Table 2. The ITd induction regimen was effective with an overall response rate of 81% and achieving at least very good partial remission in 47% of patients, which is comparable to what was obtained with VRD1. Response was not affected by cytogenetic risk status, age or frailty.

The patient flow is shown in the CONSORT diagrams (Figure S3A and B). Sixty-five/143 patients (45%) prematurely discontinued during or after induction treatment and were not randomized. Reasons for discontinuation of induction treatment were toxicity (17%), progressive disease (PD, 15%), death (3%) and other reasons (10%) (Figure S4A). The main reason for toxicity was neurotoxicity attributed to thalidomide (46%, Figure S4B). Patients >75 years had to discontinue induction treatment more often compared to patients ≤75 years (60% vs 38%, p=0.023, Figure S4C). Early mortality was 8% in patients >75 versus only 1% in patients ≤75 years. Similarly, more frail patients had to discontinue induction treatment than unfit and fit patients (59%, 39% and 27% respectively, p=0.008). Main reasons for discontinuation were PD (21% in frail, 13% in unfit and 9% in fit, p=0.34) and toxicity (17% in frail, 16% in unfit and 9% in fit, p=0.60)(Figure S4D). Hematological toxicity was limited (Table S1). The main non-hematological toxicities were infections and cardiac events. The incidence of grade 3 neuropathy was low (5%).

Seventy-eight patients proceeded to randomization (Figure S3B). During maintenance, 84% of patients discontinued treatment, mainly due to PD (61%), which was comparable between arms (59% with ixazomib, 63% with placebo). In both arms 4 patients had to discontinue therapy due to toxicity, of whom 3 due to neurotoxicity. This was ascribed to thalidomide use, as there was no new onset neurotoxicity during maintenance and the incidence of neurotoxicity was similar between arms. Older age did not negatively affect discontinuation of maintenance therapy; 71% >75 years versus 89% in patients ≤75 years, of which 5% and 13% due to toxicity. The same accounted for
frailty; 73% frail versus 87% of fit patients, with only one frail patient due to toxicity. 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 placebo maintenance therapy.

The lack of improvement in PFS with ixazomib was an unexpected finding as the TOURMALINE-MM3 study showed an improvement in PFS of 5.2 months with ixazomib maintenance therapy compared to placebo following stem cell transplantation. 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 PI and an immunomodulatory drug (mainly thalidomide), as being used on our study, there was no improvement in PFS with ixazomib maintenance. However, most importantly, the small sample size in our phase 2 study, which was calculated hypothesizing a pronounced HR 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 NTE-NDMM patients, that was reported to meet its primary endpoint, will hopefully clarify the role of ixazomib maintenance in the NTE population. Importantly, based on pre-clinical 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 for ixazomib in the nanomolar range, however 10-fold higher concentrations were required for the inhibition of cell growth as compared to bortezomib (Figure S5). In this respect, current studies investigating higher doses of ixazomib are of highly interest.

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

The lower 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. The fitness level may indeed affect treatment efficacy as recently shown by Larocca et al, observing 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. This is in accordance with the post-hoc analysis of the outcome of frail patients in the FIRST trial, showing a PFS of only 19.4 months with Rd versus 31.3 months in the non-frail patients.

In conclusion, in this phase 2 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 in 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 3 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 being independent of high risk disease would pave the way for those patient categories with a high unmet need for novel treatment options.
References


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<th>Placebo</th>
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<td>39</td>
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<td>73 (67-82)</td>
<td>72 (66-80)</td>
<td>73 (66-82)</td>
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<td>36 (92%)</td>
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<td>1/3 (3)</td>
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<td>Standard risk cytogenetics</td>
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<td>28/34 (82)</td>
<td>27/34 (79)</td>
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FISH: fluorescence in situ hybridization; Frailty score: based on age, World Health Organization (WHO) performance and comorbidities as defined by Charlson Comorbidity Index; ISS: international staging system; ITd: ixazomib, thalidomide and dexamethasone; LDH: lactate dehydrogenase; n: number
<table>
<thead>
<tr>
<th>Response rate (%)</th>
<th>ITd induction N=143</th>
<th>On protocol placebo N=39</th>
<th>On protocol ixazomib N=39</th>
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<tr>
<td>Overall response</td>
<td>81</td>
<td>97</td>
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<td>(s)CR</td>
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<td>23</td>
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<td>VGPR</td>
<td>38</td>
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<tr>
<td>≥ VGPR</td>
<td>47</td>
<td>72</td>
<td>62</td>
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<tr>
<td>Improvement in response during maintenance</td>
<td>13</td>
<td>13</td>
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<td>Median time to response (mo)</td>
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<td>Median time to maximum response (mo)</td>
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ITd: ixazomib-thalidomide-dexamethasone; mo: months; N: number; PR: partial response; (s)CR: (stringent) complete response; VGPR: very good partial response
Figure legends

Figure 1 Survival from randomization (A-B) and registration (C-D)

Figure 1A and 1B show PFS and OS after randomization (PFS-R and OS-R, respectively). After a median follow-up of 23.4 months after randomization (range 6.9-35.5), the median PFS-R for ixazomib is 9.5 months (95% Confidence Interval (CI) 5.5-24.0) versus for placebo 8.4 months (95% CI 3.0-13.8). OS-R at 18 months for all patients is 96% (88-99%), being comparable for patients treated with ixazomib (ixa, 100%) versus placebo (92% (95% CI 77-97%), p=1.00). Figure 1C and 1D show PFS and OS after registration. After a median follow-up of 28.5 months (range 0.9 – 44.1), C) the median PFS from registration for all patients is 14.3 months (95% CI, 11.5-16.8) and; D) median OS from registration for all patients has not yet been reached.
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. 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, 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. 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. Assuming that 66% (based on the 34% discontinuation rate in the VISTA trial) 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 retrieved 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.\textsuperscript{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

TABLE S1 Adverse events according to CTCAE version 4.0

<table>
<thead>
<tr>
<th>CTCAE grade (%)</th>
<th>Induction ITd (n=143)</th>
<th>Maintenance Placebo (n=38)</th>
<th>Maintenance Ixazomib (n=39)</th>
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<tbody>
<tr>
<td>Any</td>
<td>51 10</td>
<td>18 5</td>
<td>23 -</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 1</td>
<td>- -</td>
<td>3 -</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 1</td>
<td>- -</td>
<td>- -</td>
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<tr>
<td>Neutropenia</td>
<td>1 1</td>
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<td>- -</td>
</tr>
<tr>
<td>Infections</td>
<td>11 2</td>
<td>- -</td>
<td>3 -</td>
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<tr>
<td>Neuropathy</td>
<td>5 -</td>
<td>5 -</td>
<td>5 -</td>
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<tr>
<td>VTE any grade*</td>
<td>2 3</td>
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* 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
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 baseline 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; cytogenic 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Events/Patients</th>
<th>HR &amp; 95% CI (placebo : ixa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>placebo</td>
<td>ixa</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=75</td>
<td>23 / 27</td>
<td>23 / 30</td>
</tr>
<tr>
<td>&gt;75</td>
<td>9 / 12</td>
<td>4 / 9</td>
</tr>
<tr>
<td>By proxy frailty score [age, CCI, WHO]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fit</td>
<td>11 / 13</td>
<td>7 / 12</td>
</tr>
<tr>
<td>Unfit</td>
<td>14 / 14</td>
<td>9 / 9</td>
</tr>
<tr>
<td>Frail</td>
<td>7 / 12</td>
<td>8 / 14</td>
</tr>
<tr>
<td>Cytogenetic risk revised iSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>standard</td>
<td>23 / 28</td>
<td>18 / 27</td>
</tr>
<tr>
<td>high</td>
<td>6 / 6</td>
<td>4 / 6</td>
</tr>
<tr>
<td>Best response on induction [3 groups]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(s)CR</td>
<td>5 / 6</td>
<td>3 / 6</td>
</tr>
<tr>
<td>VGPR</td>
<td>17 / 21</td>
<td>9 / 16</td>
</tr>
<tr>
<td>PR</td>
<td>10 / 12</td>
<td>15 / 17</td>
</tr>
<tr>
<td>Total</td>
<td>32 / 39</td>
<td>27 / 39</td>
</tr>
<tr>
<td></td>
<td>(82%)</td>
<td>(68%)</td>
</tr>
</tbody>
</table>

The progression free survival from randomization (PFS-R) among subgroups of patients, as defined according to baseline 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; cytogenic risk, p=0.40; best response, p=0.39.
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.
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

Registration n=147
Not eligible n= 4*

ITD n=143 (100%)
1-2 cycles n=12
3 cycles n=131

Off Protocol n=21 (15%)
- progression n=4
- excessive toxicity n=10
- intercurrent death n=3
- other n=4

ITD n=122 (85%)
4-5 cycles n=10
6 cycles n=112

Off Protocol n=16 (11%)
- progression n=5
- excessive toxicity n=7
- intercurrent death n=1
- other n=3

ITD n=106 (74%)
6-8 cycles n=15
9 cycles n=91

Off Protocol n=28 (20%)
- progression n=12
- excessive toxicity n=7
- intercurrent death n=1
- other n=8

R2 n=78

Off Protocol n=1 (1%)
- progression n=1

Maintenance/Placebo n=77 (54%)

Off Protocol n=65 (45%)
- progression n=48
- excessive toxicity n=8
- intercurrent death n=1
- other n=8

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%), gastrointestinal (GI) toxicity (8%) and other toxicity (21%).
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%).

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%).
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.