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Ixazomib-Thalidomide-Dexamethasone Induction Followed by Ixazomib or Placebo Maintenance in Nontransplant Eligible Newly Diagnosed Multiple Myeloma Patients: Long-term Results of HOVON-126/NMSG 21.13

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Treatment until progression has been found to be superior compared with fixed duration in the first-line treatment of nontransplant eligible newly diagnosed multiple myeloma (NTE-NDMM) patients.[1] Continuous therapy with proteasome inhibitors (PIs) holds potential. This is exemplified by the fact that maintenance treatment with bortezomib after induction therapy including bortezomib followed by a peripheral stem cell transplantation resulted in a superior progression-free survival (PFS). Moreover, it almost abrogated the negative impact of del17p and renal failure.[2,3] Accordingly, carfilzomib-based triplet therapy with or without stem cell transplantation was found to overcome the negative impact of one high-risk cytogenetic abnormality.[4] However, the administration of the PI bortezomib as a continuous therapy is not a viable option due to the development of neuropathy, and the limitations associated with frequent subcutaneous administration. In addition, long-term carfilzomib treatment in elderly patients is not preferable because of toxicity. In light of these findings, the continuous administration of ixazomib as maintenance therapy is a subject of interest. In the Tourmaline 4 study, comparing ixazomib versus placebo maintenance in nontransplant eligible patients, it was shown that maintenance therapy with ixazomib resulted in prolongation of PFS, which was clinically meaningful across all age and frail subgroups, without severe toxicity indeed.[5,6] However, the ultimate justification for maintenance treatment is an improvement in the overall survival (OS). Until now the effect of ixazomib maintenance treatment on OS is unknown. In the randomized HOVON-126/NMSG 21.13 phase 2 trial, which was initiated in December 2014, we investigated the efficacy and safety of an all-oral regimen, consisting of 9 cycles ixazomib, thalidomide, and dexamethasone induction (ITD) therapy, followed by a randomization between ixazomib versus placebo, in 143 NTE-NDMM patients. Efficacy and feasibility data were published previously; however, follow-up was too short for investigating OS.[7] Therefore, we present here the results of long-term survival.

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After the induction treatment, 78 of 143 patients were randomized between ixazomib maintenance or placebo treatment, 39 in each arm. As described previously, patient, frailty and disease characteristics, including high-risk cytogenetics, were comparable between arms.[7] Median follow-up from the date of randomization of the 42 patients still alive at the time of analysis was 60.0 months (interquartile range [IQR], 56.4–62.5 months). Ixazomib maintenance resulted in a superior OS from randomization as compared with placebo; median not reached (95% confidence interval [CI], 66.7-not reached [NR]) versus 50.7 months (41.3–58.1) in the placebo arm (hazard ratio [HR], ixazomib 0.39 [95% CI, 0.19-0.78]; $P = 0.008$). At 36 months, the OS was 82% (95% CI, 65-91) in the ixazomib arm, compared with 73% (56-85) in the placebo arm. At 60 months, these numbers were 71% (54-83) versus 31% (16-47), respectively (Figure 1; Suppl. Table S1).

At the time of analysis, 36 (46%) randomized patients had died; 12 of 39 (31%) in the ixazomib arm and 24 of 39 (62%) in the placebo arm. Of all patients in the ixazomib maintenance arm of the study, 5 of 39 (13%) patients died due to nonmyeloma-related causes (3 infections and 2 unknown), which occurred in 8 of 39 (21%) patients in the placebo arm (4 infection, 3 other reasons, and 1 unknown). In the ixazomib arm, 7 of 39 (18%) patients died due to progressive myeloma, which was 16 of 39 (41%) patients in the placebo arm (Suppl. Table S2). These results suggest that ixazomib maintenance treatment led to a longer OS by reducing myeloma-related deaths. However, this seems to be contradictory to the fact that PFS was not statistically different between both arms; median PFS for ixazomib 9.5 months (95% CI, 5.5-14.8) versus placebo 8.4 months (3.0-13.8) (HR, 0.94 [95% CI, 0.60-1.48]; $P = 0.79$). Although the PFS2 between arms was different, median PFS2 for ixazomib 39.8 months (28.8-59.9) versus placebo 28.7 months (22.8-43.2), a statistical significance difference was not reached (HR, ixazomib 0.69 [95% CI, 0.41-1.18]; $P = 0.18$). In order to explain why ixazomib maintenance therapy results in a superior OS while not significantly improving PFS and PFS2, we first investigated the percentage of patients receiving second and subsequent lines of therapy, which was comparable between the ixazomib versus placebo arm (second line: 82% versus 82%; third line: 51% versus 49%; fourth line: 23% versus 28%; fifth line: 8% versus 15%; and sixth line: 5% versus 5%). Furthermore, both the distribution of 2- versus 3-drug regimens and the use of different classes of anti-myeloma drugs were comparable between both the arms, except for higher use of monoclonal antibodies in the ixazomib arm; 13 of 32 (41%) patients versus 8 of 32 (25%) patients in the placebo arm, which might play a role. However, the use of PIs was higher in the placebo arm; 23 of 32 (72%) versus 19 of 32 (59%) in the ixazomib arm. The use of immunomodulatory imide drugs (IMiDs) was comparable; 26 of 32 (81%) in the ixazomib arm versus 29 of 32 (91%) in the placebo arm. For an overview of all second and subsequent lines of therapy, see Figure 2 and Suppl. Tables S3 and S4. Third, it can be hypothesized that continuous ixazomib treatment has influenced the bone marrow microenvironment by inhibiting osteoclasts while maintaining/stimulating the proliferation of osteoblasts.[8–10] Notably, osteoblasts are known to trigger apoptosis and cell cycle arrest in plasma cells.[11] Whether the indirect effects of ixazomib, through its impact on osteoblasts, contribute to the improvement in OS remains to be substantiated; and the fact why such an impact would be less in subsequent lines of therapy, as PIs were more often used in patients not having received ixazomib maintenance in first line. So, therefore, the discrepancy between the effect of ixazomib on PFS and OS remains elusive. Unfortunately, the numbers of events were too small to perform a multivariate analysis and therefore we cannot exclude that the difference may be a result of chance due to the small sample size of our study after randomization.

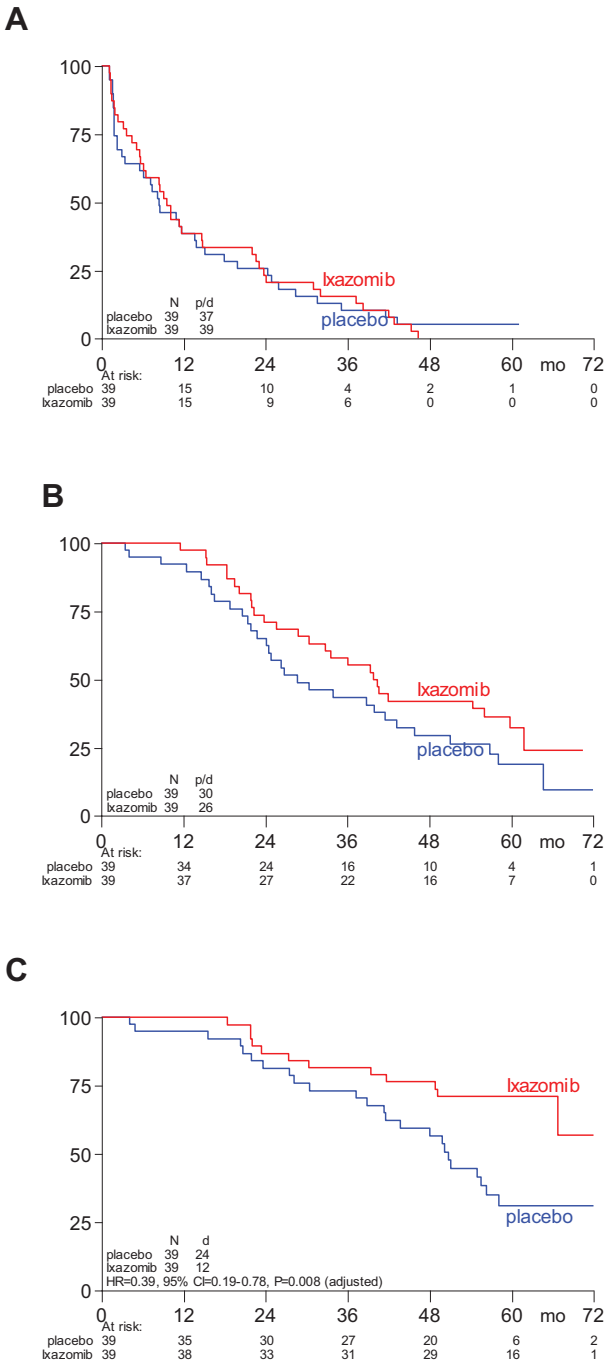

Figure 1. Kaplan-Meier curves from randomization between ixazomib vs placebo maintenance therapy for (A) progression-free survival, (B) progression-free survival 2, and (C) overall survival.

We found that ixazomib maintenance therapy was rather well tolerated. Most patients discontinued therapy due to progressive disease (72%). Toxicity requiring discontinuation of therapy or placebo occurred in 5 (13%) versus 4 (10%), respectively. In both the arms, 3 patients discontinued therapy due to polyneuropathy (detailed description of toxicity, Suppl. Table S5). Other reasons for discontinuation of maintenance therapy were intercurrent death (none versus 1 [3%]), unblinding (none versus 2 [5%]), and other reasons (6 [15%] versus 4 [10%]), in the ixazomib and placebo arm, respectively.

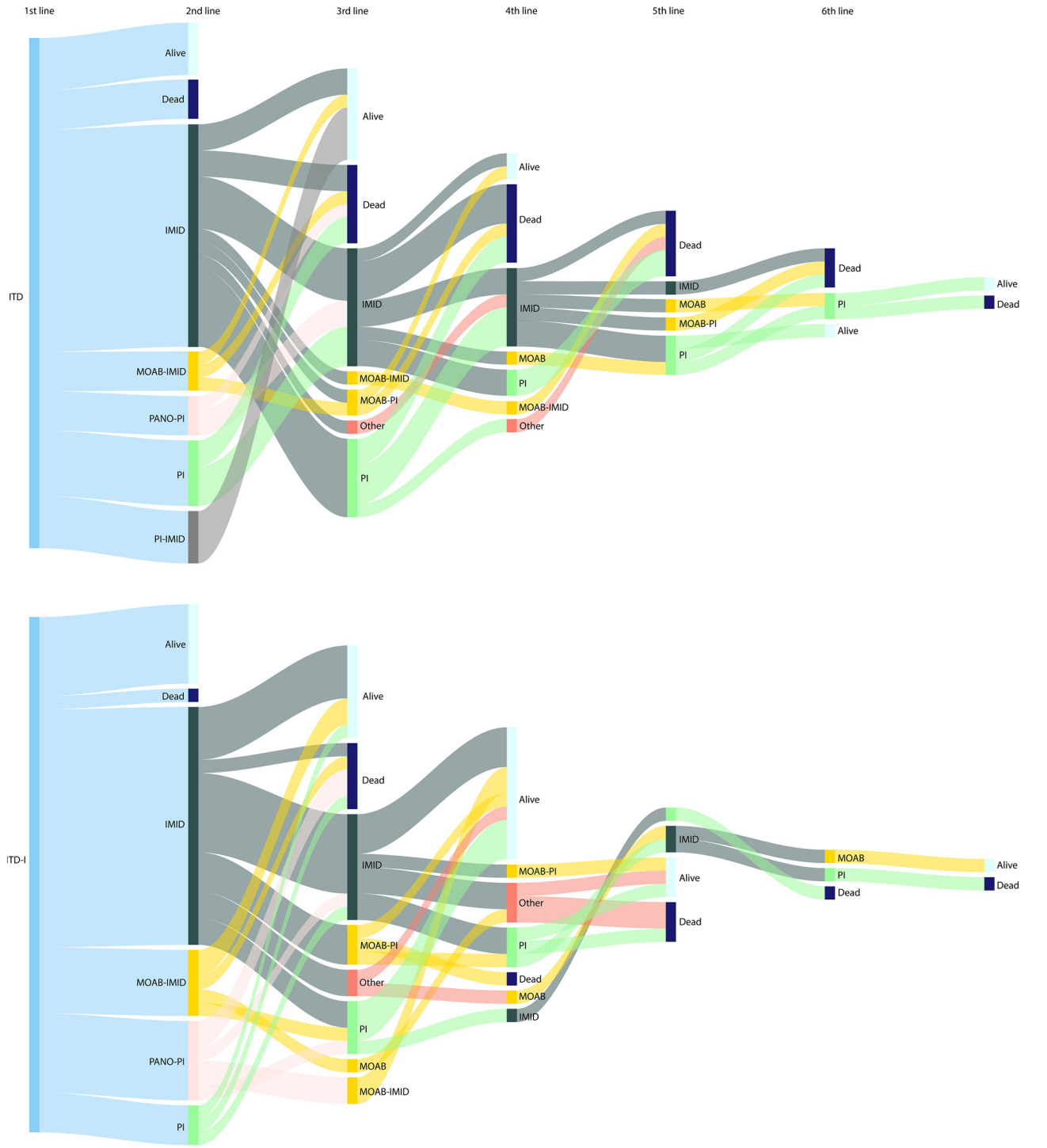

Figure 2. Sankey diagram. Visualization of second and subsequent lines of therapy, for all patients treated with placebo (above) or ixazomib (below) maintenance. IMID = immunomodulatory imide drugs; MOAB = monoclonal antibody; PANO = panobinostat; PI = proteasome inhibitor.

In view of the fact that the outcome of NTE-NDMM patients is highly dependent on frailty level, we performed a post hoc subgroup analysis, based on the simplified frailty index (S-FI), using the performance status instead of the instrumental activities of daily living (iADL) and activities of daily living (ADL), in the 143 included patients.[12] Unfortunately, the number of randomized patients did not allow a separate frailty subgroup analysis from randomization. The median follow-up from the date of registration of the 64 patients who were still alive was 67.4 months (interquartile range, 60.2–71.1 months). Treatment with ixazomib-thalidomide-dexamethasone (ITD) resulted in a median PFS of 14.3 months (95% CI, 11.5-16.8), a median PFS2 of 34.6 months (30.7-41.5), and a median OS of 58.3 months (50.5-65.0). According to S-FI, 23% of patients were fit (n = 33), 27% intermediate fit (n = 38), and 44% were frail (n = 63), while S-FI could not be assessed in 9 (6%) patients. The median PFS was 15.9, 13.6, and 12.9 months, in fit, intermediate fit, and frail patients, respectively. These numbers were 49.1, 30.1, and 30.9 months for PFS2 and not reached, 51.2 and 50.5 months for OS (Suppl. Table S1 and Suppl. Figure S1).

Remarkably, the outcome of intermediate fit and frail patients was comparable. As in the FIRST trial, in which the S-FI was developed, frail patients were compared with nonfrail patients only, which includes both intermediate fit and fit patients, and we cannot exclude as this holds true in general using the S-FI instead of the IMWG-FI. In accordance with the FIRST trial, we found an inferior OS in frail patients as compared with nonfrail (ie, intermediate fit and fit) patients; median OS 50.5 (95% CI, 32.9-59.4) versus 64.6 (51.2-not reached) months (P = 0.04) indeed. However, this did not account for the PFS (12.9 [95% CI, 10.0–17.4] versus 14.3 [11.1–17.3] months; P = 0.51) and PFS2 (30.9 [95% CI, 24.0–42.3] versus 35.8 [30.8-47.8] months; P = 0.38). Actually, also in the FIRST trial, differences in OS of frail versus intermediate and fit patients were more pronounced as compared with PFS.[12] The prognostic value of different frailty scores, especially for PFS, is an area for further optimization.

In conclusion, we show that with long-term FU that ixazomib maintenance treatment following 9 induction cycles with ITD resulted in an OS advantage as compared with placebo, due to less myeloma-related deaths, which could not be clearly explained by differences in the number and type of subsequent therapies. Therefore, ITD followed by ixazomib maintenance could be a valuable first-line treatment option in countries without access to daratumumab in combination with lenalidomide. Especially in view of the fact that the non-daratumumab containing alternative first-line treatment, bortezomib-Lenalidomide-dexamethasone, has been recently shown not to result in a superior outcome in patients >65 years old, whereas in our phase II study, long-term administration of ixazomib resulted in a superior OS.[13] The long-term outcome on OS of the Tourmaline 3 and 4 studies, also comparing ixazomib maintenance with observation in transplant eligible and noneligible patients, are eagerly awaited.

AUTHOR CONTRIBUTIONS

MDL, MH, AW, EH, UM, PS, NA, and SZ designed the research. KG, BH, MS, and SZ analyzed the data. KG and SZ wrote the article. FS, MDL, MH, MBL, JR, AW, DS, PA, TH, AS, ES, EH, DK, PY, CB, UM, ND, PS, AK, AV, NA, and SZ provided study patients. All authors approved the final version of the article.

DISCLOSURES

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