EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2023
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NINLARO

International non-proprietary name: ixazomib

Procedure No. EMEA/H/C/003844/II/0045

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	17 Jul 2023	17 Jul 2023	☐
☐	CHMP Rapporteur Assessment Report	14 Aug 2023	16 Aug 2023	☐
☐	PRAC Rapporteur Assessment Report	18 Aug 2023	17 Aug 2023	☐
☐	PRAC members comments	23 Aug 2023	23 Aug 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	24 Aug 2023	23 Aug 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	31 Aug 2023	31 Aug 2023	☐
☐	CHMP members comments	04 Sep 2023	04 Sep 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Sep 2023	08 Sep 2023	☐
☒	Opinion	14 Sep 2023	14 Sep 2023	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 30 June 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Submission of the Clinical Study Report (Addendum 2) for study C16019 listed as a Specific Obligation in the Annex II of the Product Information. This is a phase 3, randomized, double-blind, placebo-controlled study of single-agent oral ixazomib as maintenance therapy following autologous stem cell transplant (ASCT) for patients with newly diagnosed multiple myeloma. In addition, the MAH proposes to remove NINLARO from the list of medicines subject to additional monitoring and to remove the black triangle from the SmPC. The Annex II and Package Leaflet are updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

GLP/GCP inspections

N/A

2. Overall conclusion and impact on the benefit/risk balance

On November 2016 Ninlaro was granted conditional marketing authorisation (CMA) following re-examination for the treatment, in combination with lenalidomide and dexamethasone (IRd regimen), of adult patients with multiple myeloma (MM) who have received at least one prior therapy (R/R MM).

Supporting data were not considered comprehensive since OS results from pivotal study C16010 were not sufficiently mature; moreover, in the updated (yet not inferential by study design) set of data at the time of the second interim analysis (IA) for PFS, the results were less convincing, with a borderline statistical significance (PFS HR 0.82; 95% CI 0.67, 1.00; p= 0.054). Furthermore, inconsistencies were observed in the treatment effect across relevant subgroups: e.g. in the large (60% of the ITT population) subset of patients with one single prior line of treatment the HR for PFS was 0.88 (95% CI 0.65, 1.20) in the first IA and 0.99 (95% CI 0.76, 1.29) in the more mature second IA.

Four SOBs and one Annex II.D PAES were agreed with the MAH to provide additional information on ixazomib efficacy and safety: SOB002 (C16010 - China continuation study), ANX001 (final OS data from registrational Phase III study C16010) and SOB005 (observational study MSMM-5001 to provide RW data) were designed to further investigate the efficacy of the approved IRd combination in the target population; SOB003 (modified IRd in frail patients with newly diagnosed MM – Phase III Study C16014) and SOB004 (ixazomib monotherapy as post-ASCT maintenance – Study C16019) were to provide data on the activity of Ninlaro in earlier settings of disease.

SOB004 is the only SOB for Ninlaro that is still outstanding.

In the context of the Ninlaro CMA, the original aim of SOB004 was to substantiate the clinical activity and safety of Ninlaro in an earlier MM setting. PFS data from the first IA of study C16019 were submitted on December 2018 (see also procedure EMEA/H/C/003844/II/0014/G) and showed that prolonged exposure to ixazomib monotherapy after ASCT resulted in a statistically significant increase in PFS compared to placebo (median PFS by IRC 26.5 months with ixazomib and 21.3 months with placebo, HR 0.72; 95%CI 0.58, 0.89; p=0.002). No new safety concerns were identified, and the updated data submitted in the context of this variation confirmed that no increase in the risk of NPM was associated with prolonged treatment with ixazomib. However, the point estimates for OS and PFS2 did not exclude a potential detrimental effect (HR 1.165, 95%CI 0.761, 1.779 and HR 1.160; 95%CI 0.810, 1.662, respectively). A similar trend was also observed in phase III study C16021 (not a PAM for Ninlaro) which investigated the effect of ixazomib maintenance in patients with newly diagnosed MM not eligible for transplantation. Out of caution, the CHMP decided to amend SOB004 in order to provide additional OS/PFS2 data from study C16019 when approximately 200 death events would have occurred.

Updated data from study C16019 were submitted in the context of CMA annual renewal procedures and were consistent with the first IA. IA2 for OS was conducted on January 2020 with a median follow-up of approximately 4.5 years: 22% of patients (142 of 656) had died and the OS HR was 1.029 (95%CI 0.734, 1.441; p=0.868). IA3 was conducted on January 2021: 27% of patients (174 of 656) had died and the OS HR was 1.008 (95%CI 0.744, 1.367; p=0.958).

In compliance with the established timeframe, the MAH has now submitted the results from OS IA4 to fulfil SOB004. IA4 is the most recent IA for Study C16019, with a DCO date of 12 October 2022; at this time, 209 deaths occurred in Study C16019. Updated OS and PFS2 data showed that the HR for OS (1.074, 95%CI 0.812, 1.421), although reduced compared to IA2, was still slightly in favour of placebo. A similar trend could be observed for PFS2 (HR of 1.016, 95%CI 0.791, 1.305). Pre-specified and *ad hoc* sensitivity analyses for OS were provided to assess whether a true detrimental effect on survival could be associated with prolonged exposure to ixazomib. The interpretation of these analyses was, however, not straightforward because of methodological limits (e.g. the reliability of MSM and IPCW techniques was hampered by the high clinical and biological heterogeneity of MM) and because some results were, apparently, counterintuitive (e.g. the reported "protective" effect of subsequent exposure to PIs after ixazomib failure). Results from these *post hoc*, non-randomised analyses should, anyway, be considered with caution due to the significant risk of bias.

Based on HR estimates, the possibility of an actual detrimental effect on survival with ixazomib monotherapy cannot be formally excluded. However, it should be considered that KM curves for OS run largely superimposed and repeatedly crossed over time, without showing any clear trend towards differences between arms. Moreover, no unexpected safety concern was identified in study C16019.

Further, the lack of OS benefit with ixazomib maintenance is not unexpected, since no trial investigating the use of a PI as post-ASCT maintenance treatments has been able to demonstrate a significant advantage in OS (see e.g. Goldschmidt H et al, Leukemia 2018; Rosinol L et al, Leukemia 2017). Finally, several effective options have become available in the last years for subjects with R/R MM, and it is uncertain to what extent the limited 5-month PFS gain observed in study C16019 in an early setting of disease could be reflected in meaningful gains in terms of OS.

Notably, long-term OS data in the approved indication from registrational study C16010 (ANX001 Annex II PAES, see procedure EMEA/H/C/003844/II/0033) and the supportive "China continuation study" (SOB002, see procedure EMEA/H/C/003844/II/0002) were not suggestive of potential detrimental effects on survival. Further, RW data from observational study MSMM-5001 (SOB005, see procedure EMEA/H/C/003844/II/0041) also did not raise any concern with respect to a potential detrimental effect on OS of the IRd combination in the target population.

In conclusion, data from SOB004 have confirmed that prolonged exposure to ixazomib monotherapy in an early setting of MM can result in a limited yet statistically significant PFS prolongation in the absence of new safety concerns, supporting the anti-MM activity of Ninlaro. Although PFS2 and OS data from SOB004 did not allow to clearly exclude a possible detrimental effect with post-ASCT ixazomib maintenance, post-approval conditions ANX001, SOB002 and SOB005 did not identify any concern related to a potential detrimental effect with ixazomib when used in combination with lenalidomide and dexamethasone in the currently approved indication. On these grounds, SOB004 can be considered fulfilled.

Based on the totality of data from the SOBs and Annex II.D PAES, the Rapporteur's opinion is that there are no remaining grounds for the marketing authorisation of Ninlaro to remain conditional, and that the deletion of the last specific obligation from Annex II can, therefore, be agreed. Since more than 5 years have passed after the URD and all the SOBs have been fulfilled, it is also agreed that Ninlaro can be removed from the additional monitoring list.

The benefit-risk balance of Ninlaro in the approved indication is positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Submission of the Clinical Study Report (Addendum 2) for study C16019 listed as a Specific Obligation in the Annex II of the Product Information. This is a phase 3, randomized, double-blind, placebo-controlled study of single-agent oral ixazomib as maintenance therapy following autologous stem cell transplant (ASCT) for patients with newly diagnosed multiple myeloma. In addition, the MAH proposes to remove NINLARO from the list of medicines subject to additional monitoring and to remove the black triangle from the SmPC. The Annex II and Package Leaflet are updated accordingly. The RMP version 10.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

Description	**Due date**
C16019: In order to further investigate the efficacy the MAH should provide additional OS/PFS2 data when approximately 200 death events have occurred from the Phase 3,	September

Description	Due date
randomized, placebo-controlled, double-blind study of ixazomib in maintenance therapy in patients with multiple myeloma following SCT.	2023

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Ninlaro- EMEA/H/C/003844/II/0045.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

On November 2016 Ninlaro was granted conditional marketing authorisation (CMA) for the treatment, in combination with lenalidomide and dexamethasone (IRd regimen), of adult patients with multiple myeloma (MM) who have received at least one prior therapy (R/R MM). Despite the B/R of the IRd triplet in the approved indication was considered positive, the available data were not considered sufficiently comprehensive to adequately characterise the efficacy of Ninlaro. In particular, concerns were present on the extent of the long-term clinical benefit with IRD, since OS in pivotal study C16010 was not sufficiently mature and, in the more mature (yet not inferential by study design) set of data at the time of the second interim analysis for PFS, the results were less convincing, with a borderline statistical significance (PFS HR 0.82; 95% CI 0.67, 1.00; p= 0.054). Further, inconsistencies were observed in the treatment effect across relevant subgroups: e.g. in the large (60% of the ITT population) subset of patients with one single prior line of treatment the HR for PFS was 0.88 (95% CI 0.65, 1.20) in the first interim analysis and 0.99 (95% CI 0.76, 1.29) in the more mature second interim analysis.

Four SOBs and one Annex II PAES were, therefore, agreed with the MAH to provide additional information on ixazomib efficacy: SOB002 (C16010 - China continuation study), ANX001 (final OS data from registrational Phase III study C16010) and SOB005 (observational study MSMM-5001 to provide RW data) were designed to further investigate the efficacy of the approved IRd combination in the target population; SOB003 (modified IRd in frail patients with newly diagnosed MM – Phase III Study C16014) and SOB004 (ixazomib monotherapy as post-ASCT maintenance – Study C16019) were to provide data on the activity of Ninlaro in earlier settings of disease.

SOB004 is currently the only SOB for Ninlaro that is still outstanding. In line with the agreed timeframe, data from study C16019 were submitted on December 2018 in the context of procedure EMEA/H/C/003844/II/0014/G. Results from the first interim analysis (IA) showed a statistically significant PFS improvement vs. placebo (mPFS by IRC 26.5 months with ixazomib vs. 21.3 months with placebo, HR 0.72, p=0.002), yet the point estimates for OS and PFS2 did not exclude a potential detrimental effect (HR 1.165, 95%CI 0.761, 1.779 and HR 1.160; 95% CI: 0.810, 1.662, respectively). A similar trend was observed in phase III study C16021 (not included as SOB) investigating the effect of ixazomib maintenance in patients with newly diagnosed MM not eligible for transplantation. Acknowledging the significant differences in patient population and administration regimen between study C16019 and the approved indication for Ninlaro, the CHMP decided to amend SOB004 in order to provide more mature PFS2/OS data.

From a safety perspective, updated data have confirmed, so far, the known toxicity profile of ixazomib.

Updated data from study C16019 were submitted in the context of CMA annual renewal procedures and were consistent with the first IA. IA2 for OS was conducted with a DCO date of 27 January 2020 at a median follow-up of approximately 4.5 years; as of IA2, 22% of patients (142 of 656) had died and the OS HR was 1.029 (95% CI 0.734, 1.441; p=0.868). IA3 was conducted with a DCO date of 29 January 2021; as of IA3, 27% of patients (174 of 656) had died and the OS HR was 1.008 (95% CI 0.744, 1.367; p = 0.958).

Conforming with the established timeframe, the MAH has submitted the results from IA4 to comply with SOB004. IA4 is the most recent IA for Study C16019, with a DCO date of 12 October 2022; at this time, 209 deaths had occurred in Study C16019.

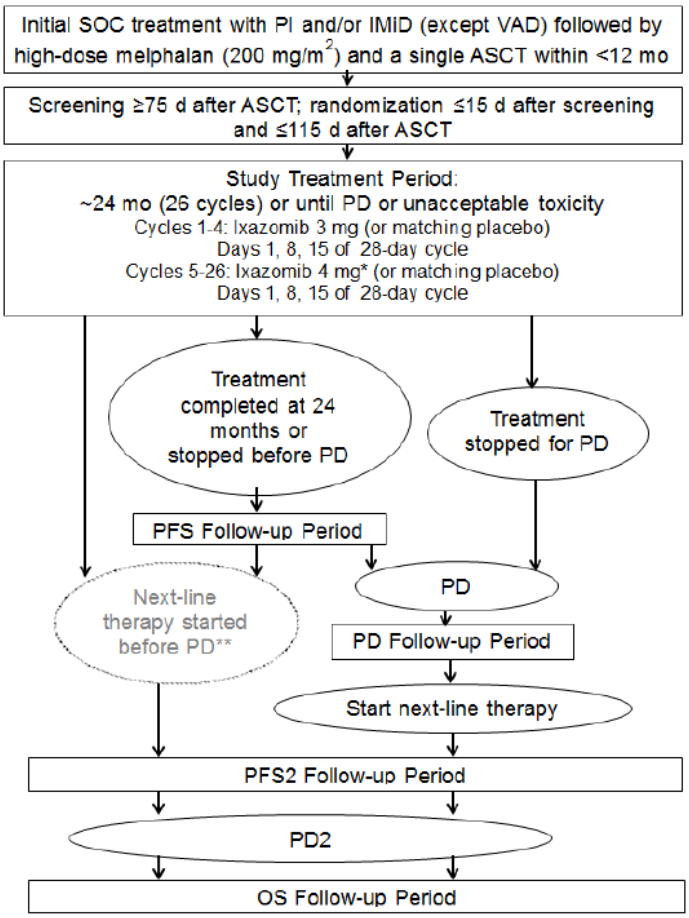
6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

Study C16019 was a phase 3, randomized, double-blind, placebo-controlled, multicenter study of patients with newly diagnosed multiple myeloma (NDMM) who had undergone induction therapy according to regional standard of care, followed by a conditioning regimen containing high-dose melphalan and autologous stem cell transplantation (SCT).

Study design is summarised in Figure below:

Figure 9.a Study Overview Diagram



ASCT: autologous stem cell transplant; IMiD: immunomodulatory drug; OS: overall survival; PD: progressive disease; PD2: progressive disease on next-line of treatment; PFS: progression-free survival; PFS2: time from the date of randomization to the date of objective disease progression on next-line treatment or death from any cause, whichever occurs first; PI: proteasome inhibitor; SOC: standard of care; VAD: vincristine, Adriamycin (doxorubicin), and dexamethasone.
* After the first 4 cycles of treatment, eligible patients had their dose of ixazomib (or matching placebo) escalated from 3 mg to 4 mg.
** If a physician chose to start next-line therapy before PD, the patient skipped the PD Follow-up period and entered directly into the PFS2 Follow-up period.

The study included adult patients 18 years or older with a confirmed diagnosis of symptomatic MM according to standard criteria, who underwent standard-of-care induction therapy (induction therapy must have included PI- and/or IMiD-based regimens as primary therapy for MM), followed by a single ASCT with a high-dose melphalan (200 mg/m^2) conditioning regimen, within 12 months of diagnosis. Vincristine, Adriamycin (doxorubicin), and dexamethasone (VAD) was not an acceptable induction

therapy for this study. A response to ASCT (PR, VGPR, CR/stringent complete response [sCR]) according to IMWG criteria should have been documented. Patients who received consolidation therapy were excluded, a s well as subjects with central nervous system involvement.

The study primary objective was to determine the effect of ixazomib maintenance on progression-free survival (PFS) by a blinded independent review committee (IRC) compared to placebo. The key secondary objective was to determine whether ixazomib maintenance could improve overall survival (OS).

Approximately 652 patients were to be randomized in a 3:2 ratio to ixazomib maintenance or placebo. There were two planned interim analyses (IAs) and one final analysis (FA): the first IA was the primary analysis (and the only analysis) for PFS for statistical testing purposes, with the opportunity to claim PFS benefit. Only if PFS was significant at the first IA, then OS was to be tested at this first IA and at subsequent analyses until statistical significance had been achieved or the FA was reached (determination of the number of OS events at FA had to occur at IA2). The total event size calculation for OS was based on an adaptive sample size reassessment approach.

PFS was tested at a 2-sided alpha level of 0.05. OS was tested at the IAs or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method). The first IA (primary analysis for PFS) was planned to be performed when approximately 328 PFS events had occurred or 25 months after the last patient has been enrolled, whichever occurred later. With 328 PFS events, it would have had 95% power to detect a hazard ratio of 0.67 (i.e., median PFS of 26 months for control versus 39 months for treatment) using a 2-sided log-rank test at a 2-sided alpha level of 0.05 and assuming approximately 15% dropout rate at month 30. This IA was expected to occur at 45 months after the first patient is enrolled, including a 20-month enrolment period and an additional 25-month follow-up after the last patient enrolled.

The second IA was originally planned to be conducted for OS when approximately 200 death events had been observed, which was expected to occur approximately 60 months after the first patient was enrolled. Due to regulatory concerns, additional interval IAs for PFS2 and OS were conducted. The test significance for the IAs of OS was determined using O'Brien-Fleming boundaries (the Lan-DeMets method) with a total of 260 death events. The minimum event size of 260 death events was based on an optimistic assumption of a hazard ratio of 0.70 (i.e., median OS of 70 months for control versus 100 months for treatment) with 80% power at a 2-sided level of significance.

Health-related QOL was measured by 3 instruments to address secondary and exploratory endpoints:

• the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core Module 30 (QLQ-C30),

• the EORTC Quality of Life Questionnaire Multiple Myeloma Module-20 (QLQ-MY20), and

• the EuroQol 5-Dimensional Health Questionnaire (EQ-5D).

Scores on the EORTC QLQ-C30 and QLQ-MY20 are linearly transformed to a 0-100 scale. High scores for the global and functional domains indicate better QOL or functioning, while high scores on the symptom scales indicate higher levels of symptomatology or problems.

For additional details on study C16019, please see procedure EMEA/H/C/003844/II/0014/G.

6.2. Results

Disposition

A total of 656 patients were randomized in a 3:2 ratio and included in the intent-to-treat (ITT)

population; 395 patients were randomized to receive ixazomib and 261 patients were randomized to receive placebo. As of the DCO date for IA4 (12 October 2022), all patients had completed study treatment; 50% of the study population was continuing follow-up (see Table below).

Table 2.a Patient Disposition—ITT Population

	2:3 Randomization		
	Placebo (N = 261)	Ixazomib (N = 395)	Total (N = 656)
Parameter	Number (%) of Patients		
ITT population [a]	261 (100)	395 (100)	656 (100)
Safety population [b]	259 (> 99)	394 (> 99)	653 (> 99)
Ongoing on treatment	0	0	0
Continuing in follow-up	131 (50)	196 (50)	327 (50)
Lost to follow-up	4 (2)	5 (1)	9 (1)
Withdrew from follow-up	44 (17)	60 (15)	104 (16)
Reason for end of study	50 (19)	70 (18)	120 (18)
Lost to follow-up	4 (2)	5 (1)	9 (1)
Withdrawal by patient	44 (17)	60 (15)	104 (16)
Other	2 (<1)	5 (1)	7 (1)

Source: Table 15.1.1.1A.

ITT: intent-to-treat.

[a] The ITT population was defined as all patients who were randomized and had post-randomization data.

[b] The safety population was defined as all patients who received at least 1 dose of ixazomib or placebo.

Study outcomes

Overall survival (OS)

With 209 deaths (32% of the ITT population; 129 [33%] in the ixazomib arm and 80 [31%] in the placebo arm), median OS was not estimable (NE) in both treatment arms (HR=1.074; 95% CI: 0.812, 1.421; p=0.616). OS results are summarised in Table and Figure below:

Table 2.b Analysis of OS—ITT Population

Parameter	2:3 Randomization Placebo N = 261	2:3 Randomization Ixazomib N = 395	HR [95% CI] [a] P-value [b]
OS (mo)			1.074 [0.812, 1.421] 0.616
Patients who died, n (%)	80 (31)	129 (33)	
Patients censored, n (%)	181 (69)	266 (67)	
Median [95% CI] (mo)	NE [NE, NE]	NE [93.04, NE]	
Minimum, maximum (mo)	0.0*, 95.9*	0.0*, 97.7*	
Median follow-up [95% CI] (mo)	83.7 [82.76, 84.70]	83.5 [82.63, 84.76]	
Reason for censoring, n (%)			
Lost to follow-up	4 (2)	5 (1)	
Still alive as of date of last contact	177 (68)	261 (66)	

Source: Table 15.2.3.1A.

CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: Internatiional Staging System; ITT: intent-to-treat; mo: months; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.

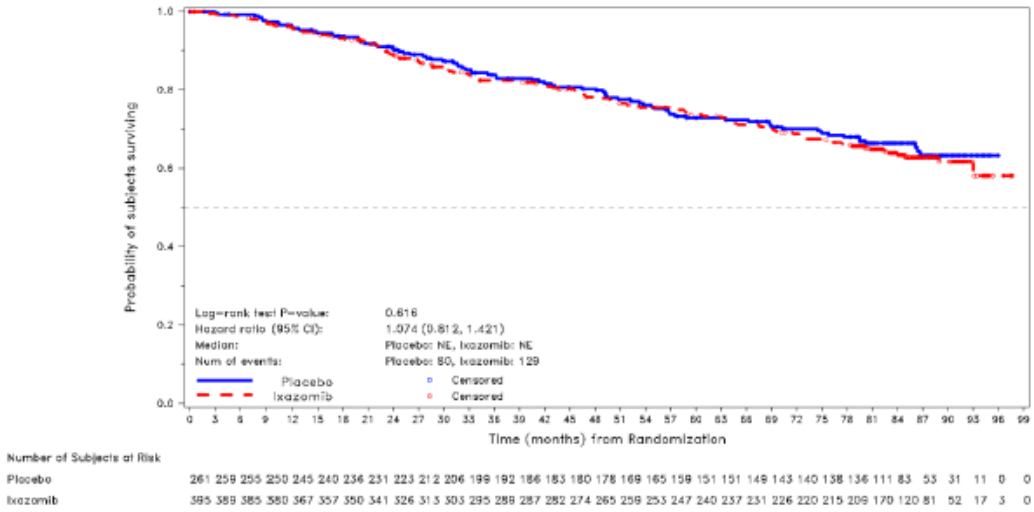
* Censored observation.

OS is defined as the time from the date of randomization to the date of death. Patients without documented death are censored at the date last known to be alive. Only nonmissing censoring categories are summarized in the table.

[a] HR is based on an unadjusted Cox's proportional hazard regression model stratified by preinduction regimen (PI vs IMiD vs both PI and IMiD), preinduction ISS (Stage I vs Stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of the ixazomib arm over the hazard rate of the placebo arm. HR of <1 indicates lower risk of death in the ixazomib arm than in the placebo arm, whereas HR > 1 indicates lower risk of death in the placebo arm than in the ixazomib arm.

[b] P-value comparing OS between treatment groups is based on log-rank test stratified by preinduction regimen (PI vs IMiD vs both PI and IMiD), preinduction ISS (Stage I vs Stage II or III), and response after transplantation (CR or VGPR vs PR).

Figure 2.a K-M Plot of OS—ITT Population



Source: Figure 15.2.2.2A.

ITT: intent-to-treat; K-M: Kaplan-Meier; Num: number; NE: not estimable; OS: overall survival.

Randomization was 3:2 ixazomib:placebo.

OS is defined as the time from the date of randomization to the date of death.

At this IA4, 281 of the 394 (71%) patients in the ixazomib arm and 187 of the 259 (72%) patients in the placebo arm had received subsequent therapy. Patients in the ixazomib arm started subsequent therapy later than patients in the placebo arm: median time to subsequent therapy, 33.1 months versus 27.6 months (HR=0.833; 95% CI: 0.690, 1.005; p = 0.056). Results from the prespecified marginal structural models (MSM) and inverse probability of censoring weighted (IPCW) analyses are shown in Table below.

Table 2.c Prespecified OS Sensitivity Analyses—ITT Population

Method	HR [95% CI]	P-value
Marginal structural models	0.760 [0.214, 2.704]	0.672
Inverse probability of censoring weighted	0.644 [0.204, 2.029]	0.452

Source: Table 15.2.3.1H.

HR: hazard ratio; ITT: intent-to-treat; MRD: measurable residual disease; OS: overall survival.

After adjusting for subsequent therapy received between the 2 arms, the HRs showed an OS advantage with ixazomib over placebo, although the effect was not statistically significant.

Ad hoc sensitivity analyses were also used to investigate further the potential impact on OS of subsequent therapies, which were not specified in the study and were administered at the discretion of the investigator. Use of a proteasome inhibitor (PI) as next-line therapy was of particular interest. Because the study was blinded, some patients had next-line therapy initiated without having been unblinded. Patients in the ixazomib arm who progressed while on ixazomib and were put on a PI as next-line therapy may have been receiving a treatment to which their disease was resistant. In contrast, patients who progressed while on placebo, having had a treatment holiday, may have been more likely to have disease that was still sensitive to PIs.

Among the 465 patients who received any subsequent therapy, median OS was 93.0 months in the ixazomib arm and NE in the placebo arm (HR=1.123; 95% CI: 0.841, 1.500; p=0.431) (see Table and Figure below).

Table 2.d OS for Patients Receiving Any Subsequent Therapy—ITT Population

Parameter	2:3 Randomization		HR [95% CI] [a] P-value [b]
	Placebo N = 187	Ixazomib N = 278	
OS (mo)			1.123 [0.841, 1.500] 0.431
Patients who died, n (%)	75 (40)	123 (44)	
Patients censored, n (%)	112 (60)	155 (56)	
Median [95% CI] (mo)	NE [86.11, NE]	93.0 [77.34, NE]	
Minimum, maximum (mo)	3.3, 95.9*	2.0, 97.7*	
Reason for censoring, n (%)			
Lost to follow-up	3 (2)	2 (<1)	
Still alive at date of last contact	109 (58)	153 (55)	

Source: Table 15.2.3.2E.

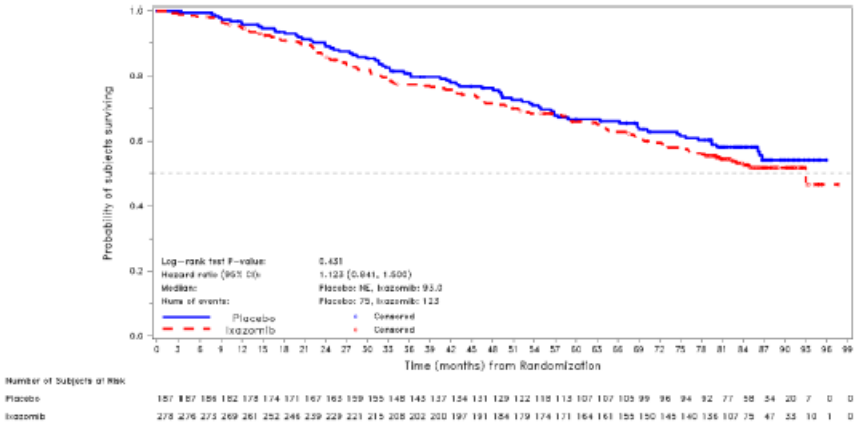
CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; mo: months; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.

* Censored observation.

[a] Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. HR <1 indicates better prevention of death in ixazomib arm as compared to placebo arm.

[b] P-value comparing OS between treatment groups is based on Log-rank test stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR).

Figure 2.b K-M Plot of OS for Patients Receiving Any Subsequent Therapy—ITT Population



Source: Figure 15.2.2.2F.
K-M: Kaplan-Meier; ITT: intent-to-treat; NE: not estimable; num: number; OS: overall survival.
Randomization was 3:2 ixazomib:placebo.

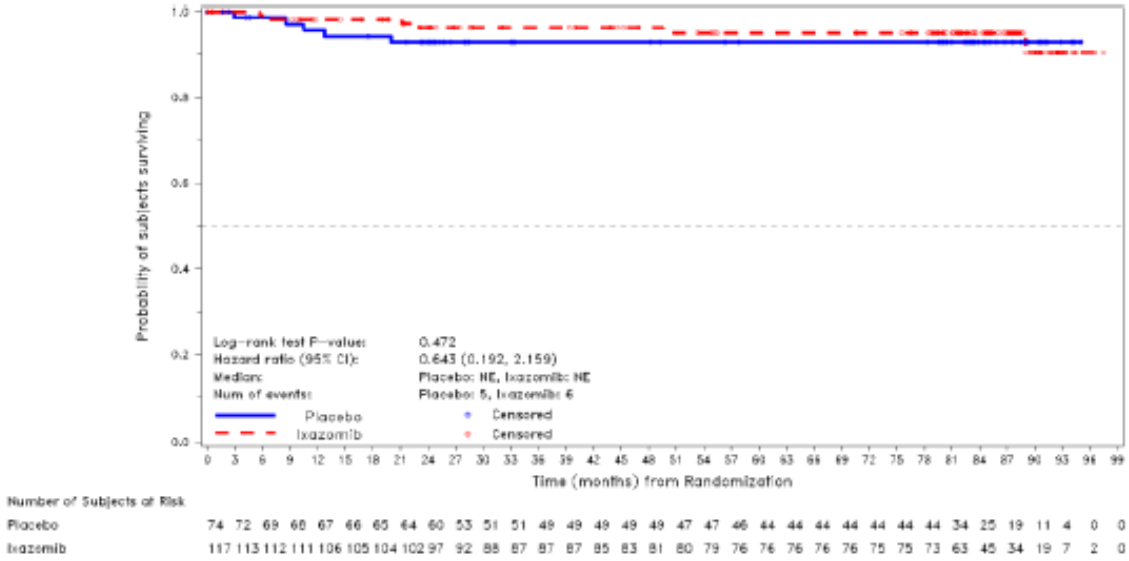
Among the remaining 191 patients who were censored at subsequent therapy, median OS was NE in both the ixazomib arm and the placebo arm (HR=0.643; 95% CI 0.192, 2.159; p=0.472) (See Table and Figure below).

Table 2.e OS for Patients Censored at Subsequent Therapy—ITT Population

Parameter	2:3 Randomization Placebo N = 74	2:3 Randomization Ixazomib N = 117	HR [95% CI] [a] P-value [b]
OS (mo)			0.643 [0.192, 2.159] 0.472
Patients who died, n (%)	5 (7)	6 (5)	
Patients censored, n (%)	69 (93)	111 (95)	
Median [95% CI] (mo)	NE [NE, NE]	NE [NE, NE]	
Minimum, maximum (mo)	0.0*, 95.0*	0.0*, 97.5*	
Reason for censoring, n (%)			
Lost to follow-up	1 (1)	3 (3)	
Still alive at date of last contact	68 (92)	108 (92)	

Source: Table 15.2.3.2D.
CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; mo: months; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.
* Censored observation.
[a] Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. HR <1 indicates better prevention of death in ixazomib arm as compared to placebo arm.
[b] P-value comparing OS between treatment groups is based on Log-rank test stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR).

Figure 2.c K-M Plot of OS for Patients Censored at Subsequent Therapy—ITT Population



Source: Figure 15.2.2.2H.
K-M: Kaplan-Meier; ITT: intent-to-treat; NE = not estimable; num: number; OS: overall survival.
Randomization was 3:2 ixazomib:placebo.

Among the 465 patients who received subsequent therapy, at second line in particular, 226 received a regimen containing a PI and 239 received a regimen that did not contain a PI.

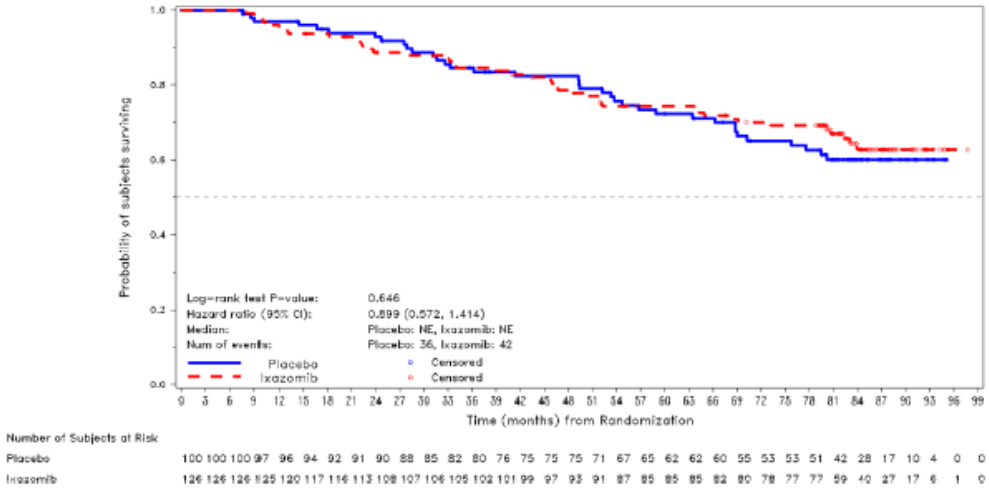
Patients who received a PI at second line had a median OS of NE in the ixazomib arm and NE in the placebo arm (HR=0.899; 95% CI: 0.572, 1.414; p=0.646) (see Table and Figure below).

Table 2.f OS for Patients Whose Second-Line Therapy Included a PI—ITT Population

Parameter	2:3 Randomization Placebo N = 100	2:3 Randomization Ixazomib N = 126	HR [95% CI] [a] P-value [b]
OS (mo)			0.899 [0.572, 1.414] 0.646
Patients who died, n (%)	36 (36)	42 (33)	
Patients censored, n (%)	64 (64)	84 (67)	
Median [95% CI] (mo)	NE [80.23, NE]	NE [NE, NE]	
Minimum, maximum (mo)	7.7, 95.1*	8.1, 97.7*	
Reason for censoring, n (%)			
Lost to follow-up	2 (2)	0	
Still alive at date of last contact	62 (62)	84 (67)	

Source: Table 15.2.3.2I.
CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; mo: months; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.
* Censored observation.
[a] Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. HR <1 indicates better prevention of death in ixazomib arm as compared to placebo arm.
[b] P-value comparing OS between treatment groups is based on Log-rank test stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR).

Figure 2.d **K-M Plot of OS for Patients Whose Second-Line Therapy Included a PI—ITT Population**



Source: Figure 15.2.2.2JA.

K-M: Kaplan-Meier; num: number; OS: overall survival; PI: proteasome inhibitor.

Randomization was 3:2 ixazomib:placebo

In contrast, among patients whose second-line therapy did not include a PI, the median OS was reached in both arms: 72.3 months in the ixazomib arm and 86.7 months in the placebo arm (HR=1.298; 95% CI: 0.877, 1.921; p=0.190) (see Table and Figure below).

Table 2.g **OS for Patients Whose Second-Line Therapy Did Not Include a PI—ITT Population**

Parameter	2:3 Randomization		HR [95% CI] [a] P-value [b]
	Placebo N = 87	Ixazomib N = 152	
OS (mo)			1.298 [0.877, 1.921] 0.190
Patients who died, n (%)	39 (45)	81 (53)	
Patients censored, n (%)	48 (55)	71 (47)	
Median [95% CI] (mo)	86.7 [57.46, NE]	72.3 [60.85, NE]	
Minimum, maximum (mo)	3.3, 95.9*	2.0, 95.3*	
Reason for censoring, n (%)			
Lost to follow-up	1 (1)	2 (1)	
Still alive at date of last contact	47 (54)	69 (45)	

Source: Table 15.2.3.2J.

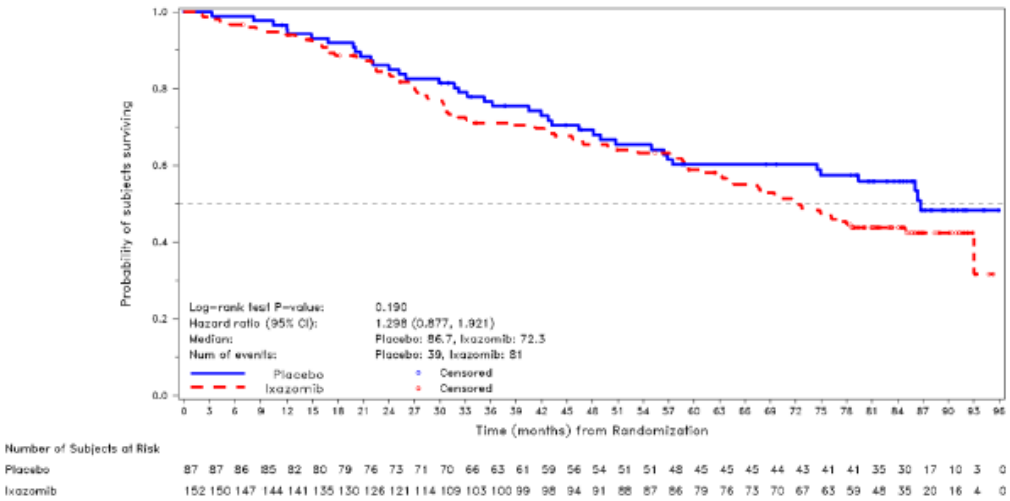
CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; mo: months; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.

* Censored observation.

[a] Hazard ratio is based on an unadjusted Cox's proportional hazard regression model stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of ixazomib arm over the hazard rate of placebo arm. HR <1 indicates better prevention of death in ixazomib arm as compared to placebo arm.

[b] P-value comparing OS between treatment groups is based on Log-rank test stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR).

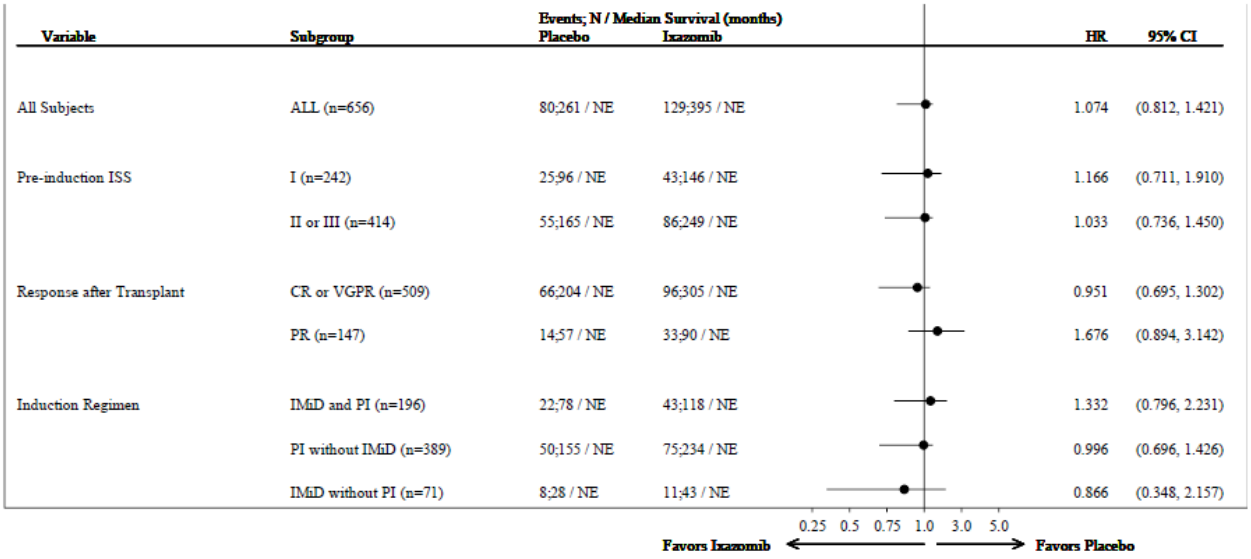
Figure 2.e K-M Plot of OS for Patients Whose Second-Line Therapy Did Not Include a PI—ITT Population

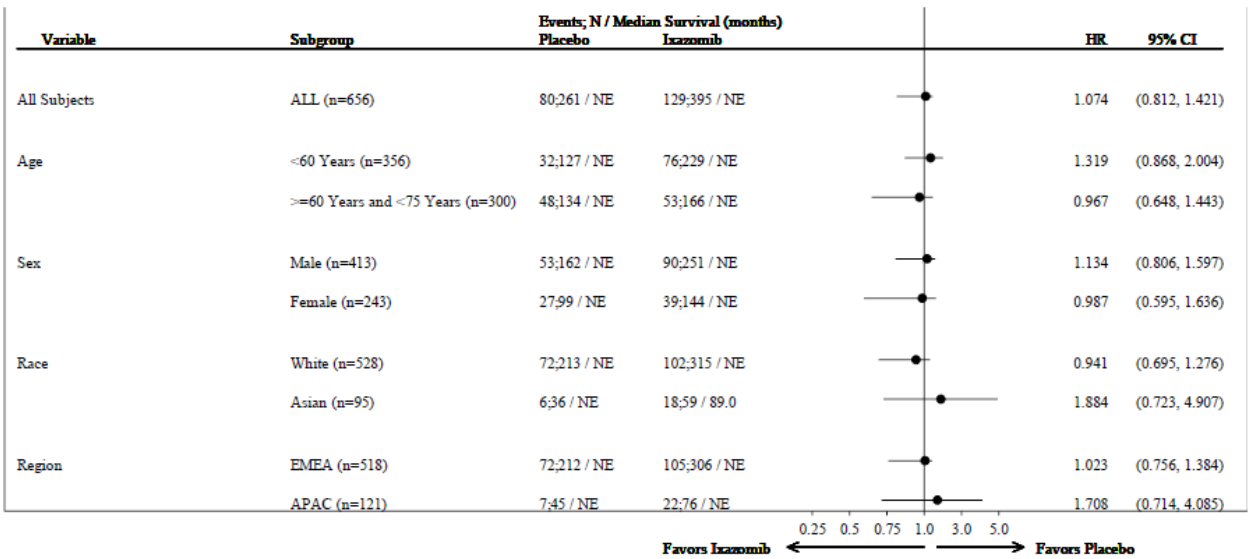


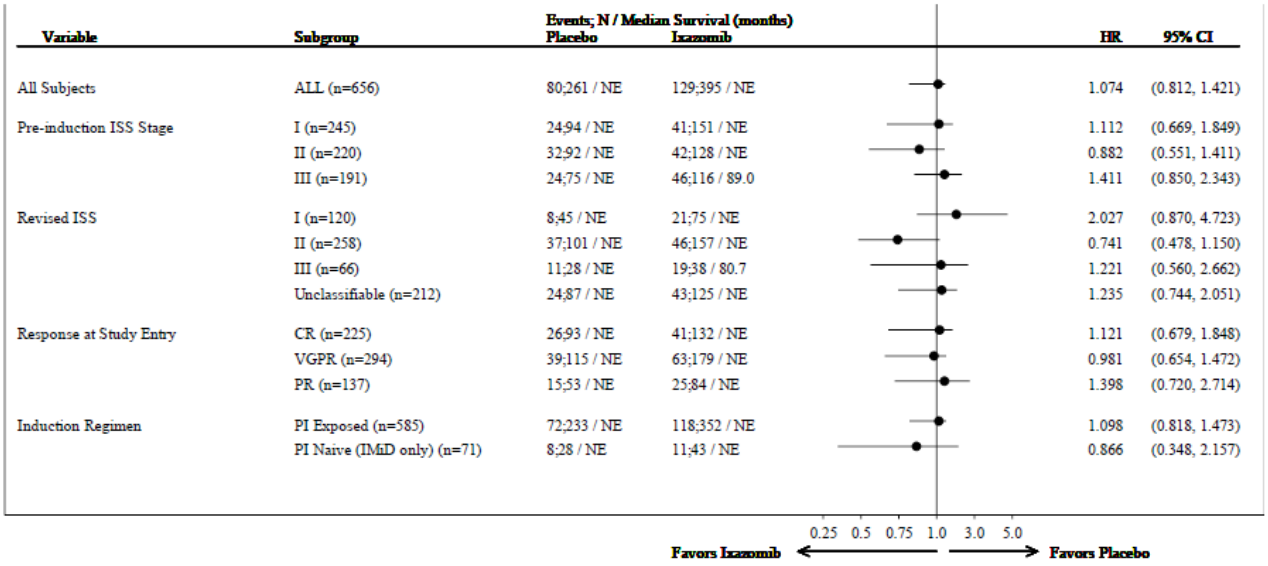
Source: Figure 15.2.2.2JC.
K-M: Kaplan-Meier; num: number; OS: overall survival; PI: proteasome inhibitor.
Randomization was 3:2 ixazomib:placebo.

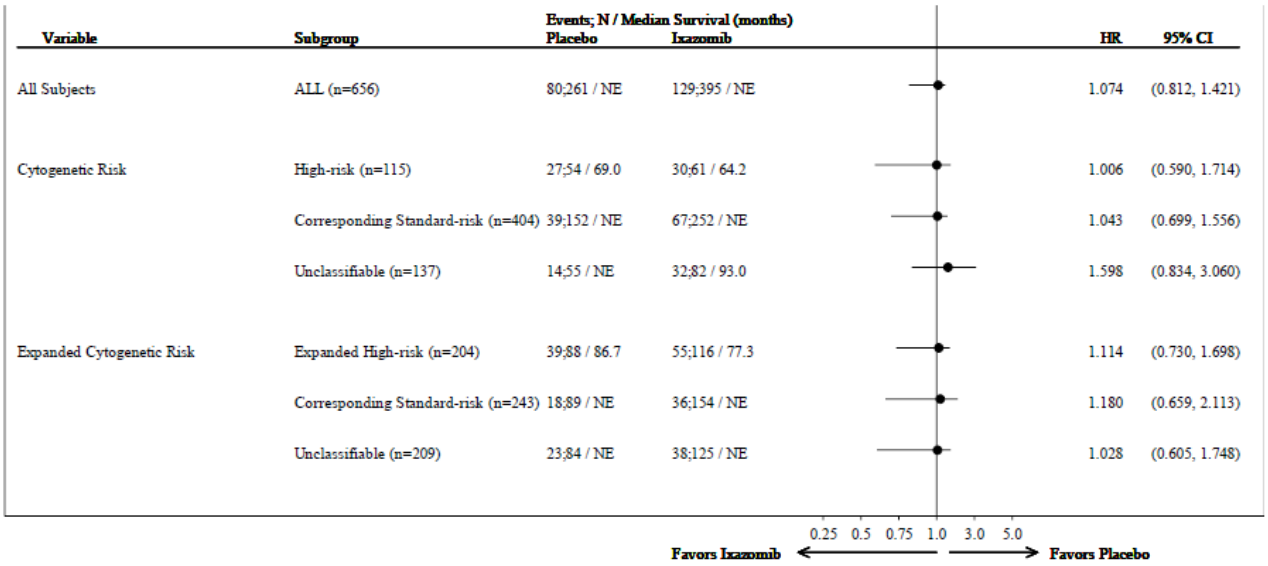
Subgroups defined by stratification factors, demographics, disease characteristics, and expanded high-risk cytogenetics are summarised in Figures below.

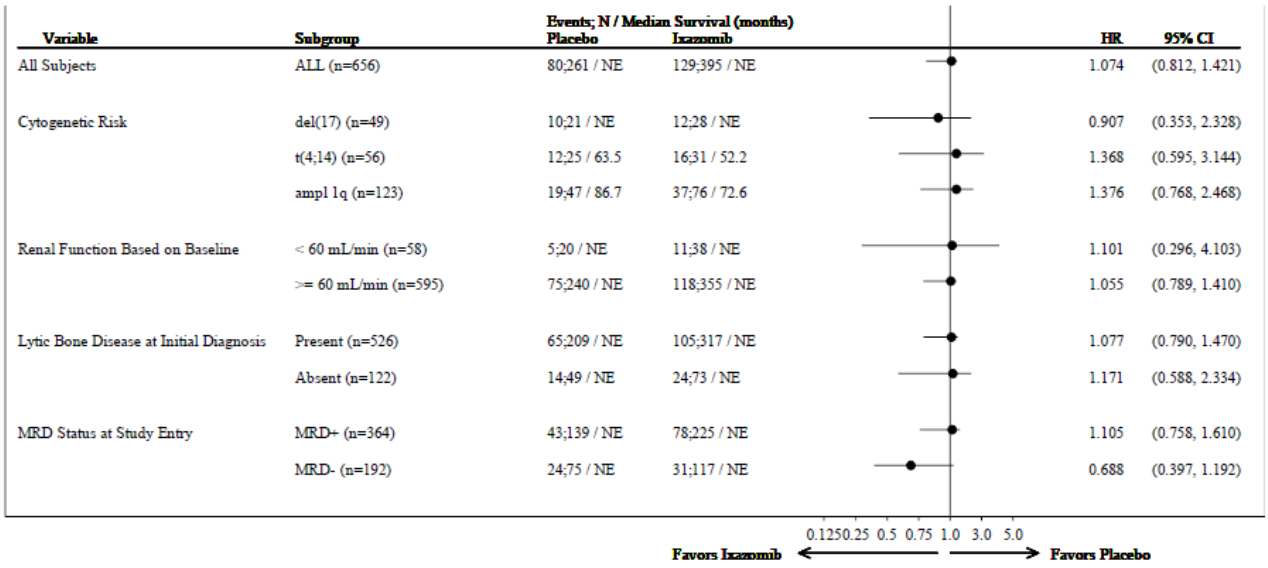
Figure 2.f Forest Plot of OS—ITT Population






Variable
Subgroup
Events; N / Median Survival (months)
Placebo
Ixazomib
HR
95% CI
All Subjects
ALL (n=656)
80;261 / NE
129;395 / NE
1.074
(0.812, 1.421)
Pre-induction ISS Stage
I (n=245)
24;94 / NE
41;151 / NE
1.112
(0.669, 1.849)
II (n=220)
32;92 / NE
42;128 / NE
0.882
(0.551, 1.411)
III (n=191)
24;75 / NE
46;116 / 89.0
1.411
(0.850, 2.343)
Revised ISS
I (n=120)
8;45 / NE
21;75 / NE
2.027
(0.870, 4.723)
II (n=258)
37;101 / NE
46;157 / NE
0.741
(0.478, 1.150)
III (n=66)
11;28 / NE
19;38 / 80.7
1.221
(0.560, 2.662)
Unclassifiable (n=212)
24;87 / NE
43;125 / NE
1.235
(0.744, 2.051)
Response at Study Entry
CR (n=225)
26;93 / NE
41;132 / NE
1.121
(0.679, 1.848)
VGPR (n=294)
39;115 / NE
63;179 / NE
0.981
(0.654, 1.472)
PR (n=137)
15;53 / NE
25;84 / NE
1.398
(0.720, 2.714)
Induction Regimen
PI Exposed (n=585)
72;233 / NE
118;352 / NE
1.098
(0.818, 1.473)
PI Naive (IMiD only) (n=71)
8;28 / NE
11;43 / NE
0.866
(0.348, 2.157)
0.25 0.5 0.75 1.0 3.0 5.0
Favors Ixazomib
Favors Placebo


Variable
Subgroup
Events; N / Median Survival (months)
Placebo
Ixazomib
HR
95% CI
All Subjects
ALL (n=656)
80;261 / NE
129;395 / NE
1.074
(0.812, 1.421)
Cytogenetic Risk
High-risk (n=115)
27;54 / 69.0
30;61 / 64.2
1.006
(0.590, 1.714)
Corresponding Standard-risk (n=404)
39;152 / NE
67;252 / NE
1.043
(0.699, 1.556)
Unclassifiable (n=137)
14;55 / NE
32;82 / 93.0
1.598
(0.834, 3.060)
Expanded Cytogenetic Risk
Expanded High-risk (n=204)
39;88 / 86.7
55;116 / 77.3
1.114
(0.730, 1.698)
Corresponding Standard-risk (n=243)
18;89 / NE
36;154 / NE
1.180
(0.659, 2.113)
Unclassifiable (n=209)
23;84 / NE
38;125 / NE
1.028
(0.605, 1.748)
0.25 0.5 0.75 1.0 3.0 5.0
Favors Ixazomib
Favors Placebo



Source: Figure 15.2.2.6B.

ampl: amplification; APAC: Asia-Pacific; CR: complete response; Crcl: creatinine clearance; del: deletion; EMEA: Europe, the Middle East, and Africa; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; MRD: measurable residual disease; NE: not estimable; OS: overall survival; PI: proteasome inhibitor; PR: partial response; VGPR: very good partial response.

* Indicates that the upper confidence limit is truncated at 5 to fit on the graph.

Randomization was 3:2 ixazomib:placebo.

Patients with MRD negative (MRD-) status at study entry (N=364) showed a nonsignificant trend toward reduced risk of death compared with patients who were known to have MRD positive (MRD+) status at study entry (N=192) (HR=0.797, 95% CI: 0.572, 1.111, p=0.180). The median OS was NE in both groups (see Table below).

Table 2.h OS for Patients With MRD- Status and Patients With MRD+ Status at Study Entry—ITT Population

	MRD- N = 364	MRD+ N = 192	HR [95% CI] P-value
OS (mo)			0.797 [0.572, 1.111] 0.180
Patients who died, n (%)	121 (33)	55 (29)	
Patients censored, n (%)	243 (67)	137 (71)	
Median [95% CI] (mo)	NE [NE, NE]	NE [93.04, NE]	
Minimum, maximum (mo)	0.0*, 97.7*	1.7*, 94.3*	
Reason for censoring, n (%)			
Lost to follow-up	3 (<1)	4 (2)	
Still alive at date of last contact	240 (66)	133 (69)	

Source: Table 15.2.3.1I.

HR: hazard ratio; ITT: intent-to-treat; mo: months; MRD: measurable residual disease; MRD-: MRD negative; MRD+: MRD positive; NE: not estimable; OS: overall survival.

* Censored observation.

For patients who were MRD- at study entry, patients in the ixazomib arm showed a nonsignificant trend toward reduced risk of death compared with patients in the placebo arm (HR=0.688, 95% CI: 0.397,

1.192, p=0.180). The median OS was NE in both groups (see Table below).

Table 2.i Analysis of OS for Patients With MRD- Status at Study Entry—ITT Population

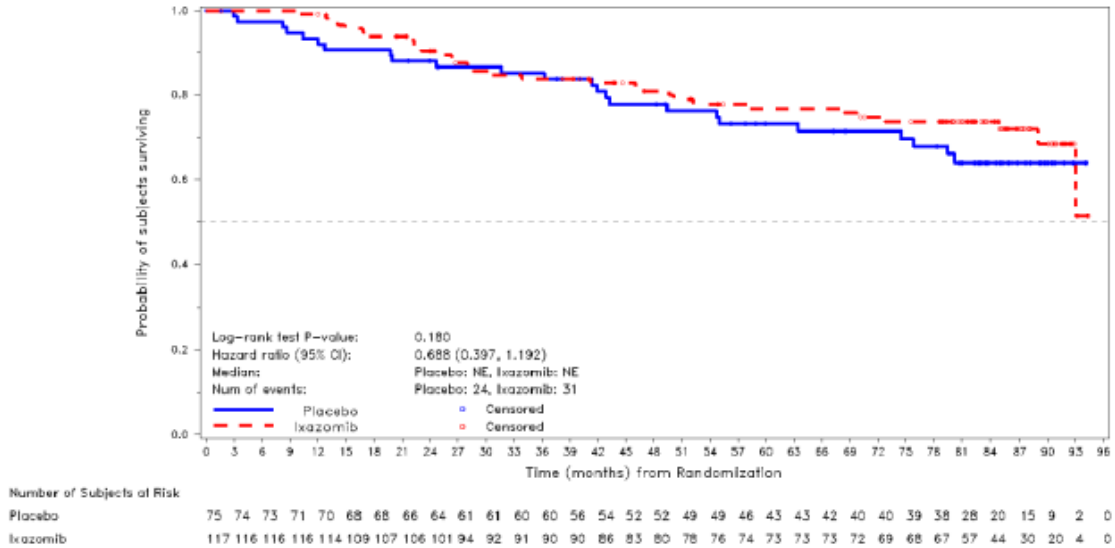
Parameter	2:3 Randomization Placebo N = 75	2:3 Randomization Ixazomib N = 117	HR [95% CI] P-value
OS (mo)			0.688 [0.397, 1.192] 0.180
Patients who died, n (%)	24 (32)	31 (26)	
Patients censored, n (%)	51 (68)	86 (74)	
Median [95% CI] (mo)	NE [NE, NE]	NE [93.04, NE]	
Minimum, maximum (mo)	2.9, 94.1*	1.7*, 94.3*	
Reason for censoring, n (%)			
Lost to follow-up	2 (3)	2 (2)	
Still alive at date of last contact	49 (65)	84 (72)	

Source: Table 15.2.3.1M.

HR: hazard ratio; ITT: intent-to-treat; mo: months; MRD: measurable residual disease; MRD-: MRD negative; MRD+: MRD positive; NE: not estimable; OS: overall survival.

* Censored observation.

Figure 2.g K-M Plot of OS for Patients With MRD- Status at Study Entry—ITT Population



Source: Figure 15.2.2.2MA.

ITT: intent-to-treat; K-M: Kaplan-Meier; MRD: measurable residual disease; MRD-: MRD negative; num: number; NE: not estimable; Num: number; OS: overall survival.

Randomization was 3:2 ixazomib:placebo.

For patients who were MRD+ at study entry, patients in the placebo arm showed a nonsignificant trend toward reduced risk of death compared with patients in the ixazomib arm (HR=1.105, 95% CI: 0.758, 1.610; p=0.604) (see Table and Figure below).

Table 2.j OS for Patients With MRD+ Status at Study Entry—ITT Population

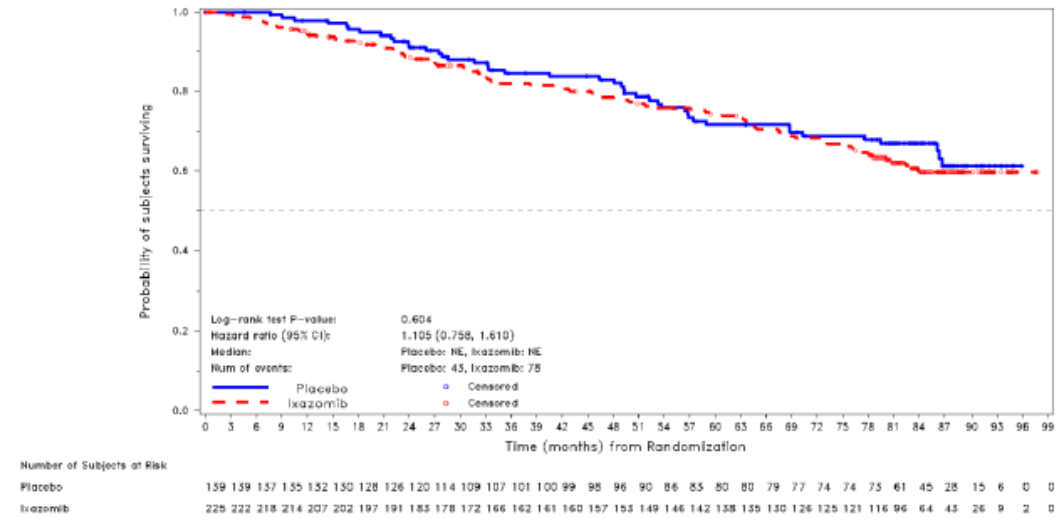
Parameter	2:3 Randomization		HR [95% CI] P-value
	Placebo N = 139	Ixazomib N = 225	
OS (mo)			1.105 [0.758, 1.610] 0.604
Patients who died, n (%)	43 (31)	78 (35)	
Patients censored, n (%)	96 (69)	147 (65)	
Median [95% CI] (mo)	NE [NE, NE]	NE [NE, NE]	
Minimum, maximum (mo)	4.5*, 95.9*	0.0*, 97.7*	
Reason for censoring, n (%)			
Lost to follow-up	1 (<1)	2 (<1)	
Still alive at date of last contact	95 (68)	145 (64)	

Source: Table 15.2.3.1N.

HR: hazard ratio; ITT: intent-to-treat; mo: months; MRD: measurable residual disease; MRD-: MRD negative; MRD+: MRD positive; NE: not estimable; OS: overall survival.

* Censored observation.

Figure 2.h K-M Plot of OS for Patients With MRD+ Status at Study Entry—ITT Population



Source: Figure 15.2.2.2MB.

ITT: intent-to-treat; K-M: Kaplan-Meier; MRD: measurable residual disease; MRD+: MRD positive; num: number; NE: not estimable; Num: number; OS: overall survival.

Randomization was 3:2 ixazomib:placebo.

At study entry, a total of 57% (225 of 395) of ixazomib patients and 53% (139 of 261) of placebo patients were known to be MRD+. Among these MRD+ patients, a higher percentage in the ixazomib arm shifted from MRD+ to MRD- status at any time after study entry (11% [24 patients], vs 7% [10 patients] in the placebo arm). Among the 34 patients whose status changed from MRD+ to MRD- during the study, patients in the placebo arm showed a nonsignificant trend toward reduced risk of death compared with patients in the ixazomib arm (HR = 1.478, 95% CI: 0.163, 13.416, p = 0.727). The median OS was NE in both groups.

At study entry, a total of 30% (117 of 395) of ixazomib patients and 29% (75 of 261) of placebo patients were known to be MRD-. Among these MRD- patients, a higher percentage in the placebo arm shifted from MRD- to MRD+ status at any time after study entry (47% [35 patients], vs 34% [40 patients] in

the ixazomib arm). Among the 75 patients whose status changed from MRD- to MRD+ during the study, the median OS was 52.2 months in the ixazomib arm and 74.5 months in the placebo arm; patients in the placebo arm showed a nonsignificant trend toward reduced risk of death compared with patients in the ixazomib arm (HR = 1.108, 95% CI: 0.553, 2.220; p = 0.772).

Subsequent Antineoplastic Therapy

At IA4, a similar proportion of patients in the ixazomib arm (71%) and the placebo arm (72%) had started subsequent antineoplastic therapy (Table 2.m). Among patients who received subsequent therapy, the ixazomib and placebo arms used several classes of agents at similar rates, including corticosteroids (91% and 89%), immunomodulatory drugs (88% and 84%), alkylating agents (36% and 38%), and other classes (22% and 24%). PI use was lower in the ixazomib arm (63%) than in the placebo arm (72%), and the use of monoclonal antibodies specific to multiple myeloma (MM) therapy was higher in the ixazomib arm (44% vs 37%).

Table 2.m Summary of Subsequent Antineoplastic Therapy Used by ≥1% of Patients in Either Treatment Arm—Safety Population

Class of Agent WHO Generic Term	2:3 Randomization Placebo N = 259	2:3 Randomization Ixazomib N = 394
	Number (%) of Patients	
Patients with ≥1 subsequent anti-cancer therapy [a]	187 (72)	281 (71)
Corticosteroids	166 (89)	256 (91)
Dexamethasone	163 (87)	254 (90)
Prednisone	9 (5)	10 (4)
Immunomodulatory drugs	157 (84)	247 (88)
Lenalidomide	146 (78)	229 (81)
Pomalidomide	43 (23)	58 (21)
Thalidomide	19 (10)	30 (11)
Proteasome inhibitors	134 (72)	178 (63)
Bortezomib	77 (41)	107 (38)
Carfilzomib	66 (35)	100 (36)
Ixazomib	20 (11)	14 (5)
Monoclonal antibodies specific to MM therapy	69 (37)	125 (44)
Daratumumab	63 (34)	112 (40)
Monoclonal antibodies	8 (4)	14 (5)
Elotuzumab	11 (6)	12 (4)
Alkylating agents	71 (38)	102 (36)
Cyclophosphamide	47 (25)	64 (23)
Melphalan	33 (18)	51 (18)
Cisplatin	7 (4)	10 (4)
Bendamustine	4 (2)	8 (3)
Other	44 (24)	61 (22)
All other therapeutic products	26 (14)	38 (14)
Other antineoplastic agents	7 (4)	7 (2)
Investigational drug	3 (2)	6 (2)
Monoclonal antibodies	3 (2)	6 (2)
Zoledronic acid	1 (<1)	4 (1)
Antineoplastic and immunomodulating agents	2 (1)	2 (<1)
Anthracyclins	16 (9)	21 (7)
Doxorubicin	16 (9)	21 (7)
Topoisomerase inhibitors	9 (5)	12 (4)
Etoposide	9 (5)	12 (4)

Table 2.m Summary of Subsequent Antineoplastic Therapy Used by ≥1% of Patients in Either Treatment Arm—Safety Population

	2:3 Randomization	
Class of Agent WHO Generic Term	**Placebo N = 259**	**Ixazomib N = 394**
Histone deacetylase inhibitor	4 (2)	8 (3)
Panobinostat	4 (2)	8 (3)
Antimetabolites	2 (1)	3 (1)
Fludarabine	2 (1)	2 (<1)
Bruton's tyrosine kinase inhibitor	2 (1)	2 (<1)
Ibrutinib	2 (1)	2 (<1)
Checkpoint inhibitor	2 (1)	0
Nivolumab	2 (1)	0

Source: Table 15.2.4.4B.
MM: multiple myeloma; WHO: World Health Organization.
Unless otherwise noted, percentages are based on the total number of patients with subsequent antineoplastic therapy.
[a] Percentages are based on the safety population in each arm.

PFS2

PFS2 (defined as the time from the date of randomization to the date of first documentation of disease progression on subsequent line of anticancer therapy or death from any cause, whichever occurs first) was another secondary endpoint. The rate of PFS2 events (progression or death) was slightly higher in the ixazomib arm (41%) than in the placebo arm (38%), with a median PFS2 of 81.8 months in the ixazomib arm and 80.2 months in the placebo arm (HR=1.016; 95% CI: 0.791, 1.305; p=0.898; See Table and Figure below).

Table 2.n PFS2—ITT Population

Parameter	2:3 Randomization		HR [95% CI] [a] P-value [b]
	Placebo N = 261	Ixazomib N = 395	
Progression or death (mo)			1.016 [0.791, 1.305] 0.898
Patients with events, n (%)			
Progression	86 (33)	135 (34)	
Death	14 (5)	27 (7)	
Patients censored, n (%)	161 (62)	233 (59)	
Median [95% CI] (mo)	80.2 [68.73, NE]	81.8 [67.22, NE]	
Minimum, maximum (mo)	0.0*, 95.1*	0.0*, 97.5*	
Reason for censoring, n (%)			
Third-line therapy	46 (18)	51 (13)	
Lost to follow-up	4 (2)	4 (1)	
No baseline/no post-baseline	9 (3)	16 (4)	
No documented death or PD	90 (34)	158 (40)	
Withdrawal of consent	12 (5)	4 (1)	

Source: Table 15.2.1.6A.

CR: complete response; HR: hazard ratio; IMiD: immunomodulatory drug; ISS: International Staging System; ITT: intent-to-treat; mo: months, NE: not estimable; PD: progressive disease; PFS2: progression-free survival 2; PI: proteasome inhibitor; PR: partial response VGPR: very good partial response.

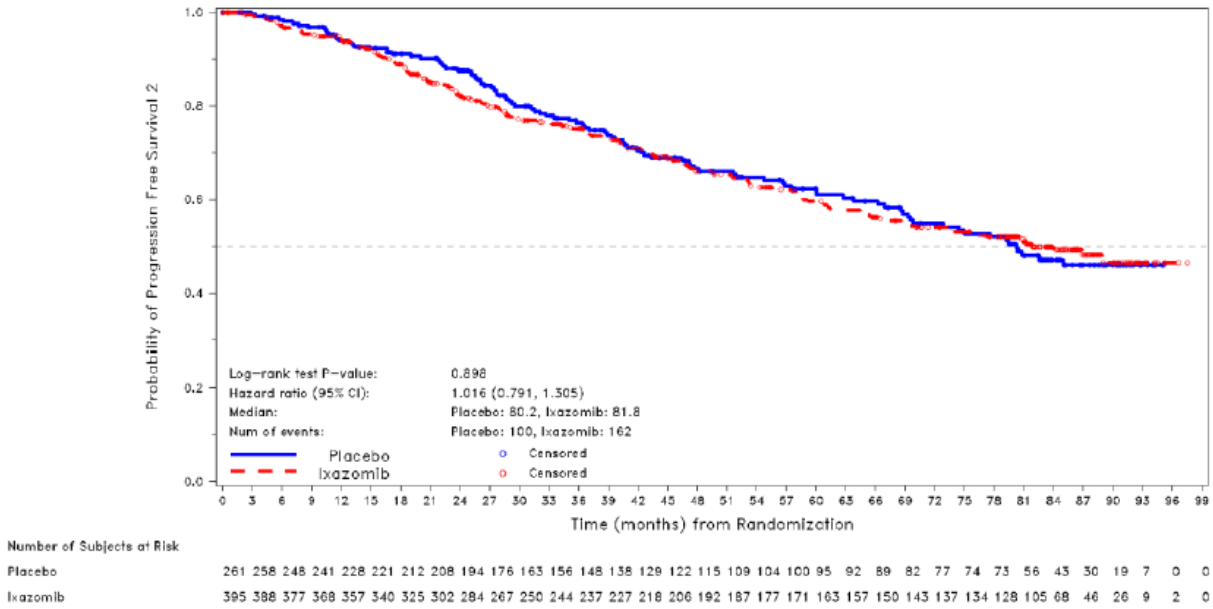
* Censored observation.

PFS2 is defined as the time from the date of randomization to the date of first documentation of PD on the next antineoplastic therapy following study treatment or death due to any cause, whichever occurs first. Patients without documentation of PD are censored at the date of last response assessment. Only non-missing censoring categories are summarized in the table.

[a] HR is based on an unadjusted Cox's proportional hazard regression model stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR), comparing the hazard rate of the ixazomib arm over the hazard rate of the placebo arm. HR <1 indicates better prevention of progression or death on the next line of treatment in the ixazomib arm as compared to the placebo arm.

[b] P-value comparing PFS2 between treatment groups is based on a log-rank test stratified by pre-induction regimen (PI vs IMiD vs both PI and IMiD), pre-induction ISS (stage I vs stage II or III), and response after transplantation (CR or VGPR vs PR).

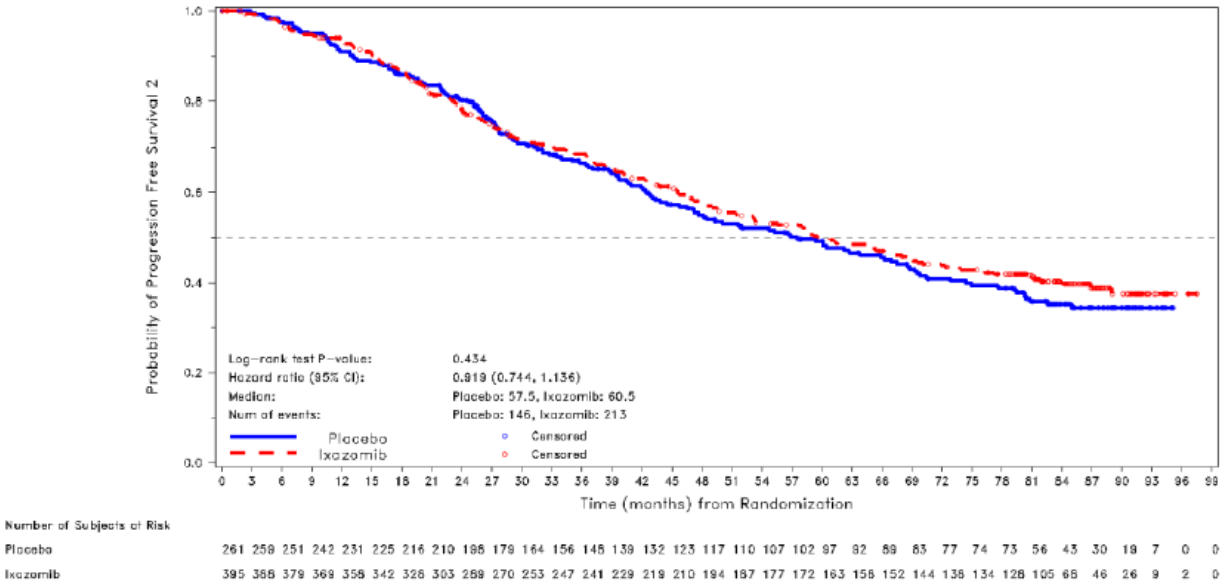
Figure 2.k K-M Plot of PFS2—ITT Population



Source: Figure 15.2.2.1R.
ITT: intent-to-treat; K-M: Kaplan-Meier; Num: number; PFS2: progression-free survival 2.
Randomization was 3:2 ixazomib:placebo.

A K-M plot of PFS2 with the alternative definition in which the start date of third line of therapy counted as an event (see Figure below) shows a median PFS2 of 60.5 months in the ixazomib arm and 57.5 months in the placebo arm (HR=0.919; 95% CI: 0.744, 1.136; p=0.454).

Figure 2.1 **K-M Plot of PFS2 With Start Date of Third-Line Therapy Counted as Event—ITT Population**



Source: Figure 15.2.2.1RA.
ITT: intent-to-treat; K-M: Kaplan-Meier; Num: number; PFS2: progression-free survival 2.
Randomization was 3:2 ixazomib:placebo.

Patient-Reported Outcomes

For both EORTC QLQ-C30 and QLQ-MY20, overall compliance throughout the follow-up period was high (≥72%) in both the ixazomib and placebo arms. As expected, these compliance rates for the EORTC QLQ instruments were lower relative to those during the treatment period but to a similar degree in each arm. EQ-5D compliance rates also had declined during the follow-up periods relative to the treatment period (to ≥51%) but again were similar between arms.

Scores on the EORTC QLQ-C30 global health status/QOL scale were similar with ixazomib maintenance and with placebo throughout the follow-up periods, by 4-week intervals, as analyzed by mean and median scores during the follow-up periods. Using linear mixed models, the least-squares mean difference between the ixazomib arm and the placebo arm in global health status/QOL from study entry over time were generally small and not statistically significantly different (not adjusted for multiple testing).

The area under the curve approach was used to examine the differential effect of treatment throughout the study. Area under the curve analyses for EORTC QLQ-C30 scores showed no detriment to QOL in the ixazomib arm compared with the placebo arm up to the 36th 4-week interval. As in previous analyses for this study, a minimal important difference (MID) threshold for the EORTC QLQ-C30 has been identified as a 10-point improvement for patients with MM. Using this MID threshold, the proportions of patients whose scores were stable or improved by at least 10 points on the EORTC QLQ-C30 global QOL/health status scale during the follow-up periods were similar in the 2 arms.

In addition to global health status/QOL, health-related QOL was generally maintained in both arms during the follow-up period for the physical, role, cognitive, emotional, and social functioning domains. Only the symptom scores for diarrhoea and nausea/vomiting showed differences between the ixazomib and placebo arms at a few time points, with somewhat higher mean change values (indicating slightly greater

symptomatology) reported in the ixazomib arm.

Results of the EORTC QLQ-MY20 were generally similar between the treatment arms during the follow-up periods. Specifically, during the treatment and follow-up periods, the results of the subscale measuring side effects of treatment and disease symptoms with treatment were similar in the 2 arms. Area under the curve analyses for EORTC QLQ-MY20 scores showed no detriment to QOL in the ixazomib arm compared with the placebo arm up to the 36th 4-week interval.

Results of the EQ-5D-3L visual analogue scale, which reflect the patients' self-reported health status, paralleled the global health status/QOL results of the EORTC QLQ-C30. EQ-5D-3L visual analogue scale scores were consistent during the treatment period and similar between the ixazomib maintenance arm and the placebo arm.

Treatment with ixazomib as maintenance therapy after SCT did not result in the use of additional healthcare resources or prolong hospitalizations compared to placebo. Healthcare utilization rates (total number of events divided by total number of patient-years) were similar in the 2 arms. The rate of hospitalizations per patient-year (0.27 for ixazomib and 0.25 for placebo) and the rate of all outpatient visits per patient-year (3.47 for ixazomib and 3.48 for placebo) were similar in the 2 arms. The median length of hospitalization per hospital stay among admitted patients was 5.0 and 4.0 days for the ixazomib and placebo arms, respectively. Among patients who reported missing days of work, the median number of days missed was similar in the ixazomib and placebo arms (29.0 and 28.0 days, respectively). The same was true for caregivers, who reported a similar median number of missed days of work in each arm (5.0 days ixazomib, 6.5 days placebo). The reasons for hospitalizations, emergency room visits, and outpatient visits were generally similar between the ixazomib and placebo arms, except for, during emergency room visits, visits due to procedures (5% vs 17%, respectively) and adverse events (AE)/toxicity (78% vs 64%, respectively). The most common reason for healthcare resource utilization was as follows: during hospitalizations, AE/toxicity (42% ixazomib and 36% placebo); during emergency room visits, AE/toxicity (78% ixazomib and 64% placebo); and during outpatient visits, medication (31% ixazomib and 35% placebo).

6.3. Discussion

Methods

Study C16019 is a randomised, double-blinded, placebo-controlled Phase III study aimed at investigating the efficacy and safety of ixazomib monotherapy as post autologous stem cell transplant (ASCT) maintenance in newly diagnosed multiple myeloma (NDMM). Ninlaro is not indicated in this setting in the EU, and no extension of the indication based on results from study C16019 is currently planned.

The inclusion/exclusion criteria in study C16019 adequately defined a population of adult subjects with NDMM who had received ASCT as consolidation therapy following successful induction, as per current clinical guidelines (see e.g. the Multiple myeloma EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Dimopoulos MA et al, Ann Oncol 2021). The MM population targeted by study C16019 was, therefore, not representative of the approved indication for Ninlaro (i.e. patients with relapsed or refractory MM who has received at least one single prior line of therapy): in particular, subjects in study C16019 had a limited MM history and were required to have chemosensitive disease (e.g. at least a PR should have been documented after induction/ASCT). Conversely, patients in registrational study C16010 were required to have failed at least one prior line of therapy, and refractory patients were allowed (e.g. 6% of patients had primary refractory disease, 23% were refractory to any prior IMiD, 8% to any prior PI and 11% had relapsed and refractory MM). Overall, this is in line with the primary aim of SOB004, which was to further substantiate the clinical activity and safety of Ninlaro in different MM settings. On the other hand, limited additional information can be inferred with respect to

the efficacy of Ninlaro in the approved indication: MM is a chronic malignancy, and in the R/R setting clinical benefit demonstration mostly relies on the ability of a new drug/combination to overcome chemoresistance, whilst chemosensitivity was a prerequisite in maintenance study C16019.

Differences between SOB003 study C16019 and registrational study C16010 could also be observed in terms of dose regimen: in study C16019 the ixazomib monotherapy starting dose was 3 mg on days 1, 8 and 15 of 28-day cycles, and ixazomib could be escalated to 4 mg starting from cycle 5 in the case it was well tolerated. In study C16010, ixazomib was administered in combination with Len-Dex starting with the higher 4 mg dose, and dose reductions were only possible in the case of recurrent/severe toxicity. The differences in dosing schedules across ixazomib trials reflected the specific aims of post-ASCT maintenance (e.g. long therapy duration, optimal tolerability etc.) compared to the treatment of progressing disease (e.g. overcoming drug resistance, achieving significant cytoreduction etc.). These differences, although justified, further hamper the possibility of inter-trial comparisons, especially in terms of efficacy.

The choice to conduct a placebo-controlled study was acceptable since, at the time of study initiation, no compound was specifically authorised in this indication.). Lenalidomide is currently approved as post-ASCT maintenance treatment in the EU, and is the current standard of care in this clinical setting (see e.g. the current ESMO guidelines for MM).

Patients were randomised to ixazomib or placebo according to an unequal allocation ratio (3:2), and randomisation was stratified according to type of induction therapy (PI only vs IMiD only vs PI plus IMiD), ISS at diagnosis (I vs II or III) and response to ASCT (CR/VGPR vs PR). The potential prognostic relevance of the selected stratification factors is acknowledged.

PFS based on IRC-assessment was the primary endpoint in study C16019, which is acceptable. MM is, in fact, a chronic and, at present, incurable disease, and a clinically relevant and statistically significant improvement in terms of disease-progression delay could be considered, per se, a measure of clinical benefit, provided that no negative impact on survival and/or quality of life is observed. In this regard, OS was the key secondary endpoint in study C16019, and patient-reported outcomes (PROs) on health-related quality of life (HR-QoL) were also collected.

Approximately 652 patients were planned to be randomized to allow for a 80% power for OS testing in the ITT population. Two interim analyses (IAs) were originally planned: the first IA was the primary (and only) analysis for PFS. Results from the primary PFS analyses were submitted in variation EMEA/H/C/003844/II/0014/G. OS was also tested at this first IA and at subsequent IAs until statistical significance was achieved or Final Analysis (FA) reached. The total event size calculation for OS was based on an adaptive sample size reassessment approach, with the actual number of OS events expected at the FA to be determined after IA2. The significance level for OS was to be determined according to the O'Brien-Fleming alpha spending function (the Lan-DeMets method) and the described sequential testing procedure was employed to control the family-wise type I error for both the primary (PFS) and key secondary (OS) endpoint.

A non statistically significant HR of 1.165 was observed for OS at the time of the PFS IA (see also the "Results" section below); both pre-specified (MSM and IPCW) and post-hoc sensitivity analyses to adjust for potential confounding by subsequent therapy on OS (e.g. methods, based on censoring "switchers" approach and on time-varying Cox model) were provided by the MAH. Although their exploratory nature is recognised, most of these methods are based on the assumption of the absence of unmeasured confounders: this is a strong assumption in a heterogeneous condition such as MM that, if not satisfied, can lead to an unknown amount of systematic error in the estimate. Since the validity of this underlying assumption is difficult to verify, the regulatory value of these sensitivity analyses is necessarily limited.

For additional details please refer to procedure EMEA/H/C/003844/II/0014/G.

Results

Results from the PFS IA have been submitted in the context of procedure EMEA/H/C/003844/II/0014/G: study C16019 met its primary endpoint, showing a statistically significant PFS improvement vs. placebo, with a median PFS by IRC of 26.5 months with ixazomib compared to 21.3 months with placebo (HR 0.72; 95%CI 0.58, 0.89; p=0.002). Although the study was formally successful, the clinical relevance of the observed PFS improvement was uncertain, especially when the long treatment duration and the change in the therapeutic landscape of MM (e.g. the approval of lenalidomide as maintenance option) were considered.

As per study design, OS was also tested at the time of the PFS IA. Immature OS data did not allow, at the time, to reasonably exclude a detrimental effect on survival, since the point estimation for the OS HR was 1.165 (95%CI 0.761, 1.779). PFS2 data were consistent with OS in showing a potential negative impact on the efficacy of subsequent treatments (HR 1.160; 95% CI: 0.810, 1.662; p=0.417). Although the significant differences between study C16019 and the approved indication for Ninlaro were acknowledged, it was noticed that both clinical settings were characterised by prolonged exposure to ixazomib in early stages of MM. Out of caution, the CHMP decided to amend SOB004 in order to provide additional OS/PFS2 data from Phase 3 study C16019 when approximately 200 death events have occurred. The MAH specified that additional IAs were introduced in study C16019 to allow for earlier looks at OS.

In the context of annual renewal procedures, updated PFS2 and OS data from IA2 and IA3 were submitted (data cut-off dates [DCOs] January 2020 and January 2021, respectively), showing no significant change compared to the initial analysis, although the HR for OS became closer to 1.0 (i.e. 1.029 and 1.008 at the time of IA2 and IA3, respectively).

In compliance with the agreed timeframe, the MAH has submitted updated data from the planned IA4 (DCO October 2022), after 209 deaths had been reported in study C16019 (32% of the ITT population). At the time of IA4, no subject was still ongoing on treatment, yet 50% of patients were still continuing in follow-up. Death events were evenly distributed across study arms (33% in the ixazomib and 31% in the placebo arm, respectively) and, with the majority of patients still alive, median OS was not reached in both treatment arms. The OS HR (1.074, 95%CI 0.812, 1.421), although reduced compared to IA2, still slightly favoured placebo, yet the KM curves for OS run largely superimposed, repeatedly crossing over time, and hardly show any clear superiority trend of one arm over the other.

To further characterised OS data, the MAH has provided several pre-specified and ad hoc sensitivity analyses. A similar proportion of subjects (~70%) received subsequent treatments in both study arms, although, consistently with PFS data, the median time to next treatment was slightly longer in the ixazomib arm (33.1 vs. 27.6 months in the experimental and placebo arms, respectively; HR 0.833, 95%CI 0.690, 1.005). The pre-specified MSM and IPCW showed that, after adjusting for subsequent therapy, the HR (0.760 and 0.644, respectively) favoured the ixazomib arm, although the effect was not statistically significant. The limits of these methods have been, however, already discussed.

A post-hoc sensitivity analysis stratified by subsequent therapy status showed that in the subgroup of patients who were censored at subsequent therapy (n=191) a "protective" HR point estimation was observed (i.e. 0.643, 95%CI 0.192, 2.159). Conversely, in the subgroup of patients who received any subsequent therapy (n=465) the HR was 1.123 (95%CI 0.841, 1.500), hinting that response to subsequent therapy could play a role in explaining the lack of significant survival benefit observed in study C16019. No significant differences in the choice of subsequent treatments could be, however, observed across study arms, with the exception that more subjects in the placebo arm received subsequent PIs compared to the ixazomib arm (72% vs. 63%). Since study C16019 was double-blinded

and a number of subjects in the ixazomib arm were not unblinded at the time subsequent treatment lines were started, the MAH has previously hypothesized (see e.g. procedure EMEA/H/C/003844/II/0014/G) that lack of unblinding could have resulted in a higher risk for patients in the active arm to receive suboptimal subsequent treatment (e.g. exposure to other PIs). However, an additional analysis exploring the impact of exposure to PI as subsequent line of therapy showed that the HR in subjects who received a subsequent PI (n=226) was 0.899 (95%CI 0.572, 1.414) compared to 1.298 (95%CI 0.877, 1.921) in subjects whose subsequent line of therapy did not include a PI (n=239). This finding is apparently counterintuitive, since ixazomib is a "second-generation" PI, and prolonged exposure to ixazomib in study C16019 would be expected to result in increased resistance to PIs. It should be considered, however, that subsequent treatment lines were not specified in study C16019, nor the criteria and timing to start a new active treatment, therefore the results of these post-hoc, non-randomised analyses should be interpreted with caution, since the risk of bias is high. In this regard, KM plots for OS stratified by exposure to a subsequent PI are of difficult interpretations, with curves running superimposed for long intervals and crossing multiple times.

Results from the updated PFS2 analysis showed that median PFS2 was slightly longer in the ixazomib (81.8 months) arm compared to placebo (80.2 months), yet more events were reported in the ixazomib (41%) compared to the placebo arm (38%), resulting in a HR of 1.016 (95%CI 0.791, 1.305). Again, KM plots for PFS2 were of difficult interpretation because of extensive superimposition and multiple crossings.

Updated subgroup analyses for OS were also provided. Although results were usually consistent across subgroups, some counterintuitive trends could be observed, such as the reduced effect in subjects with post-transplant suboptimal response (i.e. subjects who achieved a best response of PR with ASCT, who could theoretically have benefited more of additional treatment, especially since post-ASCT consolidation cycles were not allowed in study C16019). Similarly, patients with persistent post-ASCT MRD positivity apparently fared better with placebo compared to ixazomib (HR for OS 1.105, 95%CI 0.758, 1.610), despite an increased number of MRD+ patients shifted to MRD- status with ixazomib (11%) compared to placebo (7%), and a higher percentage of patients who received placebo (47%) lost their MRD negativity status compared to patients who received ixazomib (34%). The interpretation of MRD subgroup KM curves for OS was also not straightforward, with curves crossing repeatedly. Finally, the rationale for the divergent treatment effect trend reported for subjects with R-ISS stage I and R-ISS stage II was also of uncertain explanation.

PRO data were also provided to explore the impact of long-term ixazomib exposure in terms of HR-QoL. The EORTC QLQ-C30 score trends in global health status/QoL from study entry over time were generally similar across study arms, and AUC and MID (using a 10-point meaningful difference) analyses also did not capture significant detrimental effects with ixazomib compared to placebo. HR-QoL score trends were also consistent across most domains, with the exception of the symptom scores for diarrhoea and nausea/vomiting, in which higher mean change values could be observed in the ixazomib arm. This is not unexpected, since both diarrhoea and nausea/vomiting are already reported as very common ADRs with ixazomib.

Results with the QLQ-MY20 and EQ-5D tools were generally consistent with the EORTC QLQ-C30 analysis.

The analysis of the use of healthcare resources did not show a significant increase in hospitalisation rates and times with ixazomib.

7. Clinical Safety aspects

7.1. Methods – analysis of data submitted

Subsequent to the 24-month active treatment period or removal from study therapy due to disease progression or toxicity, patients were to be followed for disease status, subsequent therapies, health-related quality of life, NPM, and OS.

As of the primary analysis for Study C16019 (conducted at IA1; DCO date 16 April 2018), all patients had completed treatment. As such, data from that analysis represented the final safety analysis for Study C16019 (please, see procedure EMEA/H/C/003844/II/0014/G for additional details). The safety population included all patients who received at least 1 dose of ixazomib or placebo. Since the primary analysis, the only safety data collected have been reports of NPM received during the follow-up period.

7.2. Results

Extent of Exposure

A total of 656 patients comprise the intent-to-treat (ITT) population in Study C16019: 395 patients who received ixazomib and 261 who received placebo (due to the 3:2 randomization ratio in the study). A total of 653 patients comprise the safety population in Study C16019: 394 patients who received ixazomib and 259 who received placebo.

Disposition

As of the DCO date for IA4 (12 October 2022), 50% of the study population was continuing follow-up. All patients had completed study treatment at the time of the primary analysis (see Table below).

Table 1.a Patient Disposition—C16019 ITT Population

	2:3 Randomization		
	Placebo (N = 261)	Ixazomib (N = 395)	Total (N = 656)
Parameter	Number (%) of Patients		
ITT population [a]	261 (100)	395 (100)	656 (100)
Safety population [b]	259 (> 99)	394 (> 99)	653 (> 99)
Ongoing on treatment	0	0	0
Continuing in follow-up	131 (50)	196 (50)	327 (50)
Lost to follow-up	4 (2)	5 (1)	9 (1)
Withdrew from follow-up	44 (17)	60 (15)	104 (16)
Reason for end of study	50 (19)	70 (18)	120 (18)
Lost to follow-up	4 (2)	5 (1)	9 (1)
Withdrawal by patient	44 (17)	60 (15)	104 (16)
Other	2 (<1)	5 (1)	7 (1)

Source: Study C16019 Table 15.1.1.1A.
ITT: intent-to-treat.
[a] The ITT population was defined as all patients who were randomized and had post-randomization data.
[b] The safety population was defined as all patients who received at least 1 dose of ixazomib or placebo.

Adverse Events

All patients were off study treatment as of IA1; there was only 1 on-study death reported (a patient in the ixazomib arm who died of pneumonia). The only safety parameter that was collected during the

patient follow-up period was NPM, which is an AESI for ixazomib.

Adverse Event of Special Interest - NPM

A blinded review of the disease type and NPM Preferred Term was conducted by the MAH medical monitor in order to distinguish whether an event was an NPM, progression of the underlying multiple myeloma (MM), or progression of a previously diagnosed malignancy. The occurrence of second malignancies, herein called NPMs, is a known risk in patients with MM. Note that NPMs were assessed while patients were on treatment (up to 30 days after last dose of ixazomib or placebo) and during their follow-up participation once study drug had been discontinued.

Data for on-treatment NPM were reported at IA1, by which time all patients had completed study therapy. As of IA4, there are updated follow-up NPM data. The cumulative incidence of NPMs (on treatment and during follow-up) in the ixazomib and placebo arms was similar (7% and 8%, respectively; see Table below). The incidence of NPMs by disease type was similar in the ixazomib and placebo arms. The most common category of follow-up NPM was hematological malignancy (2% in ixazomib arm, 3% in placebo arm).

Table 2.a Cumulative NPM—C16019 Safety Population

NPM Category Preferred Term	2:3 Randomization Placebo N = 259	2:3 Randomization Ixazomib N = 394
	Number (%) of Patients	
Patients with ≥1 NPM [a]	20 (8)	27 (7)
NPM disease type [a]		
Hematological malignancy	7 (3)	6 (2)
Non-hematological malignancy	8 (3)	12 (3)
Non-hematological malignancy (skin)	5 (2)	11 (3)

Source: Study C16019 Table 15.3.1.16D.
NPM: new primary malignancy.
Some NPMs that occurred during the follow-up period were not coded to Preferred Terms.
[a] A patient may have had >1 NPM type, such that the subcategories do not sum to the overall total.

Table 2.b NPM During Follow-up Only—C16019 Safety Population

NPM Category Preferred Term	2:3 Randomization Placebo N = 259	 Ixazomib N = 394
	Number (%) of Patients	
Patients with ≥1 NPM [a]	14 (5)	19 (5)
Hematological malignancy	7 (3)	6 (2)
Myelodysplastic syndrome	1 (<1)	2 (<1)
Acute myeloid leukaemia or related precursor neoplasm	2 (<1)	2 (<1)
Acute myeloid leukemia	1 (<1)	0
Hodgkin lymphoma	1 (<1)	0
Lymphoma	1 (<1)	0
Marginal zone lymphoma	0	1 (<1)
Mature B-cell neoplasm-diffuse large B-cell lymphoma NOS	1 (<1)	0
Small lymphotic lymphoma	0	1 (<1)
Non-hematological malignancy		
Solid tumors	5 (2)	8 (2)
Anal	0	1 (<1)
Breast	2 (<1)	1 (<1)
Cholangiocarcinoma	0	1 (<1)
Chordoma	0	1 (<1)
Colon	1 (<1)	0
Esophageal	0	1 (<1)
Gastric-esophageal junction adenocarcinoma	1 (<1)	0
Gall bladder	1 (<1)	0
Non-small cell lung cancer	0	1 (<1)
Prostate adenocarcinoma	0	1 (<1)
Urothelial carcinoma of the urinary bladder	0	1 (<1)
Skin	2 (<1)	6 (2)
Basocellular carcinoma	1 (<1)	1 (<1)
Basal cell carcinoma	0	1 (<1)
Diagnosis for left cheek: morbus bowen (carcinoma insitu); diagnosis for right cheek: superficial basal cell carcinoma	0	1 (<1)
Keratosis actinica	0	1 (<1)
Squamous cell carcinoma	0	1 (<1)
Melanoma	0	1 (<1)
Nodular basal cell carcinoma	1 (<1)	0

Source: Study C16019 Table 15.3.1.16D.

NOS: not otherwise specified; NPM: new primary malignancy.

Some NPMs that occurred during the follow-up period were not coded to Preferred Terms.

[a] A patient may have had >1 NPM type, such that the subcategories do not sum to the overall total.

There was no increased risk of NPM with ixazomib maintenance therapy. No safety concerns have been identified with regard to NPMs as of IA4 (median follow-up of approximately 7 years). Patients with NPM continue to be monitored as needed.

7.3. Discussion

No patient was still receiving ixazomib at the time of IA4 and, as per study protocol, only reports of NPMs were collected in the follow-up period of study C16019.

Overall, a similar incidence of NPMs was observed across study arms (7% and 8% in the ixazomib and placebo arms, respectively), and no clear pattern in type and time of incidence could be identified. Second haematological malignancies were the most common form of NPM in both study arms (2% and 3% with ixazomib and placebo, respectively), with the exception of skin tumours (3% and 2% with ixazomib and placebo, respectively).

No new relevant safety information was available from study C16019.

Overall, the available safety data from study C16019 are not suggestive of a significant increase in the risk of NPMs with prolonged exposure to ixazomib. The safety profile of Ninlaro is, therefore, unchanged.

7.4. Direct Healthcare Professional Communication

N/A

8. PRAC advice

N/A

9. Risk management plan

The MAH submitted an updated RMP version 10.0, dated 13 June 2023, with this application. The main proposed RMP changes are the following:

Part IV Plans for post-authorisation efficacy studies	Removed completed C16019 study from list of planned and ongoing post-authorization efficacy studies
Part VI Summary of the risk management plan	Removed completed C16019 study from post-authorization development plan
Part VII Annexes	Removed Study C16019 from Annex 5; updated Annex 8 to include the summary of changes in the risk management plan

In detail, the following changes are proposed in Part IV:

Part IV: Plans for post-authorization efficacy studies

Table Part IV.1 Planned and ongoing post-authorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorization				
Not Applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
~~C16019 [Category 2]: A phase 3, randomized, placebo-controlled, double-blind study of Ixazomib in maintenance therapy in patients with multiple myeloma following ASCT~~ ~~Ongoing~~Not Applicable	~~To continue to follow for OS/PFS2~~	~~Efficacy (OS/PFS2) in patients receiving maintenance therapy post SCT~~	~~Final report for OS/PFS2 (when approximately 200 death events have occurred)~~	~~September 2023~~

~~ASCT=autologous stem cell transplantation; OS=overall survival; PFS=progression free survival; PFS2=time from the date of randomization to the date of first documentation of disease progression on subsequent line of anticancer therapy or death from any cause, whichever occurs first.~~

9.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

10. Changes to the Product Information

As a result of this variation the SmPC is being updated to medicines subject to remove the black triangle of additional monitoring. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and update the list of local representatives in the Package Leaflet.

Changes are also made to the Opinion Annex II conditions as detailed in the recommendations section above.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

10.1.1. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Ninlaro (ixazomib) is removed from the additional monitoring list as five years have passed after the URD and all the specific obligations have been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.