Oral Ixazomib Maintenance following Autologous Stem Cell Transplantation: a Double-blind, Randomised, Placebo-controlled Phase 3 Trial

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Panel: Research in context

Evidence before this study

Maintenance therapy has been extensively explored as a strategy for prolonging the duration of disease control and potentially survival following autologous stem cell transplantation (ASCT) for patients with newly diagnosed multiple myeloma (MM). Early studies investigated interferon-alpha and corticosteroids for use in this setting; however, long term administration of these agents was limited due to high discontinuation rates and severe toxicity. Prior to this study, maintenance with thalidomide was shown to improve progression-free survival (PFS) post-ASCT both in phase 3 studies and meta-analyses; however, poorer outcomes in patients with high-risk cytogenetics have been observed. The poor tolerability profile of thalidomide also limits its possible treatment duration, with discontinuation rates of up to 84% being reported.

Bortezomib maintenance has also been extensively studied in the post-transplant setting prior to the present study, and treatment guidelines recommend the use of proteasome inhibitors during maintenance in high-risk patients. In the HOVON65/GMMG-HD4 trial, patients were randomized prior to induction to receive bortezomib, doxorubicin, and dexamethasone (PAD) versus vincristine, doxorubicin, and dexamethasone (VAD) induction followed by bortezomib in the PAD group versus thalidomide in the VAD group as post-transplant maintenance. PFS was significantly longer in patients receiving PAD induction followed by bortezomib versus VAD induction followed by thalidomide as post-transplant maintenance. However, while demonstrating benefit in this setting, long-term administration of bortezomib is limited by its toxicity profile and route of administration.

At the time of publication, lenalidomide is the only agent approved for post-transplant maintenance. However, at the time of study design in early 2014 and throughout the enrolment period from July 2014 to March 2016, lenalidomide was not approved for use as post-ASCT maintenance therapy and there was no standard of care in this setting, with a majority of patients worldwide not receiving maintenance therapy. A meta-analysis of the CALGB 100104, GIMEMA RV-MM-PI-209 and IFM 2005-02 trials, published in 2017, demonstrated a significant OS benefit for lenalidomide maintenance versus placebo or no maintenance, with discontinuation rates of 29% and 12%, respectively. Subsequently, lenalidomide maintenance was approved in February 2017 for use in the United States and Europe in the post-transplant setting While the approval of lenalidomide in this setting is an important achievement in the care of patients, lenalidomide is associated with the development of second primary malignancies (SPMs) and its benefit is inconsistent in patients with high-risk features such as, but not limited to, certain cytogenetic abnormalities and renal failure.

Proteasome inhibitors are a backbone of MM treatment, and the benefit of proteasome inhibitor-based maintenance has not been demonstrated in a phase 3 trial vs placebo. Because the feasibility of bortezomib maintenance in routine clinical practice is limited, there is a need for an oral proteasome inhibitor maintenance therapy that can be administered for a prolonged period, improve depth of response without cumulative or late-onset toxicity, and improve convenience for patients.

Added value of this study

The results of this study show that post-ASCT maintenance with ixazomib significantly improves PFS with deepening of responses and increased conversions to minimal residual disease negativity over placebo. This study has also demonstrated a favourable safety profile, including an absence of risk of SPMs and low rates of peripheral neuropathy, supporting ixazomib as a valuable alternative to lenalidomide maintenance therapy in responding patients post-ASCT.

Implications of all the available evidence

MM is a heterogeneous disease, requiring individualized treatment strategies for patients. Ixazomib maintenance provides a valuable treatment alternative for patients who are unable to tolerate currently available agents.

Summary

Background Maintenance therapy following autologous stem cell transplantation can delay disease progression and prolong survival in multiple myeloma (MM). Ixazomib is ideally suited for maintenance therapy given its efficacy, convenient once-weekly oral dosing, and low toxicity profile.

Methods The phase 3, double-blind, placebo-controlled, TOURMALINE-MM3 study randomised 656 patients with newly diagnosed MM from 227 clinical/hospital sites in 30 countries in Europe, the Middle East, Africa, Asia, and North and South America between July 31, 2014 and March 14, 2016. Patients received oral ixazomib 3 mg (N=395) or placebo (N=261) on days 1, 8, and 15 in 28-day cycles for 2 years following induction, high-dose therapy, and transplantation. Dose was increased to 4 mg from cycle 5 if tolerated during cycles 1-4. Randomisation was stratified by induction regimen, pre-induction disease stage, and response post-transplantation. The primary endpoint was progression-free survival (PFS) by intent-to-treat analysis. Safety was assessed in all patients who received at least one dose of ixazomib or placebo, according to treatment actually received.

Findings With a median follow-up of 31 months (IQR 27·3–35·7), there was a 28% reduction in the risk of progression or death with ixazomib versus placebo (median PFS, 26·5 [95% CI 23·69–33·81] *vs* 21·3 [17·97–24·67] months; hazard ratio 0·72, 95% CI 0·582–0·890; p=0·002). No increase in second malignancies was noted with ixazomib therapy (12 and 8 patients, respectively; 3% in each arm) at the time of this analysis. In the ixazomib and placebo groups, 108 of 394 (27%) and 51 of 259 (20%) patients had serious adverse events; 1 versus 0 patients died on-study.

Interpretation Ixazomib maintenance prolongs PFS and represents an additional option for post-transplant maintenance therapy in patients with newly diagnosed MM.

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Introduction

Despite recent advances in the treatment of multiple myeloma (MM), relapse after autologous stem cell transplantation (ASCT) is almost inevitable. Recent studies show that maintenance therapy with the immunomodulatory drug, lenalidomide, following ASCT can improve progression-free survival (PFS) and overall survival (OS), and it has been approved for use in this setting.[1-7] A meta-analysis demonstrated discontinuation rates of 29% and 12%, in the lenalidomide maintenance and placebo or observation groups, respectively.[8] Additionally, lenalidomide has shown limited survival benefit in high-risk patients. Maintenance therapy with a proteasome inhibitor provides an alternative to lenalidomide because of the different mode of action. Data from large clinical trials both in transplant-eligible and in transplant-ineligible patients suggest that bortezomib maintenance treatment can prolong PFS.[9,10] However, bortezomib is not well suited for long-term use given the need for parenteral administration and risk of peripheral neuropathy.[4] At the time of trial design there were no approved or established maintenance therapies following induction, high-dose therapy, and transplantation for newly diagnosed MM patients. Ixazomib is a proteasome inhibitor approved for treatment of relapsed/refractory MM in combination with lenalidomide and dexamethasone.[11] Ixazomib may be suitable for maintenance therapy given its convenient once-weekly oral dosing,[12] tolerability, and favourable toxicity profile. We investigated the PFS benefit and safety/tolerability profile associated with ixazomib as maintenance therapy following ASCT.

Patients and methods

Patients

Eligible patients had a confirmed diagnosis of symptomatic MM according to International Myeloma Working Group (IMWG) criteria, achieved at least a partial response (PR) after undergoing standard-of-care induction therapy followed by high-dose melphalan (200 mg/m^2) conditioning, and received single ASCT within 12 months of diagnosis. Induction therapy must have included a proteasome inhibitor and/or an immunomodulatory drug. Patients must have started screening no earlier than 75 days post-transplant and completed screening within 15 days.

Locally obtained cytogenetic results at any time before transplant and documented International Staging System (ISS) disease staging at diagnosis were required (table 1, appendix p16 for detailed eligibility criteria). The trial was conducted in accordance with the International Conference on Harmonisation Guidelines

for Good Clinical Practice and appropriate regulatory requirements. Local ethics committees or institutional review boards approved the protocol. All patients provided written informed consent.

Study design and oversight

Patients were randomised 3:2, no later than 115 days post-transplant, to receive either oral ixazomib 3 mg or matching placebo capsule on days 1, 8, and 15 in 28-day cycles. Dose was increased to 4 mg from cycle 5 if tolerated during cycles 1–4 (appendix p6). Randomisation was stratified by induction regimen (proteasome inhibitor without an immunomodulatory drug *vs* immunomodulatory drug without a proteasome inhibitor *vs* proteasome inhibitor and immunomodulatory drug), pre-induction ISS disease stage (I *vs* II or III), and response after transplantation (complete response [CR] or very good partial response [VGPR] *vs* PR) at screening. After written informed consent was obtained, the patient was assigned an enrollment code (country-, site-, and patient-specific) using an interactive voice/web response system (IXRS). Patient eligibility was confirmed by a project clinician or designee at the Sponsor before randomisation by the investigator into the study. A centralised randomization using IXRS was used; as they became eligible at a centre, patients were randomised sequentially. If a patient discontinued from the study, their randomisation code was not reused, and the patient was not allowed to re-enter the study. The randomization scheme was generated by an independent statistician at the Sponsor. Patients, investigators, and study staff were blinded to treatment allocation.

Patients continued treatment for approximately 24 months (if no treatment delays, equivalent to 26 cycles, to the nearest complete cycle) or until progressive disease (PD) or unacceptable toxicity, whichever occurred first. Dose adjustments for toxicities were permitted using protocol-specified dose-modification guidelines.

The primary endpoint was PFS, defined as time from date of randomisation to date of first documentation of PD or death due to any cause. OS was a pre-specified key secondary endpoint, and the trial was designed to continue in a blinded manner until this endpoint could be concluded. Other secondary endpoints included best response achieved or maintained prior to PD or subsequent therapy, time-to-progression (measured as time from randomisation to date of first documented progression, with patients who die prior to PD censored at the time of last response assessment of stable disease or better), PFS2 (defined as time from the date of randomisation to date of objective PD on next-line treatment or death from any cause, whichever occurred first), OS and PFS in patients with high-risk cytogenetic abnormalities (chromosome 17p deletion [del(17p)], translocation between chromosomes 4 and 14 [t(4;14)], and translocation between chromosomes 14

and 16 [t(14;16)]), safety, and conversion to or maintenance of minimal residual disease (MRD)−negative status. Additional endpoints are listed in the appendix p5.

Assessments

Response and PD assessments were based on central laboratory M-protein results, plus local bone marrow and imaging data, using IMWG 2011 criteria (table 2, appendix p18),[13] as evaluated by an independent review committee blinded to both treatment assignment and investigator assessment of response. Response assessments were performed every treatment cycle and every 4 weeks during the PFS follow-up period until PD (figure 1, appendix p10). All cytogenetic evaluations were performed locally according to local standards and using locally defined thresholds for positivity, with no pre-specified cut-offs; cytogenetic data were centrally reviewed and interpreted based on local thresholds. Bone marrow samples were evaluated locally at screening and whenever a new CR was suspected. Bone marrow aspirate samples were collected for MRD assessment at screening and at cycle 13 and cycle 26 for all patients in CR and VGPR, and whenever a bone marrow aspiration was performed to confirm a new suspected CR. Samples were assessed for MRD by 8-color flow cytometry technology (10^{-5} sensitivity). For more details on the assessments, see appendix p6–8.

Statistical analysis

The study used a closed sequential testing procedure for the primary endpoint of PFS and key secondary endpoint of OS in this order. PFS was tested at a two-sided alpha level of 0·05, and OS was tested at a significance level determined by the O'Brien-Fleming alpha spending function (Lan-Demets method[14]). Due to the closed sequential testing property, the family-wise type I error was strongly controlled for both PFS and OS. Two interim analyses, plus a final analysis, were planned to test OS. Total sample size was calculated to provide 80% power (two-sided alpha 0·05) to test for a 43% improvement in OS (assumed hazard ratio [HR] of 0·70), based on a minimum event size of 260 deaths. The first interim analysis, which was also the primary and only analysis of PFS, was planned when 50% of patients had experienced a PFS event (328 events) or 25 months after the last patient was enrolled, whichever occurred later; at this event size, and assuming a 15% drop-out rate by month 30, the study had 95% power to detect a HR of 0·67 using a log-rank test at a two-sided alpha of 0·05 for PFS benefit. All other efficacy endpoints were tested at a two-sided alpha level of 0·05.

Analysis populations are defined in the appendix p8. The intent-to-treat (ITT) population was used for all primary and secondary efficacy analyses. Kaplan-Meier methodology was used to estimate time-to-event

distributions, with stratified log-rank tests and Cox models (alpha=0·05, two-sided) used for inter-arm comparisons of time-to-event endpoints. Pre-specified subgroup analyses were conducted for PFS relative to baseline stratification factors and demographic data.

Role of the funding source

The trial was designed by the authors in collaboration with the sponsor, Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Data were gathered by the investigators and sponsor, and analysed by the sponsor. The initial draft of the manuscript was written by the senior and lead authors, S Vincent Rajkumar and Meletios A Dimopoulos. Professional medical writing support was provided by the sponsor for subsequent manuscript editing, incorporation of comments and revisions from authors, formatting of tables, figures and references, and submission preparation. All authors contributed to subsequent drafts and made the decision to submit the manuscript for publication. The investigators, participating institutions, and sponsor agreed to maintain confidentiality of the data. All the authors had access to the data and vouch for the integrity, accuracy, and completeness of the data and analyses, and for the fidelity of the study to the protocol.

Results

Patients

Between July 31, 2014 and March 14, 2016, 656 patients from 227 sites in 30 countries were enroled (figure 2, appendix p12), including 395 to receive ixazomib maintenance therapy and 261 to receive placebo. Baseline patient demographic and disease characteristics were generally well balanced between groups (table 1). Median age at study entry was 58 years (IQR 52–64), with a slightly higher proportion of younger patients in the ixazomib versus placebo group. Cytogenetic analysis results showed that 18% of the ITT population (n=115) had high-risk cytogenetic abnormalities, with a slightly higher proportion in the placebo versus ixazomib group. Median time from diagnosis to first maintenance dose was 9·5 (IQR 8·2–11·2) and 9·4 (8·3–11·4) months in the ixazomib and placebo groups, respectively.

Efficacy

At data cut-off for this analysis (April 16, 2018), median follow-up was 30·9 (IQR 27·1–35·6) and 31·3 (27·4–35·7) months in the ixazomib and placebo groups, respectively. With 198 and 156 independent review

committee-assessed progression or death events, there was a significant 28% reduction in risk of progression or death in the ixazomib versus placebo group (HR 0·72, 95% CI 0·582–0·890; p=0·002); median PFS was 26·5 [95% CI 23·69–33·81] versus 21·3 [17·97–24·67] months (figure 1A). Median time to progression in the ixazomib and placebo groups was 26·6 [95% CI 23·69–33·81] and 21·4 [18·10–24·67] months, respectively. Median time from randomisation to start of next line of therapy with ixazomib and placebo maintenance therapy was 33·1 [95% CI 29·14–not estimable] and 27·6 [24·48–30·95] months, respectively.

The benefit of ixazomib was analysed based on key baseline patient characteristics; the study was not powered to compare the primary endpoint between these patient subgroups. In patients who were aged ≥60 years, there was there was a PFS benefit in the ixazomib group versus the placebo group (HR 0·662, 95% CI 0·480–0·914; p=0·012; figure 1B). In patients with ISS disease stage III, there was a PFS benefit in the ixazomib group (HR 0·661, 95% CI 0·438–0·998; p=0·047). In patients with high-risk [del(17p), t(4;14), t(14;16)] cytogenetics, there was a trend for PFS benefit in the ixazomib group (HR 0·625, 95% CI 0·383–1·019; p=0·058). In high-risk patients, the PFS rate at 24 months was greater in the ixazomib group than the placebo group (Kaplan-Meier estimate: 39% versus 20%). PFS was improved in the ixazomib group versus the placebo group in both proteasome inhibitor−naïve patients (HR 0·497, 95% CI 0·254–0·973; p=0·038) and in proteasome inhibitor−exposed patients (HR 0·750, 95% CI 0·600–0·938; p=0·011).

Time from randomisation to start of next line of therapy with ixazomib and placebo maintenance therapy was 33·1 and 27·6 months, respectively. PFS2 data were not mature at data cut-off for this analysis (only 20% [n=129] of patients had experienced PFS2 events of death or disease progression on next line of therapy), and so PFS2 analysis was inconclusive due to limited events. Similarly, as OS data were not mature (only 14% of death events [n=93] had occurred at data cut-off for this analysis), OS analysis was inconclusive due to limited events. Thus, the study remains blinded, and follow-up for PFS2 and OS continues.

Response status at study entry and following maintenance therapy is shown in table 2. Depth of response improved during maintenance in 139 (46%) and 60 (32%) patients with VGPR or PR post-transplantation in the ixazomib and placebo groups, respectively (relative risk 1·407, 95% CI 1·102–1·797; p=0·004).

At study entry, of the 357 patients examined for MRD in the ixazomib group, 117 (33%) patients were negative for MRD, 225 (63%) tested positive, and 53 (13%) were either not evaluable or not tested. Of the 228 patients tested for MRD in the placebo group, 75 (33%) patients were negative for MRD, 139 (61%) tested positive and 47 (18%) were either not evaluable or not tested. A PFS benefit was observed in the ixazomib

group versus the placebo group irrespective of MRD status at study entry (figure 3, appendix p13). Median PFS in patients who had MRD-negative status at study entry was 38·6 [95% CI 33·81–not estimable] versus 32·5 [19·32–not estimable] months in the ixazomib and placebo groups, respectively. Among those who were MRD-positive, 28/225 (12%) and 10/139 (7%) patients in the ixazomib and placebo arms, respectively, converted to MRD-negative status during maintenance therapy. Among patients who were already negative for MRD at study entry, 73/117 (62%) and 38/75 (51%) retained this status over the course of therapy (table 2).

Safety

The safety population included 394 patients in the ixazomib group and 259 in the placebo group (figure 2, appendix p12). Patients received a median of 25 (IQR 13–26) and 22 (IQR 12–26) treatment cycles in the ixazomib and placebo groups, respectively. Fifty percent (n=198) and 42% (n=109) of patients completed 24 months of treatment. In the ixazomib and placebo groups, 317 (86%) and 222 (92%) patients received a dose escalation from the starting dose of 3 mg to 4 mg (table 3). At data cut-off, 72% (n=286) and 75% (n=195) of patients were ongoing on study. Rates of discontinuation of study treatment due to adverse events (AEs) were similar in both groups, 7% (n=28) and 5% (n=12) of the patients in the ixazomib and placebo groups, respectively.

Safety profiles for each group are summarised in table 3; the rate of serious AEs was greater in the ixazomib group versus the placebo group (27% [n=108] *vs* 20% [n=51]). The number of on-study deaths was very low in both groups (1 *vs* 0 patients). The most common haematologic and nonhaematologic AEs are summarised in table 4.

The incidence of peripheral neuropathy was 19% (n=73) and 15% (n=39) in the ixazomib and placebo groups, respectively (1 [<1%] patient and 0 patients grade ≥3). Fifty-five of 73 (75%) patients who developed peripheral neuropathy events in the ixazomib group and 29 (74%) of 39 patients in the placebo group had improved symptoms at last follow-up, with 52 (71%) and 27 (69%) having complete resolution of symptoms. Cardiovascular events were reported in 3% (n=12) and 2% (n=6) of patients. Thrombosis was reported in 0 and 1 patient in the ixazomib and placebo groups, respectively.

Thrombocytopenia occurred more frequently in the ixazomib group compared with the placebo group (13% [n=53] *vs* 3% [n=8]). Gastrointestinal AEs were mostly low-grade in both groups and were more common in the ixazomib arm compared with the placebo arm (any grade: 69% [n=270] *vs* 48% [n=124]; grade ≥3 6% [n=25] *vs* 1% [n=3]; table 4). The rate of antiemetic use was 19% (n=76) versus 4% (n=11). Herpes zoster

occurred in 10% (n=39) and 5% (n=14) of patients overall with ixazomib and placebo, respectively; the protocol was amended during the trial to require prophylaxis. Rates of herpes zoster without prophylaxis were 60% (n=33, N=55) and 26% (n=12, N=47) in the ixazomib and placebo groups, respectively, and the corresponding rates with prophylaxis were 2% (n=6, N=339) and 1% (n=2, N=212), respectively. AEs within the pooled term of 'rash' were reported in 120 (30%) and 57 (22%) patients in the ixazomib and placebo groups, respectively; 7 (2%) patients in the ixazomib group and none in the placebo group reported grade 3 events (table 4). At the current follow-up, there was no difference in the rate of new primary malignancy (3% [n=12] *vs* 3% [n=8]; table 4).

Data from patient self-reported instruments including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 indicated similar patient-reported quality of life in the ixazomib and placebo groups. For the secondary endpoint of overall health-related quality of life, as measured by the global health domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, mean scores were similar in the ixazomib and placebo groups (figure 4, appendix p14). Analyses of other functioning, symptoms and side effects subscales of this instrument and the MY20 instrument (appendix p7-8) also showed similar scores between treatment groups and preservation of patient-related quality of life from baseline (data not shown), except for the subscales associated with nausea/vomiting and diarrhoea, which were negatively impacted in the ixazomib group.

Significant overlap in ixazomib concentration-time profiles between patients enrolled to the ixazomib group of the present TOURMALINE-MM3 study and patients enrolled to the ixazomib-lenalidomide-dexamethasone arm of the TOURMALINE-MM1 study in relapsed/refractory MM (figure S5, appendix p15) suggested no readily apparent pharmacokinetic differences between the two patient populations. Previous clinical pharmacology conclusions across specific clinical contexts of use (e.g., in patients with renal or hepatic impairment, or during co-administration with interacting drugs) can be translated to this patient population.[15,16]

Discussion

Although ASCT prolongs PFS and OS in MM, most patients eventually relapse.[17-19] In this study, we show that a 2-year fixed duration of ixazomib in the post-transplant maintenance setting significantly improves PFS for all patients. Furthermore, this is achieved with little toxicity and preserved quality of life.

Attempts to delay progression with older agents, used in the maintenance setting, for example, interferon, dexamethasone or thalidomide, resulted in toxicity, without consistent or significant clinical

benefit.[20-24] Lenalidomide maintenance therapy has consistently resulted in a significant improvement in PFS, which is the current approved treatment standard in many countries; however, lenalidomide has several limitations including risk of fatigue, diarrhoea and second malignancies.[1-7] There is no study that has specifically addressed the role of maintenance therapy with bortezomib and, although promising, bortezomib maintenance is limited by practicalities of parenteral administration and the risk of peripheral neuropathy.[25] The magnitude of benefit with ixazomib observed in this study is in line with what is expected from a proteasome inhibitor used as maintenance therapy as evidenced in the HOVON65/GMMG-HD4 trial.[4,9] Once-weekly ixazomib combined with lenalidomide and dexamethasone as an induction, consolidation, and maintenance remission strategy has been investigated and reported favourable outcomes and tolerability.[26] In the TOURMALINE-MM3 double-blind, placebo-controlled trial, we show that ixazomib, an orally administered proteasome inhibitor, significantly prolongs PFS. Moreover, treatment was well tolerated, with minimal increase in serious AEs, and in peripheral neuropathy and thrombotic events, and no increase in second primary malignancies at the time of this analysis, after a median follow-up of 31 months. With a similar follow up for lenalidomide maintenance, an increase in the incidence of second primary malignancies was already evident.[8]

Post-transplant maintenance therapy in MM has been shown to be an effective intervention, with the ability to prolong OS. The Intergroupe Francophone du Myélome (IFM)-2005-02 study reported median PFS of 41 months for patients who received lenalidomide maintenance until progression compared with 23 months for patients who received placebo (HR 0·50; p<0·001).[1] Furthermore, the Cancer and Leukemia Group B (CALGB)-100104 study reported median PFS of 46 versus 27 months in patients who received lenalidomide maintenance until progression versus placebo (HR 0·48; 95% CI 0·36–0·63; p<0·001), and this was accompanied by an improvement in OS.[2] Furthermore, a meta-analysis showed that the risk of progression or death was reduced by 52% with lenalidomide maintenance versus placebo or observation (HR 0·48; 95% CI 0·41–0·55), and the 7-year survival rates were 62% and 50% with lenalidomide maintenance and placebo or observation.[8] A recent meta-analysis of 6 maintenance therapy regimens showed that lenalidomide maintenance was superior in terms of OS (HR 0·76; 95% CI 0·51–1·16), although the result was not statistically significant.[27]

Ixazomib and lenalidomide maintenance therapy each have their own risk/benefit profiles to consider, and these must be considered in the context of each individual patient. Our study provides additional support to the value of maintenance therapy in MM and confirms the single-agent efficacy of a fixed duration of ixazomib in this disease. While comparison of absolute values of median PFS between clinical trials should be avoided due to confounding factors such as differences between patient populations, treatment durations, and prior

treatment exposure, assessing the relative benefit versus a common comparator is appropriate. The PFS benefit observed with ixazomib compared with placebo in this study was over 5 months, whereas a benefit of over 2 years has been shown with lenalidomide maintenance therapy versus placebo/observation.[8] Although the benefit of lenalidomide maintenance is substantial, it is inconsistent in patients with high-risk cytogenetic abnormalities, and this represents an unmet medical need. We found that the improvement in PFS with ixazomib was consistent in patients with characteristics associated with poorer prognosis, including ISS stage III disease and presence of high-risk cytogenetics (acknowledging that the study was not powered for these subgroups), consistent with the known benefit of proteasome inhibitors in these settings.[9] Importantly, our study shows that ixazomib is well tolerated, with a low discontinuation rate of 7%, similar to placebo (5%), compared with up to 29% previously reported for lenalidomide.[8] However, the difference in time on therapy may have contributed to discontinuation rates. Therefore, for patients in whom lenalidomide therapy is not tolerated or not appropriate, the use of oral ixazomib maintenance may be an option, although it is acknowledged that the findings of the present study do not specifically address the use of ixazomib in this population.

Future maintenance approaches incorporating ixazomib will likely favour a combination approach, e.g., potentially in high-risk patients. Indeed, more broadly, there is a need for further investigation to determine the most appropriate maintenance approaches to be utilised in different patient subgroups defined according to patient-related, disease-related, and prior treatment-related characteristics. There are several combination regimens currently being investigated and used in practice, including ixazomib and lenalidomide combination maintenance therapy in newly diagnosed MM patients, which may impact the future utility of ixazomib maintenance therapy.[28] Ongoing studies are investigating the benefit of ixazomib and lenalidomide in combination compared with lenalidomide or ixazomib alone as maintenance (NCT03733691, NCT02406144, NCT02389517), and the combination is being evaluated specifically in high-risk patients (NCT03641456) as well as in an alternating approach (NCT02619682), while the two agents are also being compared in this setting in one study (NCT02253316). The findings of these investigations will contribute to an improved understanding the optimal maintenance therapy approaches for different patient populations.

Quality-of-life assessments showed that at the end of treatment, both the ixazomib and placebo groups had no change from study entry in mean global health status score. Improvements in quality of life scores among the patients, who were in response post-ASCT at baseline and thus largely asymptomatic, were not expected. However, the preservation of quality of life scores and the similar scores between treatment groups during the study both indicate that ixazomib maintenance did not have a negative impact on overall patient-

reported quality of life. The only subscales that were negatively impacted in the ixazomib group were those associated with nausea/vomiting and diarrhoea; this reflects the reported safety profile of ixazomib maintenance, in which gastrointestinal events were more common than in the placebo group.

Ixazomib maintenance was associated with a significantly greater rate of deepening of response compared with placebo. Additionally, although modest, the proportion of patients who converted to MRD-negative status was higher with ixazomib (12%) versus placebo (7%); it should be noted that the study was not powered for the comparison of this parameter and the difference was not tested statistically. Furthermore, the median time to documented MRD-positive status, progression, or death was significantly prolonged with ixazomib.

Our study has a number of limitations. While a placebo-controlled trial represents a powerful treatment design, in the context of currently approved therapies it does not provide a direct comparison versus lenalidomide, which is the only agent approved specifically in this setting. However, this is due to the timing of the study design, which took place approximately 3 years prior to the approval of lenalidomide as post-ASCT maintenance therapy. At the time of study design in early 2014 and throughout the enrolment period from July 2014 to March 2016, there were no maintenance therapies approved for the treatment of MM, and, other than in the United States, the majority of patients worldwide did not receive maintenance during this time period and there was no standard of care. Subsequently, lenalidomide maintenance has been approved for use in the United States and Europe in the post-transplant setting.[29,30] Another limitation of this study is that the optimal duration of maintenance therapy with a proteasome inhibitor was not tested in this study. It is now well-established that use of continuous lenalidomide maintenance until PD results in a significant OS benefit as well as PFS gain.[2,3] However, median duration of lenalidomide maintenance therapy reported in a meta-analysis was 28 months, 22 months in the placebo or observation group.[8] Notably, in this study the PFS curve for ixazomib maintenance therapy did not show a sharp decline after completion of 24 months of therapy. This is in contrast to the results reported in the FIRST trial whereby sudden acceleration in progression or death occurred at the end of the treatment period in patients who received a fixed duration of 18 cycles of lenalidomide and dexamethasone.[6] While maintenance therapies are currently available, additional options are needed, along with consideration of optimal sequencing of therapies. Our study continues in a blinded fashion, and OS analysis will be performed when the preplanned number of events have been reached.

In this first randomized, placebo-controlled Phase 3 study of the treatment effect of a proteasome inhibitor in maintenance, we conclude that ixazomib is an effective, well-tolerated, once-weekly oral drug for

2-year fixed duration maintenance therapy following ASCT in MM. It is an important alternative treatment option in this setting, and it is suggested that it may have particular utility for patients who lack access to or are unable to tolerate lenalidomide, and potentially including patients with high-risk cytogenetics.

Contributions

MAD, HG, ZT, TS, NG, and RL designed the study. MAD, FG, FS, MB, RH, KCW, HG, VM, PM, CKM, AP, W-JC, MK, SZ, M-VM, AS, SI, GM, and SVR were study investigator and enroled patients to participate in the study. HG, KS, ZT, TS, ABD, NG, and RL analysed the data. All authors interpreted the data, prepared the manuscript and reviewed all revisions. All authors approved the final draft of manuscript for submission.

Declaration of interests

MAD is a consult for AMGEN, Celgene, Takeda, Janssen, BMS, he has received honoraria from AMGEN, Celgene, Takeda, Janssen, and has participated in speaker bureaus for AMGEN, Celgene, Takeda, Janssen.
FG has received honoraria from Amgen, Celgene, Takeda, Janssen, BMS and a member of the advisory committee for Celgene, Takeda, Seattle Genetics, Roche.
FS has participated in speaker bureaus for Amgen, Celgene, Takeda, Abbvie, Janssen and a member of advisory boards for Amgen, Celgene, Takeda, Janssen, BMS, Bayer, Adaptive, Oncopeptides.
MB has been a member on advisory boards for Janssen Cilag, Takeda, Amgen, Sanofi and has participated in speaker bureaus for Janssen Cilag, Celgene, Takeda, Amgen.
RH provides consultancy for Takeda, BMS, Amgen, Janssen, Celgene and has received research funding from Takeda, Amgen, Janssen, Novartis; Honoraria: Takeda, BMS, Amgen, Janssen, Celgene.
KCW has received honoraria from Amgen, BMS, Celgene, Janssen, Takeda and research funding from Amgen, Celgene, Janssen, Sanofi.
HG has participated in advisory boards for Adaptive Biotechnology, Amgen, BMS, Celgene, Janssen, Sanofi, Takeda, he has received research funding from Amgen, BMS, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda, Novartis, and honoraria from ArtTempi, BMS, Celgene, Chugai, Janssen, Novartis.
PM has participated in advisory boards and received honoraria from Celgene, Amgen, Janssen, Abbvie.
W-JC has received honoraria from Takeda.
MK provides consultancy for Amgen, Janssen, Takeda, Celgene and has received research funding from Celgene and travel support from Takeda.

SZ has received research funding from Takeda, Celgene, Janssen and has participated in advisory boards for Takeda, Celgene, Janssen.

M-VM has received personal fees from Takeda, Janssen, AMGEN, Celgene, GSK, Abbvie.

AS provides consultancy for Specialised Therapeutics Australia and has received honoraria from Takeda, Celgene, Janssen, Amgen. He has participated in speaker bureau's for Takeda, Celgene, Janssen and received research funding from Takeda, Celgene, Janssen, GSK.

SI has received research funding from Takeda, Ono, Janssen, Celgene, Novartis, Chugai, Abbvie, Bristol-Myers Squibb, Kyowa-Hakko Kirin, MSD, Daiichi Sankyo, Gilead, Teijin Pharma, Astellas; Honoraria: Takeda, Janssen, Celgene, Ono, Bristol-Myers Squibb.

TS is employed by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited and is also affiliated with Department of Hematology, Charles University General Hospital, Prague, Czech Republic

KS, ZT, ABD, NG, and RL are employed by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

AP is employed by and has ownership interests (stock options) in Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, he is a consultant and has received honoraria for Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis and Merck, he has received research funding from Amgen, Novartis, Bristol-Myers Squibb, Genmab A/S, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, Merck and Binding Site, and has participated in a speaker's bureau for Bristol-Myers Squibb.

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VM, CKM, and GM have nothing to disclose.

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TABLES

Table 1: **Baseline characteristics of patients in the intention-to-treat population**

Characteristic	Ixazomib group (n=395)	Placebo Group (n=261)	Overall (N=656)
Age			
Median **(IQR)** – years	58 (52–63)	60 (54–64)	58 (52–64)
<60 years – no. (%)	229 (58)	127 (49)	356 (54)
≥60 and <75 years – no. (%)	166 (42)	134 (51)	300 (46)
White race – no. (%)	315 (80)	213 (82)	528 (80)
Type of myeloma at initial diagnosis – no. (%)			
IgG	230 (58)	149 (57)	379 (58)
IgA	87 (22)	60 (23)	147 (22)
Light chain	66 (17)	46 (18)	112 (17)
Other	12 (3)	6 (2)	18 (3)
ISS disease stage at initial diagnosis[*] – no. (%)			
I	151 (38)	94 (36)	245 (37)
II	129 (33)	92 (35)	221 (34)
III	115 (29)	75 (29)	190 (29)
ECOG performance status at study entry[†] – no. (%)			
0	259 (66)	181 (69)	440 (67)
1	125 (32)	74 (28)	199 (30)
2	11 (3)	5 (2)	16 (2)
Creatinine clearance at study entry[‡] – no. (%)			
30 to <60 ml/min	38 (10)	20 (8)	58 (9)
60 to <90 ml/min	101 (26)	80 (31)	181 (28)
≥90 ml/min	254 (64)	160 (61)	414 (63)
Cytogenetic features – no. of patients (%)			
High-risk cytogenetic abnormalities[#]	61 (15)	54 (21)	115 (18)
Standard-risk cytogenetic abnormalities[#]	252 (64)	152 (58)	404 (62)
Unclassifiable[#]	82 (21)	55 (21)	137 (21)
Induction regimen – no. (%)[§]			
PI without IMiD	234 (59)	155 (59)	389 (59)
IMiD without PI	43 (11)	28 (11)	71 (11)
PI + IMiD	118 (30)	78 (30)	196 (30)
Response after ASCT (by investigator) – no. (%)			
sCR	52 (13)	39 (15)	91 (14)
CR	80 (20)	54 (21)	134 (20)
VGPR	179 (45)	115 (44)	294 (45)
PR	84 (21)	53 (20)	137 (21)
MRD status at study entry[¥] – no. of patients tested (%)	357 (90)	228 (87)	585 (89)
MRD-negative	117 (33)	75 (33)	192 (33)
MRD-positive	225 (63)	139 (61)	364 (62)
Not evaluable	15 (4)	14 (6)	29 (5)

Patients not tested for MRD – no. (%)	38 (10)	33 (13)	71 (11)
Median time from diagnosis to first maintenance dose (IQR) – months	9·5 (8·2–11·2)	9·4 (8·3–11·4)	9·5 (8·3–11·3)
Median time from ASCT to first maintenance dose (IQR) –months	3·4 (3·1–3·6)	3·4 (3·1–3·6)	3·4 (3·1–3·6)

ASCT=autologous stem cell transplantation. CR=complete response. ECOG=Eastern Cooperative Oncology Group. IMiD=immunomodulatory drug. ISS=International Staging System. MRD=minimal residual disease. PI=proteasome inhibitor. PR=partial response. sCR=stringent complete response. VGPR=very good partial response.

*The International Staging System (ISS) consists of three stages: stage I, serum β2-microglobulin level lower than 3·5 mg per liter (300 nmol per liter) and albumin level 3·5 g per deciliter or higher; stage II, neither stage I or III; and stage III, serum β2-microglobulin 5·5 mg per liter or higher (470 nmol per liter). Higher stages indicate more severe disease.

†ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability related to tumour. Data missing for 1 patient in the placebo group.

‡Creatinine clearance data missing for 3 patients, 2 in the ixazomib group, 1 in the placebo group.

#High-risk cytogenetic abnormalities were detected by fluorescence in situ hybridisation or karyotype analysis and were defined as chromosome 17p deletion [del(17p)], translocation between chromosomes 4 and 14 [t(4;14)], and translocation between chromosomes 14 and 16 [t(14;16)]. If all three abnormalities were unknown, indeterminate or missing, the patient was called unclassifiable. There was no cut-off for defining the presence of del(17p).

§Per stratification data.

¥Minimal residual disease (MRD) limit of detection was $\geq 10^{-5}$ in 162 (19%) and 103 (19%) of assessments in patients in the ixazomib (870 assessments) and placebo (551 assessments) groups, $\geq 10^{-6}$ but $<10^{-5}$ in 705 (81%) and 447 (81%), and $<10^{-6}$ in 3 (<1) and 1 (<1). The protocol required MRD assessment at study entry in patients whose response to ASCT as assessed by the investigator was CR or VGPR. However, some patients who had MRD assessments done were later found to have only a PR.

***Table 2*: Response improvements with study regimen and time-to-event data in the intent-to-treat population**

Endpoint	Ixazomib group (n=395)	Placebo group (n=261)	Statistical comparison HR/RR (95% CI), p value
ITT population			
Response at study entry as determined by Independent Review Committee			
CR – no. (%)	60 (15)	54 (21)	–
VGPR – no. (%)	213 (54)	152 (58)	–
VGPR patients converting to CR during study – no. (%)	92 (43)	48 (32)	RR 1·368 (1·034–1·810)
PR – no. (%)	89 (23)	35 (13)	–
PR patients converting to VGPR or better during study – no. (%)	47 (53)	12 (34)	RR 1·540 (0·935–2·537)
Stable disease – no. (%)	2 (<1)	1 (<1)	–
PD – no. (%)	1 (<1)	0	–
Either VGPR or PR – no.	302	187	
VGPR/PR patients with deepening response during treatment – no. (%)	139 (46)	60 (32)	RR 1·407 (1·102–1·797); p=0·004
Patients with documented MRD-positive status at study entry	225	139	
Patients who converted to MRD-negative status at any time post-study entry – no. (%)	28 (12)	10 (7)	
By 6 months post-study entry – no. (%)	3 (1)	0	
By 12 months post-study entry – no. (%)	17 (8)	8 (6)	
By 18 months post-study entry – no. (%)	21 (9)	9 (6)	
By 24 months post-study entry – no. (%)	23 (10)	10 (7)	
Median time to MRD-negative status (95% CI) – mos	NE	NE	HR 1·641 (0·787–3·420); p=0·18
Median PFS (95% CI) – mos	20·3 (16·33–23·06)	17·6 (14·72–20·80)	HR 0·772 (0·588–1·014); p=0·062
Patients who were MRD-negative at study entry	117	75	
Patients with MRD-negative status retained at any subsequent evaluation – no. (%)	73 (62)	38 (51)	p=0·11
Median time to documented MRD-positive status, progression, or death (95% CI) – mos	NE (38·64–NE)	24·6 (12·06–NE)	HR 0·574 (0·368–0·898); p=0·014
Median PFS (95% CI) – mos	38·6 (33·81–NE)	32·5 (19·32–NE)	HR 0·612 (0·386–0·969); p=0·034

CI=confidence interval. CR=complete response. HR=hazard ratio. ITT=intent-to-treat. MRD=minimal residual disease. NE=not estimable. PD=progressive disease. PR=partial response. RR=relative risk. VGPR=very good partial response.

*Response at study entry is different than the investigator-determined response to autologous stem cell transplantation used to randomise patients.

Table 3: **Overall safety profile in the safety population**

Variable	Ixazomib group (n=394)	Placebo group (n=259)
Median follow-up (IQR) – months	30·9 (27·1–35·6)	31·3 (27·4–35·7)
Median treatment cycles (IQR) – no.	25 (13–26)	22 (12–26)
Dose escalated to 4 mg at cycle 5 – no. (%)	317 (86)	222 (92)
Median duration of treatment at a dose/placebo equivalent of 4 mg (IQR) – months	15·2 (4·9–19·6)	16·6 (8·3–19·4)
Any AE – no. (%)	382 (97)	241 (93)
Any drug-related AE – no. (%)	307 (78)	149 (58)
Any grade ≥3 AE – no. (%)	166 (42)	67 (26)
Any drug-related grade ≥3 AE – no. (%)	73 (19)	13 (5)
Any serious AE – no. (%)	108 (27)	51 (20)
AE resulting discontinuation of the study drug – no. (%)	28 (7)	12 (5)
AE resulting in dose reduction of the study drug – no. (%)	73 (19)	13 (5)
Death during the treatment period – no. (%)	1 (<1)	0

AE=adverse event.

Death during the treatment period was recorded through 30 days after receiving the last dose of the study drug or placebo.

Table 4: **Common AEs in the safety population**

AE No. of patients (%)	Ixazomib group (n=394) Any grade	 Grade 3	 Grade 4	Placebo group n=259) Any grade	 Grade 3	 Grade 4
Common haematologic AEs of any cause						
Neutropenia*	36 (9)	17 (4)	3 (<1)	20 (8)	9 (3)	0
Thrombocytopenia*	53 (13)	14 (4)	5 (1)	8 (3)	0	2 (<1)
Anaemia	29 (7)	4 (1)	0	10 (4)	2 (<1)	0
Common nonhaematologic AEs of any cause						
Infections and infestations (MedDRA SOC)†	292 (74)	55 (14)	3 (<1)	166 (64)	21 (8)	0
Upper respiratory tract infection	101 (26)	2 (<1)	0	54 (21)	1 (<1)	0
Viral upper respiratory tract infection	94 (24)	0	0	69 (27)	0	0
Pneumonia†	40 (10)	23 (6)	1 (<1)	21 (8)	11 (4)	0
Gastrointestinal disorders (MedDRA SOC)	270 (69)	25 (6)	0	124 (48)	3 (1)	0
Nausea	154 (39)	1 (<1)	0	40 (15)	0	0
Diarrhoea	137 (35)	10 (3)	0	61 (24)	2 (<1)	0
Vomiting	106 (27)	6 (2)	0	28 (11)	0	0
Rash*	120 (30)	7 (2)	0	57 (22)	0	0
Cough	87 (22)	0	0	55 (21)	1 (<1)	0
Arthralgia	86 (22)	3 (<1)	0	30 (12)	1 (<1)	0
Pyrexia	84 (21)	1 (<1)	0	38 (15)	0	0
Fatigue	79 (20)	5 (1)	0	43 (17)	1 (<1)	0
Back pain	77 (20)	5 (1)	0	49 (19)	1 (<1)	0
Peripheral neuropathy*	73 (19)	1 (<1)	0	39 (15)	0	0
Headache	43 (11)	0	0	23 (9)	0	0
Influenza	42 (11)	3 (<1)	0	30 (12)	1 (<1)	0
Other AEs of clinical interest						
Acute renal failure	11 (3)	1 (<1)	0	8 (3)	1 (<1)	0
Cardiac arrhythmias	19 (5)	7 (2)	0	7 (3)	2 (<1)	0
Liver impairment	24 (6)	9 (2)	0	11 (4)	3 (1)	1 (<1)
Orthostatic hypotension / hypotension	4 (1)	1 (<1)	0	1 (<1)	0	0
New primary malignant tumour	12 (3)			8 (3)		

AE=adverse event.

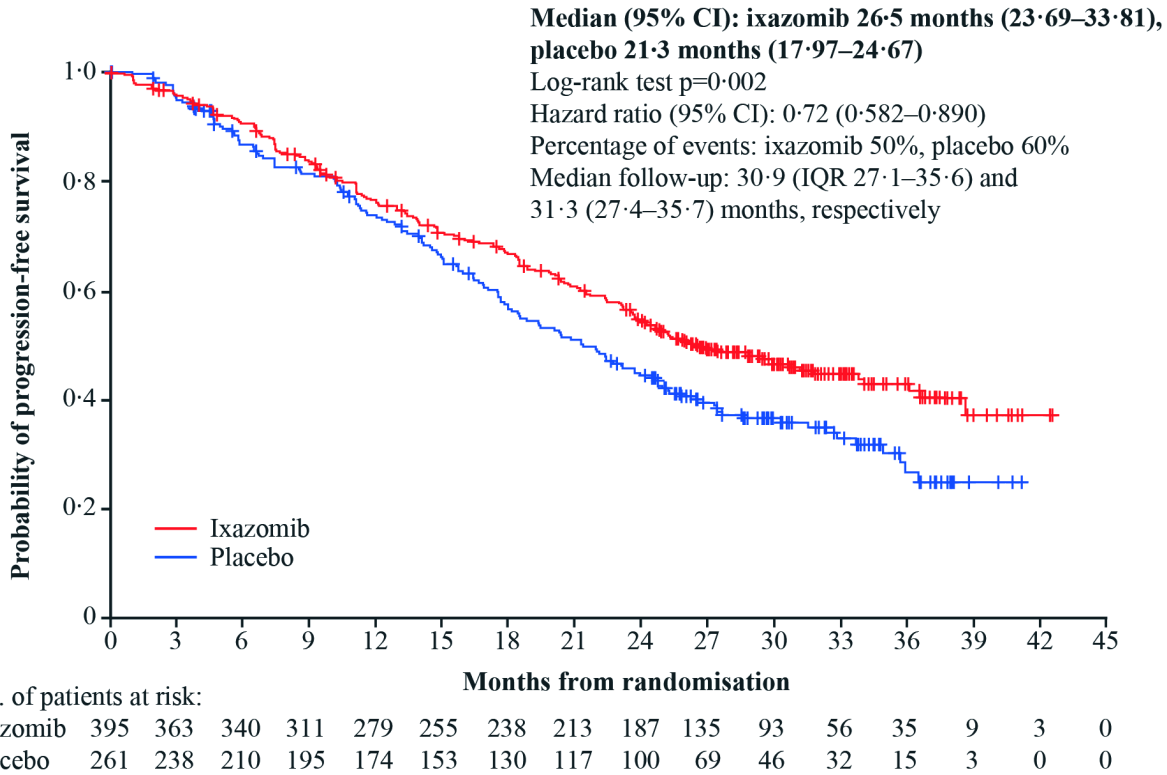
*Data were based on a standardised Medical Dictionary for Regulatory Activities (MedDRA) query that incorporated pooled preferred terms or multiple preferred terms. "Thrombocytopenia" was coded according to the preferred terms of thrombocytopenia and decreased platelet count. "Neutropenia" was coded according to the preferred terms of neutropenia and decreased neutrophil count. "Peripheral neuropathy" represents the high-level term peripheral neuropathies not elsewhere classified, excluding neuritis; preferred terms included peripheral neuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, and peripheral motor neuropathy. "Rash" included preferred terms of pruritus, rash maculo-papular, rash macular, rash popular, rash erythematous, rash pruritic, drug eruption, pruritus generalised, rash, urticarial, dermatitis allergic, rash generalised, dermatitis acneiform, erythema multiforme, rash pustular, and rash vesicular.

†1 patient in the ixazomib group had a grade 5 adverse event (AE) of pneumonia.

FIGURES

Figure 1: **Kaplan-Meier analysis of progression-free survival by independent review in the intent-to-treat population (A) and by pre-specified patient subgroups (B). The study was not powered to compare the primary endpoint between these patient subgroups.**

A

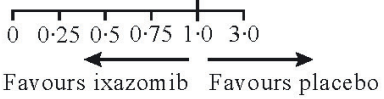


No. of patients at risk:

Ixazomib	395	363	340	311	279	255	238	213	187	135	93	56	35	9	3	0
Placebo	261	238	210	195	174	153	130	117	100	69	46	32	15	3	0	0

B

Variable	Subgroup	% of patients Ixazomib	% of patients Placebo	HR	95% CI
All subjects	All (n=656)	100	100	0·720	(0·582–0·890)
Pre-induction ISS	I (n=242)*	37	37	0·703	(0·492–1·006)
	II or III (n=414)	63	63	0·729	(0·560–0·949)
Response after transplant	CR or VGPR (n=509)	77	78	0·714	(0·558–0·913)
	PR (n=147)*	23	22	0·737	(0·485–1·122)
Induction regimen	IMiD and PI (n=196)	30	30	0·966	(0·647–1·442)
	PI without IMiD (n=389)	59	59	0·667	(0·510–0·874)
	PI exposed (n=585)	89	89	0·750	(0·600–0·938)
	IMiD without PI (n=71)	11	11	0·497	(0·254–0·973)
Age	<60 years (n=356)	58	49	0·835	(0·620–1·125)
	≥60 years and <75 years (n=300)	42	51	0·662	(0·480–0·914)
Race	White (n=528)	80	82	0·650	(0·511–0·827)
	Asian (n=95)	15	14	0·858	(0·500–1·474)
Region	EMEA (n=518)	77	81	0·717	(0·565–0·910)
	APAC (n=121)	19	17	0·865	(0·518–1·444)
Pre-induction ISS stage	I (n=245)*	38	36	0·678	(0·471–0·975)
	II (n=221)	33	35	0·876	(0·611–1·256)
	III (n=190)	29	29	0·661	(0·438, 0·998)
Response at study entry	CR (n=225)	33	36	0·881	(0·593–1·307)
	VGPR (n=294)	45	44	0·686	(0·498–0·945)
	PR (n=137)*	21	20	0·693	(0·440–1·093)
Cytogenetic risk	High-risk (n=115)	15	21	0·625	(0·383–1·019)
	Corresponding standard-risk (n=404)	64	58	0·648	(0·490–0·857)
	Unclassifiable (n=137)	21	21	1·126	(0·685–1·850)
Renal function based on baseline creatinine clearance	<60 mL/min (n=58)	10	8	0·708	(0·240–2·090)
	≥60 mL/min (n=595)	90	92	0·738	(0·592–0·920)



APAC=Asia-Pacific. CI=confidence interval. CR=complete response. EMEA=Europe, the Middle East and Africa. HR=hazard ratio. IMiD=immunomodulatory drug. ISS=International Staging System. PI=proteasome inhibitor. PR=partial response. VGPR=very good partial response.

Some subgroup data are not shown due to small patient numbers.

*There are two different N-values for pre-induction ISS I and response of PR because the first rows are the stratification variables and are per local site data, whereas the latter rows are per sponsor/ independent review committee review.