Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial

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Summary

Background Maintenance therapy following autologous stem cell transplantation (ASCT) can delay disease progression and prolong survival in patients with multiple myeloma. Ixazomib is ideally suited for maintenance therapy given its convenient once-weekly oral dosing and low toxicity profile. In this study, we aimed to determine the safety and efficacy of ixazomib as maintenance therapy following ASCT.

Methods The phase 3, double-blind, placebo-controlled TOURMALINE-MM3 study took place in 167 clinical or hospital sites in 30 countries in Europe, the Middle East, Africa, Asia, and North and South America. Eligible participants were adults with a confirmed diagnosis of symptomatic multiple myeloma according to International Myeloma Working Group criteria who had achieved at least a partial response after undergoing standard-of-care induction therapy followed by high-dose melphalan (200 mg/m²) conditioning and single ASCT within 12 months of diagnosis. Patients were randomly assigned in a 3:2 ratio to oral ixazomib or matching placebo on days 1, 8, and 15 in 28-day cycles for 2 years following induction, high-dose therapy, and transplantation. The initial 3 mg 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 intention-to-treat analysis. Safety was assessed in all patients who received at least one dose of ixazomib or placebo, according to treatment actually received. This trial is registered with ClinicalTrials.gov, number NCT02181413, and follow-up is ongoing.

Findings Between July 31, 2014, and March 14, 2016, 656 patients were enrolled and randomly assigned to receive ixazomib maintenance therapy (n=395) or placebo (n=261). With a median follow-up of 31 months (IQR 27·3–35·7), we observed a 28% reduction in the risk of progression or death with ixazomib versus placebo (median PFS 26·5 months [95% CI 23·7–33·8] *vs* 21·3 months [18·0–24·7]; hazard ratio 0·72, 95% CI 0·58–0·89; p=0·0023). No increase in second malignancies was noted with ixazomib therapy (12 [3%] patients) compared with placebo (eight [3%] patients) at the time of this analysis. 108 (27%) of 394 patients in the ixazomib group and 51 (20%) of 259 patients in the placebo group experienced serious adverse events. During the treatment period, one patient died in the ixazomib group and none died in the placebo group.

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

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Introduction

Despite recent advances in the treatment of multiple myeloma, 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, and it has been approved for use in this setting.[1–4] A meta-analysis[5] showed discontinuation as a result of treatment-emergent adverse events in 29% of the lenalidomide maintenance group and 12% of the placebo or observation group. Additionally, this meta-analysis showed that lenalidomide did not demonstrate an overall survival benefit in high-risk patients.[5] 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.[6–8] However, bortezomib is not well suited for long-term use given the need for parenteral administration and risk of peripheral neuropathy.[6] At the time of trial design, there were

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Research in context

Evidence before this study

Studies of post-autologous stem cell transplantation (ASCT) maintenance therapy in newly diagnosed multiple myeloma have been extensively published and include phase 3 studies and meta-analyses. These reports are widely available and well known to the authors; therefore, no further literature search was conducted.

Maintenance therapy has been extensively explored as a strategy for prolonging the duration of disease control and potentially survival following ASCT for patients with newly diagnosed multiple myeloma. Early studies investigated interferon alfa and corticosteroids for use in this setting; however, long-term administration of these agents was limited by high discontinuation rates and severe toxicity. Prior to this study, maintenance with thalidomide has been 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 HOVON-65/GMMG-HD4 trial, patients were randomly assigned prior to induction to receive bortezomib, doxorubicin, and dexamethasone (PAD) or 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 most patients worldwide not receiving maintenance therapy. A 2017 meta-analysis of the CALGB 100104, GIMEMA RV-MM-PI-209, and IFM 2005-02 trials showed a significant overall survival benefit for lenalidomide maintenance versus placebo or no maintenance, with rates of discontinuation as a result of treatment-emergent adverse events of 29% and 12%, respectively. Subsequently, lenalidomide maintenance was approved in February, 2017, for use in the USA and Europe in the post-transplant setting. Although 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 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 treatment for multiple myeloma, and the benefit of proteasome inhibitor-based maintenance has not been shown in a placebo-controlled phase 3 trial. 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 second primary malignancies and low occurrence of peripheral neuropathy, supporting ixazomib as a valuable alternative to lenalidomide maintenance therapy in responding patients post ASCT.

Implications of all the available evidence

Multiple myeloma is a heterogeneous disease, requiring individualised treatment strategies for patients. Ixazomib maintenance provides a valuable treatment alternative for patients who are unable to tolerate currently available agents. Additional studies of ixazomib combinations and treatment to progression are ongoing to further improve patient outcomes.

no approved or established maintenance therapies following induction, high-dose therapy, and transplantation for newly diagnosed patients with multiple myeloma. Ixazomib is a proteasome inhibitor approved for treatment of relapsed or refractory multiple myeloma in combination with lenalidomide and dexamethasone.[9,10] Ixazomib might be suitable for maintenance therapy given its convenient once-weekly oral dosing,[11] tolerability, and favourable toxicity profile. We investigated the PFS benefit and safety and tolerability profile associated with ixazomib as maintenance therapy following ASCT.

Methods

Study design and participants

This phase 3, double-blind, placebo-controlled trial was done in 167 clinical or hospital sites in 30 countries in Europe, the Middle East, Africa, Asia, and North and South America (appendix). Eligible participants were adults with a confirmed diagnosis of symptomatic multiple myeloma according to International Myeloma Working Group (IMWG) criteria who had achieved at least a partial response after undergoing standard-of-care induction therapy followed by high-dose melphalan

(200 mg/m²) conditioning and single ASCT within 12 months of diagnosis. Induction therapy must have included a proteasome inhibitor or an immunomodulatory drug. Patients must have started screening no earlier than 75 days post transplant and completed screening within 15 days. Patients must have had an Eastern Cooperative Oncology Group performance status of 0–2. Patients required an absolute neutrophil count of at least 1000 per mm³ and a platelet count of at least 75 000 per mm³. Platelet transfusions to help patients meet the eligibility criteria were not allowed within 3 days before randomisation. Patients must have had a total bilirubin no greater than 1·5 times the upper limit of the normal range (ULN), alanine aminotransferase and aspartate aminotransferase no greater than 3×ULN, and a calculated creatinine clearance of at least 30 mL/min. Locally obtained cytogenetic results at any time before transplant and documented International Staging System (ISS) disease staging at diagnosis were required (see appendix for detailed eligibility criteria). Patients with multiple myeloma that had relapsed following primary therapy or was not responsive to primary therapy, including patients with stable disease following ASCT, were not eligible for this study. Patients must not have received post-ASCT consolidation therapy or a double (tandem) ASCT. 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.

Randomisation and masking

Patients were randomised 3:2 to receive either ixazomib or matching placebo capsule, no later than 115 days post-transplant. 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 or very good partial response *vs* partial response) at screening. Patient eligibility was confirmed by a project clinician or designee at the sponsor before randomisation by the investigator into the study. After written informed consent was obtained, the patient was assigned an enrolment code (country specific, site specific, and patient specific) using an interactive voice or web response system; randomisation was centralised, with patients randomised sequentially as they became eligible at a centre. 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 randomisation scheme was generated by an independent statistician at the sponsor. Patients, investigators, and study staff were blinded to treatment allocation.

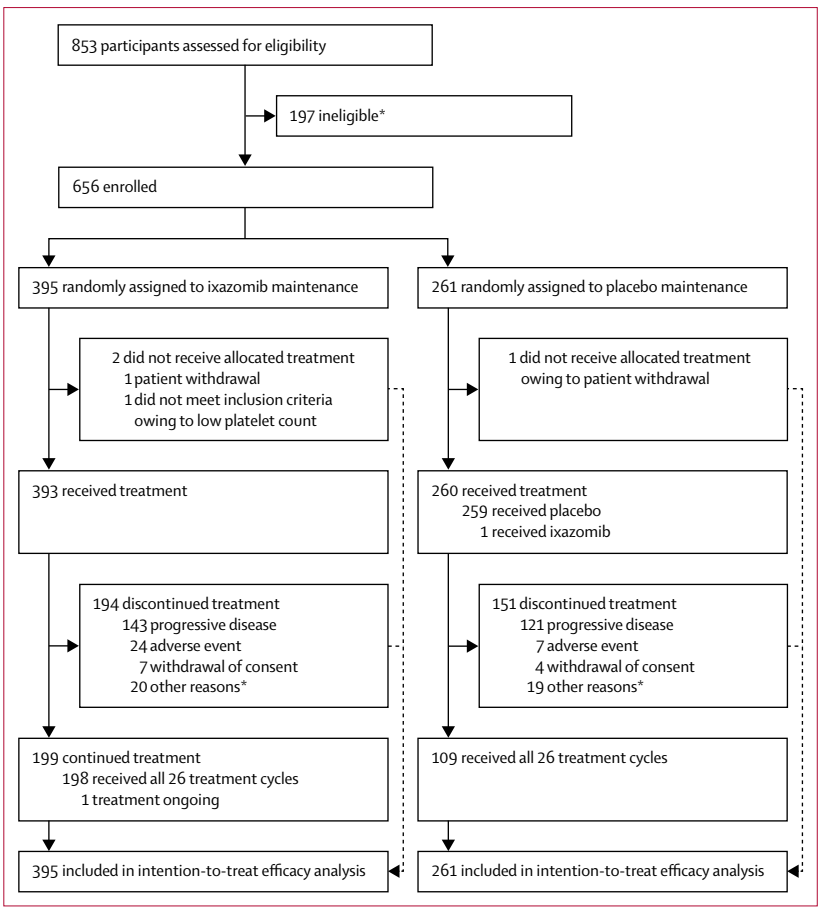

Figure 1: **Trial profile**
At data cutoff for this analysis, 41 participants assigned to ixazomib had discontinued the study (38 because of patient withdrawal, one was lost to follow-up, and two for other reasons) and 28 participants assigned to placebo had discontinued the study (26 because of patient withdrawal, one was lost to follow-up, and one for other reasons; see appendix for details). *Additional details on patient ineligibility are provided in the appendix.

Procedures

Patients received 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). Both study drugs were provided by the study sponsor. Dose adjustments for toxicities were permitted using protocol-specified dose-modification guidelines. Patients continued treatment for approximately 24 months (to the nearest complete cycle; if there were no treatment delays, this would be equivalent to 26 cycles) or until progressive disease or unacceptable toxicity, whichever occurred first. Study visits occurred on day 1 of each cycle, or every 28 days. Patients attended an end-of-treatment visit 30 days after receiving their last dose of study drug, and were followed until death, unless withdrawn.

Response and progressive disease assessments were based on central laboratory M-protein results, plus local bone marrow and imaging data, using IMWG 2011 criteria,[12] as evaluated by an independent review committee blinded to both treatment assignment and

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See Online for appendix

	Ixazomib group (n=395)	Placebo group (n=261)	All participants (n=656)
Age			
Median (years)	58 (52–63)	60 (54–64)	58 (52–64)
<60 years	229 (58%)	127 (49%)	356 (54%)
≥60 years and <75 years	166 (42%)	134 (51%)	300 (46%)
Sex			
Female	143 (36%)	99 (38%)	242 (37%)
Male	252 (64%)	162 (62%)	414 (63%)
Race*			
Asian	59 (15%)	36 (14%)	95 (14%)
White	315 (80%)	213 (82%)	528 (80%)
Other or not reported	21 (5%)	12 (5%)	33 (5%)
Type of myeloma at initial diagnosis			
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†			
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‡			
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§			
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¶			
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‖			
Proteasome inhibitor without immunomodulatory drug	234 (59%)	155 (59%)	389 (59%)
Immunomodulatory drug without proteasome inhibitor	43 (11%)	28 (11%)	71 (11%)
Proteasome inhibitor plus immunomodulatory drug	118 (30%)	78 (30%)	196 (30%)
Response after ASCT (by investigator)			
Stringent complete response	52 (13%)	39 (15%)	91 (14%)
Complete response	80 (20%)	54 (21%)	134 (20%)
Very good partial response	179 (45%)	115 (44%)	294 (45%)
Partial response	84 (21%)	53 (20%)	137 (21%)
MRD testing			
Tested	357 (90%)	228 (87%)	585 (89%)
Not tested	38 (10%)	33 (13%)	71 (11%)
MRD status at study entry**			
Negative	117/357 (33%)	75/228 (33%)	192/585 (33%)
Positive	225/357 (63%)	139/228 (61%)	364/585 (62%)
Not evaluable	15/357 (4%)	14/228 (6%)	29/585 (5%)

(Table 1 continues on next page)

investigator assessment of response. Response assessments were done every treatment cycle and every 4 weeks during the PFS follow-up period until progressive disease (appendix). All cytogenetic evaluations were done locally according to local standards and using locally defined thresholds for positivity, with no prespecified cutoffs; cytogenetic data were centrally reviewed and interpreted based on local thresholds. Bone marrow samples were evaluated locally at screening and whenever a new complete response was suspected. Bone marrow aspirate samples were collected for minimal residual disease (MRD) assessment at screening and at cycle 13 and cycle 26 for all patients in complete response and very good partial response, and whenever a bone marrow aspiration was done to confirm a new suspected complete response. Samples were assessed for MRD by eight-colour flow cytometry technology (10^{-5} sensitivity). We assessed overall health-related quality of life through patient self-reported instruments including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and MY-20 instruments. These assessments were completed by the patient at screening; at the start of every cycle (C30) or at the start of cycles 1, 4, 7, 10, 13, 16, 19, 22, and 25 (MY-20); at end of treatment, and then every 4 weeks until disease progression, and every 12 weeks following disease progression. Blood samples for ixazomib were collected for population pharmacokinetic analysis during day 1 cycle 1, 1 h and 4 h post-dose, and within 4 h pre-dose on days 8 and 15 of cycle 1, days 1 and 8 of cycle 2, and day 1 of cycles 3–10. For more details, see the appendix.

Outcomes

The primary endpoint was PFS, defined as time from date of randomisation to date of first documentation of progressive disease or death due to any cause. Overall survival was a prespecified 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 progressive disease or subsequent therapy, time to progression (measured as time from randomisation to date of first documented progression, with patients who die prior to progressive disease 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 progressive disease on next-line treatment or death from any cause, whichever occurred first), overall survival 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 MRD-negative status. Additional endpoints are listed in the appendix.

Statistical analysis

The study used a closed sequential testing procedure for the primary endpoint of PFS and key secondary endpoint of overall survival in this order. PFS was tested at a two-sided α of 0·05, and overall survival was tested at a significance level determined by the O'Brien-Fleming α spending function (Lan-Demets method[13]). Due to the closed sequential testing property, the family-wise type I error was strongly controlled for both PFS and overall survival. Two interim analyses, plus a final analysis, were planned to test overall survival. Total sample size was calculated to provide 80% power (two-sided α of 0·05) to test for a 43% improvement in overall survival (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 α of 0·05 for PFS benefit. All other efficacy endpoints were tested at a two-sided α of 0·05. The second interim analysis will take place when approximately 200 deaths have occurred. If overall survival significance is not claimed, the number of death events at final analysis will be determined according to a prespecified event size adaptation rule, with an event cap of approximately 350 events.

Analysis populations are defined in the appendix. The intention-to-treat 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 (two-sided α of 0·05) used for inter-arm comparisons of time-to-event endpoints. Patients without progressive disease data were censored at the date of last response assessment that was stable disease or better. Subgroup analyses were done 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. 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, SVR and MAD. 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.

	Ixazomib group (n=395)	Placebo group (n=261)	All participants (n=656)
(Continued from previous page)			
Time from diagnosis to first maintenance dose (months)	9·5 (8·2–11·2)	9·4 (8·3–11·4)	9·5 (8·3–11·3)
Time from ASCT to first maintenance dose (months)	3·4 (3·1–3·6)	3·4 (3·1–3·6)	3·4 (3·1–3·6)

Data are n (%), n/N (%), or median (IQR). ISS=International Staging System. ECOG=Eastern Cooperative Oncology Group. ASCT=autologous stem cell transplantation. MRD=minimal residual disease. *Race was self-reported. Additional categories were black or African American (seven [2%] patients in the ixazomib group and three [1%] patients in the placebo group) or other (two [<1%] in the ixazomib group and one [<1%] in the placebo group). 12 (3%) patients in the ixazomib group and eight (3%) patients in the placebo group did not report race. †The ISS consists of three stages: stage I: serum β2-microglobulin level lower than 3·5 mg/L (300 nmol/L) and albumin level 3·5 g/dL or higher; stage II: neither stage I or III; and stage III: serum β2-microglobulin 5·5 mg/L or higher (470 nmol/L). 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 one patient in the placebo group. §Creatinine clearance data missing for three patients, two in the ixazomib group, one in the placebo group. ¶High-risk cytogenetic abnormalities were detected by fluorescence in-situ hybridisation or karyotype analysis and were defined as del(17p), t(4;14), and t(14;16). If all three abnormalities were unknown, indeterminate or missing, the patient was called unclassifiable. There was no cutoff for defining the presence of del(17p). ||Per stratification data. **MRD limit of detection was $\geq 10^{-5}$ in 162 (19%) and 103 (19%) 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%) assessments, and $<10^{-6}$ in three (<1%) and one (<1%) assessment. The protocol required MRD assessment at study entry in patients whose response to ASCT as assessed by the investigator was complete response or very good partial response. However, some patients who had MRD assessments done were later found to have only a partial response.

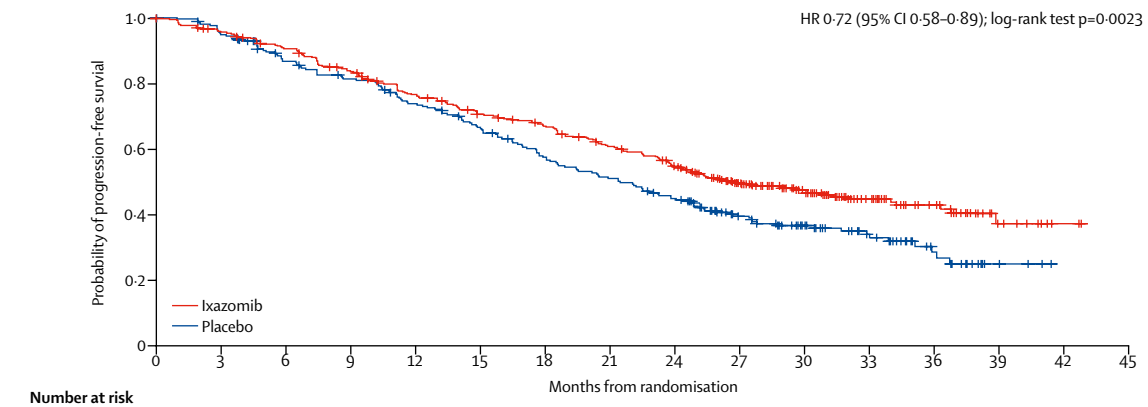
Table 1: **Baseline characteristics of patients in the intention-to-treat population**

Results

Between July 31, 2014 and March 14, 2016, 853 patients were assessed for eligibility, of whom 656 were enrolled and randomly assigned to receive ixazomib maintenance therapy (n=395) or placebo (n=261; figure 1; appendix). Baseline patient demographic and disease characteristics seemed 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 (table 1). Cytogenetic analysis results showed that 115 (18%) participants 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 months (IQR 8·2–11·2) in the ixazomib group and 9·4 months (8·3–11·4) in the placebo group.

At data cutoff for this analysis (April 16, 2018), median follow-up was 30·9 months (IQR 27·1–35·6) in the ixazomib group and 31·3 months (27·4–35·7) in the placebo group. With 198 and 156 independent review committee-assessed progression or death events, we found a significant 28% reduction in risk of progression or death in the ixazomib group versus the placebo group, with median PFS of 26·5 months (95% CI 23·7–33·8) in the ixazomib group versus 21·3 months (18·0–24·7) in the placebo group (HR 0·72, 95% CI 0·58–0·89; p=0·0023; figure 2). Median time to progression was 26·6 months (23·7–33·8) in the ixazomib group and 21·4 months (18·1–24·7) in the placebo group.

The benefit of ixazomib was analysed on the basis of key baseline patient characteristics; the study was not powered to compare the primary endpoint between



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	Events/patients		HR (95% CI)
	Ixazomib (n=395)	Placebo (n=261)	
All subjects (n=656)	**198/395**	**156/261**	**0·72 (0·58–0·89)**
Pre-induction ISS stage (local)			
I (n=242)*	68/146	56/96	0·70 (0·49–1·01)
II or III (n=414)	130/249	100/165	0·73 (0·56–0·95)
Response after transplant			
Complete or very good partial (n=509)	142/305	118/204	0·71 (0·56–0·91)
Partial (n=147)*	56/90	38/57	0·74 (0·48–1·12)
Induction regimen			
Immunomodulatory drug and proteasome inhibitor (n=196)	61/118	41/78	0·97 (0·65–1·44)
Proteasome inhibitor without immunomodulatory drug (n=389)	120/234	97/155	0·67 (0·51–0·87)
Proteasome inhibitor exposed (n=585)	181/352	138/233	0·75 (0·60–0·94)
Immunomodulatory drug without proteasome inhibitor (n=71)	17/43	18/28	0·50 (0·25–0·97)
Age			
<60 years (n=356)	118/229	74/127	0·84 (0·62–1·12)
≥60 years and <75 years (n=300)	80/166	82/134	0·66 (0·48–0·91)
Race			
White (n=528)	148/315	126/213	0·65 (0·51–0·83)
Asian (n=95)	36/59	25/36	0·86 (0·50–1·47)
Region			
EMEA (n=518)	150/306	129/212	0·72 (0·56–0·91)
APAC (n=121)	44/76	26/45	0·86 (0·52–1·44)
Pre-induction ISS stage			
I (n=245)*	69/151	55/94	0·68 (0·47–0·98)
II (n=221)	76/129	55/92	0·88 (0·61–1·26)
III (n=190)	53/115	46/75	0·66 (0·44–1·00)
Response at study entry			
Complete (n=225)	56/132	47/93	0·88 (0·59–1·31)
Very good partial (n=294)	93/179	73/115	0·69 (0·50–0·94)
Partial (n=137)*	49/84	36/53	0·69 (0·44–1·09)
Cytogenetic risk			
High risk (n=115)	38/61	38/54	0·62 (0·38–1·02)
Corresponding standard risk (n=404)	118/252	90/152	0·65 (0·49–0·86)
Unclassifiable (n=137)	42/82	28/55	1·13 (0·68–1·85)
Renal function based on baseline creatinine clearance			
<60 mL/min (n=58)	14/38	10/20	0·71 (0·24–2·09)
≥60 mL/min (n=595)	184/355	146/240	0·74 (0·59–0·92)

Figure 2: **Kaplan-Meier analysis of progression-free survival in the intention-to-treat population (A) and by patient subgroups (B)**
Patient subgroups were prespecified apart from renal function (post-hoc analysis). The study was not powered to compare the primary endpoint between the patient subgroups shown in panel (B). Some subgroup data (eg, other categories under race) are not shown due to small patient numbers. APAC=Asia Pacific. EMEA=Europe, the Middle East and Africa. HR=hazard ratio. ISS=International Staging System. *Different total numbers of patients are given for pre-induction ISS I and patients achieving partial response because the first rows are per the stratification variables whereas the latter rows are per the raw patient-level data.

	Ixazomib group (n=395)	Placebo group (n=261)	HR (95% CI) or RR (95% CI); p value
Response at study entry*			
Complete response	60 (15%)	54 (21%)	..
Very good partial response	213 (54%)	152 (58%)	..
Converted to complete response during study	92/213 (43%)	48/152 (32%)	RR 1·37 (1·03–1·81)
Partial response	89 (23%)	35 (13%)	..
Converted to very good partial response or better during study	47/89 (53%)	12/35 (34%)	RR 1·54 (0·94–2·54)
Stable disease	2 (<1%)	1 (<1%)	..
Progressive disease	1 (<1%)	0	..
Either very good partial response or partial response	302 (76%)	187 (72%)	..
Deepening response during treatment	139/302 (46%)	60/187 (32%)	RR 1·41 (1·10–1·80); p=0·0042
MRD status			
MRD-positive status at study entry	225/357 (63%)	139/228 (61%)	..
Converted to MRD-negative status at any time post-study entry	28/225 (12%)	10/139 (7%)	..
By 6 months post-study entry	3/225 (1%)	0	..
By 12 months post-study entry	17/225 (8%)	8/139 (6%)	..
By 18 months post-study entry	21/225 (9%)	9/139 (6%)	..
By 24 months post-study entry	23/225 (10%)	10/139 (7%)	..
Time to MRD-negative status (months)	Not estimable	Not estimable	HR 1·64 (0·79–3·42); p=0·18
Progression-free survival (months)	23·1 (20·2–25·7)	18·5 (15·7–21·9)	HR 0·70 (0·54–0·92); p=0·010
MRD-negative status at study entry	117/357 (27%)	75/228 (33%)	..
Patients with MRD-negative status retained at any subsequent evaluation	73/117 (62%)	38/75 (51%)	p=0·11
Time to documented MRD-positive status, progression, or death (months)	Not estimable (38·6–not estimable)	24·6 (12·1–not estimable)	HR 0·57 (0·37–0·90); p=0·014
Progression-free survival (months)	38·6 (33·8–not estimable)	32·5 (19·3–not estimable)	HR 0·61 (0·39–0·97); p=0·034

Data are n (%), n/N (%), or median (95% CI). HR=hazard ratio. RR=relative risk. MRD=minimal residual disease. IRC=independent review committee. *Response at study entry is different than the investigator-determined response to autologous stem cell transplantation used to randomly assign patients. Based on the information provided by the investigator, the IRC was unable to establish an initial response state at the time of study entry for 30 patients in the ixazomib group and 18 patients in the placebo group. Additionally, there was one patient missing response by IRC at study entry in the placebo group.

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

these patient subgroups. We observed benefit for PFS in the ixazomib group versus the placebo group in patients who were aged 60 years or older (p=0·012) or who had ISS disease stage III before induction (p=0·047; figure 2). In patients with high cytogenetic risk, the proportion of patients achieving PFS at 24 months was numerically greater in the ixazomib group than the placebo group (Kaplan-Meier estimate 46% *vs* 24%). PFS was improved in the ixazomib group versus the placebo group in both proteasome inhibitor-naive patients (p=0·038) and in proteasome inhibitor-exposed patients (p=0·011).

Median time from randomisation to start of next line of therapy was 33·1 months (29·1–not estimable) in the ixazomib group and 27·6 months (24·5–31·0) in the placebo group. PFS2 data were not mature at data cutoff for this analysis (only 129 [20%] patients had experienced PFS2 events of death or disease progression on next line of therapy), and so PFS2 analysis was inconclusive due to insufficient events. Similarly, because overall survival data were not mature (only 93 [14%] deaths had occurred at data cutoff for this analysis), overall survival analysis was inconclusive due to insufficient events. Thus, the study remains blinded, and follow-up for PFS2 and overall survival continues.

Depth of response improved during maintenance therapy in 139 (46%) of 302 patients in the ixazomib group and 60 (32%) of 187 patients in the placebo group with very good partial response or partial response post transplantation (table 2). At study entry, of the 585 patients examined for MRD, most tested positive; the proportions testing positive or negative, or who were not evaluable or not tested seemed similar between treatment groups (table 1). A PFS benefit was observed in the ixazomib group versus the placebo group irrespective of MRD status at study entry (appendix). Median PFS in patients who had MRD-negative status at study entry was 38·6 months (95% CI 33·8–not estimable) in the ixazomib group versus 32·5 months (19·3–not estimable) in the placebo group. Among those who were MRD-positive, 28 (12%) patients in the ixazomib group and ten (7%) patients in the placebo group converted to MRD-negative status during maintenance therapy (table 2). Among patients who were

	Ixazomib group (n=394)	Placebo group (n=259)
Treatment and follow-up		
Follow-up (months)	30·9 (27·1–35·6)	31·3 (27·4–35·7)
Number of treatment cycles	25 (13–26)	22 (12–26)
Dose escalated to 4 mg at cycle 5	317/368 (86%)	222/242 (92%)
Duration of treatment at a dose of 4 mg (months)	15·2 (4·9–19·6)	16·6 (8·3–19·4)
Adverse events		
Any adverse event	382 (97%)	241 (93%)
Any drug-related adverse event	307 (78%)	149 (58%)
Any grade ≥3 adverse event	166 (42%)	67 (26%)
Any drug-related grade ≥3 adverse event	73 (19%)	13 (5%)
Any serious adverse event	108 (27%)	51 (20%)
Adverse event resulting in discontinuation of the study drug	28 (7%)	12 (5%)
Adverse event resulting in dose reduction of the study drug	73 (19%)	13 (5%)
Death during the treatment period*	1 (<1%)	0

Data are n (%) or median (IQR). *Death during the treatment period was recorded through 30 days after receiving the last dose of study drug.

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

already negative for MRD at study entry, 73 (62%) in the ixazomib group and 38 (51%) in the placebo group retained this status over the course of therapy (table 2).

We observed no difference in patient-reported quality of life in the ixazomib and placebo groups, with similar mean scores maintained in both groups from study entry to end of treatment (appendix). Analyses of other functioning, symptoms, and side-effects subscales (appendix) 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 or vomiting and diarrhoea, which were negatively affected 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[14] in relapsed or refractory multiple myeloma suggested no readily apparent pharmacokinetic differences between the two patient populations (appendix).

The safety population included 394 patients in the ixazomib group (two were excluded from the analysis and one patient from the placebo group was included in the analysis) and 259 in the placebo group (one was excluded from the analysis and another was instead included in the ixazomib group; appendix). Patients received a median of 25 treatment cycles (IQR 13–26) in the ixazomib group and 22 cycles (12–26) in the placebo group (table 3). 198 (50%) patients in the ixazomib group and 109 (42%) patients in the placebo group completed 24 months of treatment. Most patients in either group received a dose escalation from the starting dose of 3 mg to 4 mg (table 3). At data cutoff, 286 (72%) patients in the ixazomib group and 195 (75%) patients in the placebo group were still on study. A similar proportion of patients discontinued study treatment due to adverse events in both groups (table 3).

The most common haematological adverse events were neutropenia, thrombocytopenia, and anaemia whereas the most common non-haematological adverse events were infection, gastrointestinal disorders, and rash (table 4). A numerically higher proportion of patients experienced serious adverse events in the ixazomib group compared with the placebo group (table 3). One patient died during the treatment period in the ixazomib group and none died in the placebo group.

Peripheral neuropathy occurred in 73 (19%) patients in the ixazomib group and in 39 (15%) patients in the placebo group (table 4). 55 (75%) of the 73 patients who developed peripheral neuropathy events in the ixazomib group and 29 (74%) of the 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 12 (3%) patients in the ixazomib group and six (2%) patients in the placebo group. Thrombosis was reported in no patients in the ixazomib group and one (<1%) patient in the placebo group.

Thrombocytopenia occurred more frequently in the ixazomib group compared with the placebo group (table 4). Gastrointestinal adverse events were mostly low grade in both groups and were more common in the ixazomib group compared with the placebo group (table 4). 76 (19%) patients in the ixazomib group were given antiemetics compared with 11 (4%) in the placebo group. Herpes zoster occurred in 39 (10%) patients in the ixazomib group and in 14 (5%) patients in the placebo group; the protocol was amended during the trial to require prophylaxis. Herpes zoster without prophylaxis occurred in 33 (60%) of 55 patients in the ixazomib group and 12 (26%) of 47 patients in the placebo group; with prophylaxis, herpes zoster occurred in six (2%) of 339 patients and two (1%) of 212 patients, respectively. Adverse events within the pooled term of rash were reported in less than a third of patients, of whom seven (2%) in the ixazomib group and none in the placebo group reported grade 3 events (table 4). At the current follow-up, we observed no difference in the rate of new primary malignancy (table 4).

Discussion

Although ASCT prolongs PFS and overall survival in multiple myeloma, most patients eventually relapse.[15–17] 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—eg, interferon, dexamethasone, or thalidomide—have resulted in toxicity, without consistent or significant clinical benefit.[18–22] Lenalidomide

	Ixazomib group (n=394)			Placebo group (n=259)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Common haematological adverse events 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 non-haematological adverse events 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 adverse events 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%)
Hypotension or orthostatic hypotension	4 (1%)	1 (<1%)	0	1 (<1%)	0	0
New primary malignant tumour‡	12 (3%)	..	..	8 (3%)	..	..

Table includes all adverse events that occurred in at least 10% of all patients or were of clinical interest; additional adverse events that occurred, by MedDRA high-level term, are listed in the appendix. MedDRA=Medical Dictionary for Regulatory Activities. SOC=system organ classes. *Data were based on a standardised 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 papular, rash erythematous, rash pruritic, drug eruption, pruritus generalised, rash, urticarial, dermatitis allergic, rash generalised, dermatitis acneiform, erythema multiforme, rash pustular, and rash vesicular. †One patient in the ixazomib group had a grade 5 adverse event of pneumonia. ‡Occurrency of a new primary malignant tumour is not graded.

Table 4: **Common adverse events in the safety population**

maintenance therapy has consistently resulted in a significant improvement in PFS and is the current approved treatment standard in many countries; however, lenalidomide has several limitations including risk of fatigue, diarrhoea, and second malignancies.[1–5] To our knowledge, no study 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.[23] 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 HOVON-65/GMMG-HD4 trial.[6,7] Once-weekly ixazomib combined with lenalidomide and dexamethasone as an induction, consolidation, and maintenance remission strategy has been investigated and has shown favourable outcomes and tolerability.[24] In the TOURMALINE-MM3 double-blind, placebo-controlled trial, we show that ixazomib significantly prolongs PFS. Moreover, treatment was well tolerated, with minimal increase in serious adverse events 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.[5]

Post-transplant maintenance therapy in multiple myeloma has been shown to be an effective intervention, with the ability to prolong overall survival. The Intergroupe

Francophone du Myélome 2005-02 study[1] 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). Furthermore, the Cancer and Leukemia Group B 100104 study[2] 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 overall survival. A meta-analysis[5] has also shown 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 that 7-year survival was achieved by 62% of patients with lenalidomide maintenance and 50% of patients with placebo or observation. Another meta-analysis[25] of six maintenance therapy regimens suggested that lenalidomide maintenance was superior in terms of overall survival (HR 0·76, 95% CI 0·51–1·16), although the result was not statistically significant.

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 for the value of maintenance therapy in multiple myeloma and confirms the single-agent efficacy of a fixed duration of ixazomib in this disease. Although 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 longer than 5 months, whereas a benefit of longer than 2 years has been shown with lenalidomide maintenance therapy versus placebo or observation.[5] 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.[7] Previous clinical pharmacology conclusions across specific clinical contexts of use (eg, in patients with renal or hepatic impairment or during co-administration with interacting drugs) can be translated to this patient population.[26,27] Importantly, our study shows that ixazomib is well tolerated, with low rates of discontinuation (7% of patients) as a result of treatment-emergent adverse events, similar to placebo (5%), compared with up to 29% previously reported for lenalidomide.[5] However, the difference in time on therapy between ixazomib and lenalidomide trials might have contributed to the lower proportion of patients discontinuing treatment in the former. Therefore, for patients in whom lenalidomide therapy is not tolerated or not appropriate, the use of oral ixazomib maintenance might be an option, although we acknowledge that the findings of the present study do not specifically address the use of ixazomib in this population.

Future maintenance approaches incorporating ixazomib will probably favour a combination approach—eg, 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 multiple myeloma patients, which might 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 of 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 or 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 numerically higher with ixazomib (12%) than 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 several limitations. Although 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 multiple myeloma, and, other than in the USA, most 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 USA 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. It is now well established that use of continuous lenalidomide maintenance until progressive disease results in a significant overall survival benefit as well as PFS gain.[2,3] However, median duration of lenalidomide maintenance therapy reported in a meta-analysis was 28 months, with 22 months in the placebo or observation group.[5] 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 contrasts with the results reported in the FIRST trial,[31] 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. Although 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 overall survival analysis will be done when the preplanned number of events have been reached.

In this randomised, 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 multiple myeloma. It is an important alternative treatment option in this setting, and might have particular utility for patients who do not have access to or are unable to tolerate lenalidomide and potentially for patients with high-risk cytogenetics.

Contributors

MAD, HG, ZT, TS, NG, and RL designed the study. MAD, FG, FS, MB, RH, KCW, HG, VM, PM, CKM, APl, W-JC, MK, SZ, M-VM, AS, SI, GM, APa, and SVR were study investigators and enrolled 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 the manuscript for submission.

Declaration of interests

MAD is a consultant for Amgen, Celgene, Takeda, Janssen, and Bristol-Myers Squibb; has received honoraria from Amgen, Celgene, Takeda, and Janssen; and has participated in speaker bureaus for Amgen, Celgene, Takeda, and Janssen. FG has received honoraria from Amgen, Celgene, Takeda, Janssen, and Bristol-Myers Squibb and is a member of the advisory committee for Celgene, Takeda, Seattle Genetics, and Roche. FS has participated in speaker bureaus for Amgen, Celgene, Takeda, Abbvie, and Janssen and is a member of advisory boards for Amgen, Celgene, Takeda, Janssen, Bristol-Myers Squibb, Bayer, Adaptive, and Oncopeptides. MB has been a member on advisory boards for Janssen Cilag, Takeda, Amgen, and Sanofi and has participated in speaker bureaus for Janssen Cilag, Celgene, Takeda, and Amgen. RH provides consultancy for Takeda, Bristol-Myers Squibb, Amgen, Janssen, and Celgene; has received research funding from Takeda, Amgen, Janssen, and Novartis; and has received honoraria from Takeda, Bristol-Myers Squibb, Amgen, Janssen, and Celgene. KCW has received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, and Takeda and research funding from Amgen, Celgene, Janssen, and Sanofi. HG has participated in advisory boards for Adaptive Biotechnology, Amgen, Bristol-Myers Squibb, Celgene, Janssen, Sanofi, and Takeda; has received research funding from Amgen, Bristol-Myers Squibb, Celgene, Chugai, Janssen, Sanofi, Mundipharma, Takeda, and Novartis; and has received honoraria from ArtTempi, Bristol-Myers Squibb, Celgene, Chugai, Janssen, and Novartis. PM has participated in advisory boards for and received honoraria from Celgene, Amgen, Janssen, and Abbvie. W-JC has received honoraria from Takeda. MK provides consultancy for Amgen, Janssen, Takeda, and Celgene and has received research funding from Celgene and travel support from Takeda. SZ has received research funding from and participated in advisory boards for Takeda, Celgene, and Janssen. M-VM has received personal fees from Takeda, Janssen, Amgen, Celgene, GlaxoSmithKline, and Abbvie. AS provides consultancy for Specialised Therapeutics Australia; has received honoraria from Takeda, Celgene, Janssen, and Amgen; has participated in speaker bureaus for Takeda, Celgene, and Janssen; and has received research funding from Takeda, Celgene, Janssen, and GlaxoSmithKline. SI has received research funding from Takeda, Ono, Janssen, Celgene, Novartis, Chugai, Abbvie, Bristol-Myers Squibb, Kyowa-Hakko Kirin, Merck Sharp & Dohme, Daiichi Sankyo, Gilead, Teijin Pharma, and Astellas, and has received honoraria from Takeda, Janssen, Celgene, Ono, and Bristol-Myers Squibb. TS, KS, ZT, ABD, NG, and RL are employed by Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company. TS is also affiliated with the Department of Hematology, Charles University General Hospital, Prague, Czech Republic. APa is employed by and has ownership interests (stock options) in Millennium Pharmaceuticals; he is a consultant for and has received honoraria from Amgen, Novartis, Bristol-Myers Squibb, Genmab, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, and Merck; has received research funding from Amgen, Novartis, Bristol-Myers Squibb, Genmab, Celgene, Janssen-Cilag, Takeda, Sanofi Aventis, Merck and Binding Site; and has participated in a speakers bureau for Bristol-Myers Squibb. SVR declares no competing interests; their employer, the Mayo Clinic, received research funding for this clinical trial. VM, CKM, APl, and GM declare no competing interests.

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