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Ixazomib as consolidation and maintenance versus observation in patients with relapsed multiple myeloma eligible for salvage autologous stem-cell transplantation (Myeloma XII [ACCoRD]): interim analysis of a multicentre, open-label, randomised, phase 3 trial

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Summary

Background The efficacy of consolidation and maintenance in the context of salvage autologous haematopoietic stem-cell transplantation (HSCT) for relapsed multiple myeloma remains unclear. We aimed to assess whether consolidation after salvage autologous HSCT, using ixazomib, thalidomide, and dexamethasone, followed by maintenance with single agent ixazomib is superior to observation.

Methods This is an interim analysis of Myeloma XII (ACCorD; referred to as ACCorD hereafter), an open-label, randomised, controlled, phase 3 trial done at 79 hospitals in the UK. Eligible patients were aged 18 years or older, had relapsed multiple myeloma with measurable disease, an ECOG performance status of 2 or less with adequate renal, hepatobiliary, pulmonary, and cardiac function, and required treatment for first progressive disease occurring at least 12 months after first autologous HSCT. In a first randomisation, patients were assigned (1:1) to receive either conventional autologous HSCT with melphalan or augmented autologous HSCT with melphalan and ixazomib. In the second randomisation, reported here, patients were assigned (1:1) to consolidation using ixazomib, thalidomide, and dexamethasone (oral ixazomib 4 mg per day on days 1, 8, and 15, oral thalidomide 100 mg per day on days 1–28, and oral dexamethasone 40 mg per day on days 1, 8, 15 and 22 of 28-day cycles), followed by maintenance with single agent ixazomib (oral ixazomib 4 mg per day on days 1, 8, and 15 of 28-day cycles until disease progression or intolerance), or observation. The primary endpoint was progression-free survival, analysed by intention-to-treat. Safety was analysed per-protocol. This study is registered with ISRCTN, ISRCTN10038996, and EudraCT, 2016-000905-35, and recruitment is complete.

Findings Between Dec 12, 2017, and April 21, 2023, 206 patients entered the second randomisation (103 in the consolidation and maintenance group and 103 in the observation group). This prespecified interim analysis (data cutoff April 21, 2023), was done at a median follow-up of 27 months (IQR 13–38). Median progression-free survival was 20 months (95% CI 15–29) in the consolidation and maintenance group and 13 months (11–18) in the observation group (hazard ratio 0·55 [95% CI 0·39–0·78]; p=0·0006). Serious adverse events were reported in 29 (32%) of 92 patients in the consolidation and maintenance group compared with seven (7%) of 103 patients in the observation group. The most common serious adverse events were infections and infestations in both the consolidation and maintenance group and the observation group. The most common grade 3, 4, or 5 adverse events for patients in the consolidation and maintenance group were upper respiratory infection (seven [8%] of 92 patients). No deaths in the consolidation and maintenance group were deemed treatment related.

Interpretation ACCorD provides evidence that an orally administered, deliverable, and tolerable post-salvage autologous HSCT treatment regimen can improve the durability of response for transplantation-eligible patients at first relapse. The findings are of relevance to patients who had durable disease control from autologous HSCT in the first line, representing a viable alternative to continuous parentally-administered relapse therapies.

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Research in context

Evidence before this study

We searched PubMed on Dec 21, 2023, for clinical trials published since Jan 1, 2010, using the terms "myeloma", "transplant" and "salvage". Our search identified two randomised phase 3 studies of salvage autologous haematopoietic stem-cell transplantation (HSCT) in patients with multiple myeloma: Myeloma X and GMMG ReLApsE. Data from the Myeloma X study showed the superiority of salvage transplantation over non-transplantation consolidation in terms of progression-free survival and overall survival. Data from GMMG ReLApsE did not show an advantage of salvage transplantation over extended lenalidomide-based treatment.

Added value of this study

To the best of our knowledge, the UK Myeloma Research Alliance Myeloma XII (ACCoRD) trial registered more patients with relapsed multiple myeloma suitable for salvage transplantation from UK National Health Service hospitals than any previous interventional study; because of this, patients were representative of real-world practice. This is the only study to examine the effect of post-salvage autologous HSCT consolidation and maintenance. We observed a significant benefit of consolidation and maintenance on progression-free survival. This benefit was observed irrespective of the depth of response to re-induction therapy and salvage transplantation, tumour genomic risk stratification, or the duration of disease control from first autologous HSCT.

Implications of all the available evidence

The results of UK-MRA Myeloma XII trial provide the first randomised, prospective evidence for the use of consolidation and maintenance treatment following salvage transplantation. The durability of disease control with salvage autologous HSCT and maintenance, even when used with an orally administered, highly tolerable and affordable induction regimen, is comparable to many current parentally-delivered continuous novel-agent based non-transplantation strategies. Salvage autologous HSCT, combined with an appropriate consolidation and maintenance strategy, continues to have an important role in the management of relapsed transplantation-eligible myeloma.

Introduction

Multiple myeloma is one of the most common haematological malignancies, with an annual incidence of 7·2 cases per 100 000 population in the UK.[1] Despite therapeutic advances, multiple myeloma remains incurable with a 5-year net survival from diagnosis of 49·6% (95% CI 47·3–52·0).[2]

Salvage autologous haematopoietic stem-cell transplantation (HSCT) in multiple myeloma, defined as a second or subsequent intervention with high-dose chemotherapy and autologous HSCT after relapse from a previous autologous HSCT, induces superior durability of response[3] and improves overall survival[4] compared with non-transplantation consolidation. The availability of an increasing number of therapeutic options at first relapse (eg, continuous triplet regimens) has led to reduced use of salvage autologous HSCT, but at present there is no prospective evidence about whether consolidation and maintenance strategies could enhance outcomes from salvage autologous HSCT, which has been shown compellingly at first line. This is an important evidence gap. Since most patients who relapse after first autologous HSCT are lenalidomide refractory following maintenance treatment, which is recommended by international guidance[5] and approved for use in the UK,[6] the efficacy of a proteasome inhibitor-containing post-salvage autologous HSCT consolidation and maintenance strategy using the second-generation oral proteasome inhibitor ixazomib is therefore a question of relevance.

Ixazomib is a second generation small molecule inhibitor of the 20S proteasome that is licensed for the treatment of multiple myeloma. Inhibition of the 20S proteasome with bortezomib has been validated as a therapeutic target in myeloma. However, ixazomib, an oral formulation, might be more suitable for use as a maintenance therapy. The established safety profile indicates that ixazomib is generally well tolerated, with less peripheral neuropathy than bortezomib, although upper and lower gastrointestinal toxicity has been reported.[7] Ixazomib has shown efficacy as treatment in relapsed myeloma in combination with an immunomodulatory agent and steroid,[8] and as maintenance treatment following first-line autologous HSCT.[9]

The UK Myeloma Research Alliance (UK-MRA) Myeloma XII (ACCoRD; referred to as ACCoRD hereafter) trial compared the efficacy and safety of consolidation after salvage autologous HSCT, using ixazomib, thalidomide, and dexamethasone, followed by maintenance with single agent ixazomib, compared with observation, in patients with first relapse of multiple myeloma. In this report, we describe the initial outcomes of the second randomisation in the ACCoRd trial following the second formal interim analysis.

Methods

Study design and participants

The UK-MRA ACCorD study[10] is a phase 3, open-label, randomised controlled trial with a single arm registration phase. Participants were initially enrolled to receive re-induction treatment (due to relapse after successful first-line treatment including first autologous HSCT) and, if required, peripheral blood stem-cell (PBSC) mobilisation and harvest. Subsequently, there were two potential randomisations in the study: the first was a transplantation randomisation that compared conventional salvage autologous HSCT (standard dose

melphalan conditioning) with augmented salvage autologous HSCT (melphalan augmented with ixazomib 4 mg given 4 days and 1 day before autologous HSCT). After successful completion of post-HSCT response assessment patients underwent a second randomisation to consolidation and maintenance treatment with ixazomib or observation. In this study, we report the results of consolidation and maintenance randomisation. Results of the single arm reinduction stage and the transplantation randomisation will be published elsewhere. Participants were recruited from 79 National Health Service (NHS) hospitals in England, Wales, and Scotland (appendix pp 2–3).

To commence treatment, eligible patients had to have a diagnosis of relapsed[11] multiple myeloma[12] with measurable disease[13] (according to International Myeloma Working Group [IMWG] criteria), required treatment for first progressive disease occurring at least 12 months after first autologous HSCT, and were aged at least 18 years with an Eastern Cooperative Oncology Group performance status of 2 or less with adequate renal, hepatobiliary, pulmonary, and cardiac function. Key exclusion criteria were having received treatment for relapsed disease other than local radiotherapy, therapeutic plasma exchange, or dexamethasone up to a maximum of 160 mg, CNS involvement with myeloma, grade 2 peripheral neuropathy, or failure to have recovered from the reversible effects of previous chemotherapy. Full eligibility criteria are in the appendix (pp 6–9). All participants provided written informed consent.

This study was approved by the national ethics review board (National Research Ethics Service, London, UK), institutional review boards of the participating centres, and the competent regulatory authority (Medicines and Healthcare Products Regulatory Agency, London, UK), and was conducted according to the Declaration of Helsinki and the principles of Good Clinical Practice as espoused in the Medicines for Human Use (Clinical Trials) Regulations.

This trial is registered with ISCRTN, ISRCTN10038996, and EudraCT, 2016-000905-35.

Randomisation and masking

Details of the first randomisation for salvage autologous HSCT are in the appendix (p 4). Participants who completed salvage autologous HSCT and had response assessment at 100 days were randomly assigned (1:1) at the second randomisation, to consolidation and maintenance or observation. A similar computer-generated minimisation algorithm with a random element was used to avoid chance imbalances in two variables determined at consolidation and maintenance randomisation: allocated salvage autologous HSCT (conventional or augmented) and response to allocated autologous HSCT (very good partial response [VGPR] or better [≥VGPR]).

Randomisations were done at the Clinical Trials Research Unit (University of Leeds, Leeds, UK) by authorised members of staff with a centralised automated 24 h web system according to a validated minimisation algorithm developed under the supervision of the lead trial statistician (DAC). Because of the nature of the intervention, the study was open-label, and study investigators and patients were aware of treatment assignment. The funders remained masked to treatment results until data cutoff.

Procedures

Sex and ethnicity were collected from electronic medical records where possible, and self-reported otherwise. Patients were free to refuse to disclose this information.

See Online for appendix

Re-induction procedures are described in the appendix (p 4). Participants with at least stable disease proceeded to PBSC mobilisation (if required, as per local institutional protocols). However, if sufficient PBSC were available from first-line autologous HSCT, this procedure was not compulsory. Patients were eligible for salvage autologous HSCT randomisation if they had adequate stem-cell mobilisation (defined as $\geq 2\times10^6$ CD34$^+$ cells per kg or $\geq 2\times10^8$ peripheral-blood mononuclear cells per kg) and maintained at least stable disease. Salvage autologous HSCT procedures are described in the appendix (p 4). Participants attaining at least a minimal response (according to International Myeloma Working Group Uniform Response Criteria[14]) following response assessment at 100 days after salvage autologous HSCT proceeded to consolidation and maintenance randomisation.

Participants allocated to consolidation and maintenance received two cycles of consolidation therapy using the same schedule as re-induction. Ixazomib (4 mg per day) was administered orally on days 1, 8, and 15 of each 28-day cycle. Thalidomide (100 mg per day) was administered orally on days 1–28. Dexamethasone (40 g per day) was administered orally on days 1, 8, 15, and 22 of each 28-day cycle. This was followed by maintenance treatment in 28-day cycles with ixazomib (4 mg per day) administered on days 1, 8, and 15 of each cycle. Maintenance treatment continued until progressive disease in the absence of toxicity. Participants allocated to observation received no further treatment as per protocol. The detailed dose reduction schedules are shown in the study protocol (appendix p 20).

Bone marrow aspirate samples at trial entry were enriched for CD138$^+$ cells (autoMACS; Miltenyi Biotec, Cologne, Germany) and plasma cell suspensions were fixed in methanol and acetic acid solution and stored at –20°C. The presence of translocations were investigated using interphase fluorescence in-situ hybridisation, with commercial probes, scored and image-captured using an AxioPlan microscope (Zeiss, Jena, Germany) with Isis software (version 5.0; MetaSystems, Altlußheim, Germany). CD138-purified plasma cells were tested with probes to identify the presence of *IGH*::*FRGR3* [t(4;14)(p16.3; q32)], *IGH*::*MAF* [t(14;16)(q32;q23)], *IGH*::*MAFB*

[t(14;20)(q32;q12)], and *CCND1*::*IGH* [t(11;14)(q13; q31)] fusion genes and *MYC* gene rearrangements. CD138-purified plasma cells were also assessed for copy number abnormalities in 17p (*TP53*), 1p, and 1q using multiplex ligation-dependent probe amplification (MLPA), with a commercial kit (SALSA MLPA P425 Multiple Myeloma; MRC-Holland, Amsterdam, the Netherlands) and analysed using Coffalyser software (MRC-Holland). For the detection of *TP53* deletion, a cutoff of 20% plasma-cell involvement was used, and for fusion gene detection the reporting was absolute (present *vs* absent). Adverse cytogenetic abnormalities were defined as gain(1q), t(4;14), t(14;16), t(14;20), or del(17p). Patients were classified into three cytogenetic risk groups for the preplanned analysis of outcomes: standard risk (no adverse cytogenetic abnormalities), high risk (one adverse abnormality), or ultra-high risk (≥2 adverse abnormalities).

Response and disease progression were assessed according to the IMWG Uniform Response Criteria[14] (appendix p 4). Bone marrow aspirates were obtained at trial entry 100 days after salvage autologous HSCT, 8 weeks after consolidation and maintenance randomisation, or after consolidation treatment and at 12 months after consolidation and maintenance randomisation. The presence of measurable residual disease was assessed using a validated flow cytometry assay performed at a single central laboratory (Haematological Malignancy Diagnostic Service, Leeds Cancer Centre, Leeds, UK) as previously reported.[15] Limit of detection of the assay met the IMWG sensitivity criteria (0·001% of leukocytes).

Adverse events were assessed at the start of each treatment cycle and were graded according to the US National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and categorised according to Medical Dictionary for Regulatory Activities System Organ Class. Adverse events were collected in the consolidation and maintenance group only, from registration until 30 days after the last dose of treatment. Serious adverse events were reported for all patients in both groups, from the date of consolidation and maintenance randomisation until 30 days after progression.

Outcomes

The primary endpoint of the first randomisation in the study was overall response rate to augmented salvage autologous HSCT at day 100; results will be reported separately. The primary endpoint of the second randomisation in the trial, reported here, was progression-free survival, defined as the time from consolidation and maintenance randomisation to progressive disease or death. Patients without an event were censored at time of last follow-up.

Secondary endpoints were: overall survival, defined as the time from randomisation to death from any cause or last follow-up; time to disease progression, defined as the time from randomisation to progressive disease or death (from multiple myeloma); upgrade in response after consolidation; second progression-free survival, defined as the time from randomisation to second progressive disease or death; time to next treatment, defined as the time from randomisation to commencement of next line treatment; safety and toxicity; and health-related quality of life assessed by the 30-item European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire, EORTC Myeloma Module Quality of Life Questionnaire (EORTC QLQ-MY20), and EQ-5D to estimate quality-adjusted life-years; and proportion of patients negative for measurable residual disease. Overall response rate following ixazomib, thalidomide, and dexamethasone re-induction, duration of response, continuous measurable residual disease, and engraftment kinetics were additional secondary endpoints, and will be reported elsewhere. Health-related quality of life will be reported elsewhere. Further subgroup analyses of progression-free survival and all subgroup analysis of overall survival will be reported at the final analysis, when the number of events will be higher.

Statistical analysis

The data cutoff date for this analysis was April 21, 2023. The hypothesis being tested was that consolidation and maintenance treatment improved progression-free survival compared with observation in patients with relapsed multiple myeloma after salvage autologous HSCT. The consolidation and maintenance randomisation of the trial was designed to have 80% power to show a 9-month increase in median progression-free survival in the consolidation and maintenance group (median 27 months) compared with observation group (median 18 months; hazard ratio [HR] 0·67) when a total of 192 progression-free survival events had been observed, at a two-sided 5% significance level. This calculation[16] assumed the time-to-event was exponentially distributed and that recruitment would last 60 months with a further 24 months of follow-up. A minimum recruitment target of 248 patients for randomisation to consolidation and maintenance or observation was specified, allowing for 5% dropout. These assumptions and estimated outcomes were based on improvements observed with maintenance therapy in first-line myeloma treatment.[17,18] A single formal interim analysis was prespecified in the original study protocol for the primary endpoint of progression-free survival. This was prespecified to occur when at least 50% of required progression-free survival events had been observed (n=124). However, due to the COVID-19 pandemic there were concerns regarding slow recruitment and following discussion with the internal trial team, the trial management group and independent oversight committees, it was agreed that the interim analysis would be done earlier (when 33% of required progression-free survival events had been observed) and that a second interim analysis would be required when 67% of required progression-free survival events had been observed, to allow the possibility of the release of

positive results allowing an early closure of recruitment. This was included in a protocol amendment on Feb 12, 2021 (appendix p 5). The first interim analysis for the second randomisation was completed and presented to the data monitoring and ethics committee on June 16, 2021, and no recommendation was made to release the interim anaylsis. The second interim analysis for the second randomisation was completed and presented to the data monitoring and ethics committee on June 2, 2023, and following their recommendation to report the interim anaylsis the results are presented in this manuscript.

Efficacy analyses were done in the intention-to-treat population, which included all randomly assigned patients. The safety population included all patients who received at least one dose of study treatment or agreed to participate in the observation intervention. For the primary endpoint, we estimated summaries of time to event per treatment group using the Kaplan-Meier method. We made comparisons between the allocated groups using the Cox proportional hazards model adjusted for the minimisation factors, to estimate HRs and 95% CIs. Second progression-free survival and overall survival were analysed in the same manner. The proportional hazards assumptions were assessed by plotting the hazards over time for each treatment group and by using the Kolmogorov-Type supremum test described by Lin and colleagues.[19] None of the model terms showed statistically significant evidence of violation of the assumption. Subgroup analysis methods are described in the appendix (p 5). The number and proportion of patients in each response and measurable residual disease category was summarised descriptively and exact 95% CIs were calculated using the Clopper-Pearson method.

We summarised toxicity, in terms of adverse events, descriptively. Cumulative incidence function curves were estimated by non-parametric maximum likelihood estimation.[20] Fine and Gray competing risks regression[21] was used to compare the hazard of second primary malignancies, adjusting for the minimisation factors, with death specified as a competing risk.

All reported p values are two-sided and were considered significant at an overall significance level of 5%. We used SAS (version 9.4) for statistical analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 31, 2017, and July 20 2022, 496 participants were enrolled in the study. 478 participants received ixazomib, thalidomide, dexamethasone (ITD) reinduction and 247 participants received salvage autologous HSCT (figure 1). The most common reasons for not undergoing salvage HSCT randomisation were progressive disease (n=131), withdrawal (n=51), and death without progression (n=19). The median time from salvage HSCT to consolidation and maintenance randomisation was

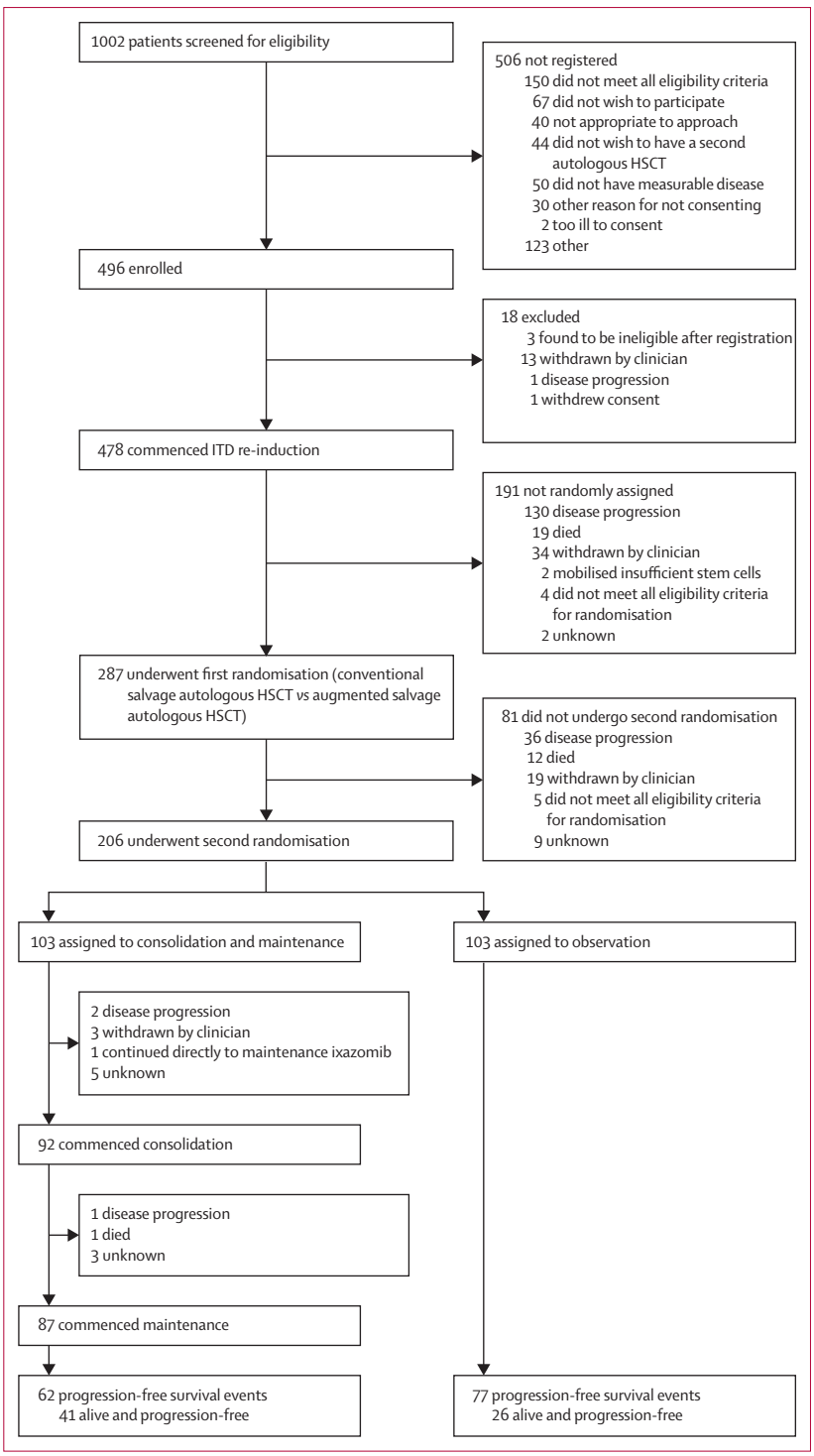

Figure 1: **Trial profile**
HSCT=haematopoietic stem-cell transplantation. IDT=ixazomib, thalidomide, and dexamethasone.

	Consolidation and maintenance (n=103)	Observation (n=103)
Age at registration, years		
Mean (SD)	60·2 (7·23)	61·7 (6·88)
Median (range)	61·0 (34·0–74·0)	63·0 (41·0–74·0)
Age at registration, years		
≤65	80 (78%)	68 (66%)
>65	23 (22%)	35 (34%)
Ethnicity		
White	91 (88%)	89 (86%)
Mixed	1 (1%)	1 (1%)
Asian	3 (3%)	2 (2%)
Black	5 (5%)	7 (7%)
Other ethnic group	0	1 (1%)
Not stated	0	2 (2%)
Missing data	3 (3%)	1 (1%)
Sex		
Male	75 (73%)	68 (66%)
Female	28 (27%)	35 (34%)
Time from first autologous HSCT to first disease progression, months		
Mean (SD)	41·3 (22·67)	40·5 (28·37)
Median (range)	34·0 (12·0–144·2)	33·5 (14·0–211·8)
Missing data	2 (2%)	0
ECOG performance status		
0	73 (71%)	73 (71%)
1	24 (23%)	29 (28%)
2	5 (5%)	0
Missing data	1 (1%)	1 (1%)
Serum lactate dehydrogenase		
Normal	80 (78%)	83 (81%)
Abnormal	10 (10%)	13 (13%)
Missing data	13 (13%)	7 (7%)
Serum calcium concentration at registration, mmol/L		
Mean (SD)	2·4 (0·13)	2·4 (0·12)
Median (Range)	2·4 (2·2–3·0)	2·4 (2·2–3·0)
Missing data	2 (2%)	0
Serum creatinine at registration, μmol/L		
Mean (SD)	88·1 (40·85)	85·0 (20·16)
Median (Range)	80·0 (49·0–421·0)	81·0 (49·0–172·0)
Missing data	1 (1%)	0
Paraprotein type at initial diagnosis		
IgG	61 (59%)	69 (67%)
IgA	22 (21%)	17 (17%)
IgM	3 (3%)	1 (1%)
Light chain only	14 (14%)	15 (15%)
Non-secretor	1 (1%)	0
Missing data	2 (2%)	1 (1%)
(Continued from previous column)		
International Staging System stage		
1	64 (62%)	65 (63%)
2	28 (27%)	28 (27%)
3	4 (4%)	3 (3%)
Missing data	7 (7%)	7 (7%)
Cytogenetic risk		
Standard	39 (38%)	43 (42%)
High	16 (16%)	18 (17%)
Ultra-high	6 (6%)	6 (6%)
Cytogenetics not performed	42 (41%)	36 (35%)
Thalidomide exposed	68 (66%)	65 (63%)
Lenalidomide exposed	17 (17%)	17 (17%)
Bortezomib exposed	53 (51%)	60 (58%)
Carfilzomib exposed	8 (8%)	7 (7%)
Previous lenalidomide maintenance received (lenalidomide refractory)	11 (11%)	5 (5%)
Previous carfilzomib maintenance received (carfilzomib refractory)	0	1 (1%)
Previous exposure to proteasome inhibitor	59 (57%)	66 (64%)
Relapse established		
Clinical	10 (10%)	9 (9%)
Biochemical	91 (88%)	94 (91%)
Missing data	2 (2%)	0
Haematopoietic cell transplantation-specific comorbidity index score		
0–1	96 (93%)	90 (87%)
2–3	5 (5%)	11 (11%)
≥4	1 (1%)	2 (2%)
Missing	1 (1%)	0
Response to re-induction		
≥VGPR	36 (35%)	41 (40%)
<VGPR	67 (65%)	62 (60%)
Response to allocated autologous HSCT		
≥VGPR	68 (66%)	60 (58%)
<VGPR	35 (34%)	43 (42%)

Data are n (%), unless otherwise stated. Additional baseline characteristics are included in the appendix (p 16). HSCT=haematopoietic stem-cell transplantation. ECOG=Eastern Cooperative Oncology Group. VGPR=very good partial response.

Table 1: **Baseline characteristics at initial trial registration**

4·3 months (range 3·4–6·7). 36 patients had disease progression and 12 patients died between the autolous HSCT randomisation and the consolidation and maintenance randomisation. 206 patients were randomly assigned between Dec 21, 2017, and April 21, 2023. 103 participants were assigned to the observation group and 103 participants were assigned to receive consolidation and maintenance. Patient and disease characteristics are shown in table 1. The median age was 62·5 years (range 34·0–78·0), 45 (9%) of 496 patients were older than 70 years, and 143 participants (69%) of 206 participants were men. The median time to progression from first autologous HSCT was 32 months (range 2–212). A single patient was registered to the trial in error after progressing 2 months after first autologous HSCT on serological criteria. 125 (61%) of

206 participants had received a proteasome inhibitor as part of their first-line treatment and 16 (8%) of 206 participants had previously received lenalidomide maintenance. 128 (62%) of 206 participants had an evaluable complete set of cytogenetic results, of whom 82 (64%) of 128 participants were classified as standard risk, 34 (27%) participants as high-risk, and 12 (9%) participants as ultra-high risk.

For this interim analysis of the maintenance randomisation, 103 patients were included in each group, of whom 77 (75%) of 103 participants in the observation group and 62 (60%) of 103 participants in the consolidation and maintenance group had progressive disease or had died. No participants were excluded from this analysis. After a median follow-up of 27 months (IQR 13–38), median progression-free survival from randomisation was 13 months (95% CI 11–18) in the observation group and 20 months (15–29) in the consolidation and maintenance group (HR 0·55 [95% CI 0·39–0·78]; p=0·0006; figure 2). 6-month progression-free survival estimates are in the appendix (p 16). Time to progression results were similar (appendix pp 10, 14). Median progression-free survival from the initiation of relapse therapy was 25 months (95% CI 21–28) in the observation group versus 30 months (26–38) in the consolidation and maintenance group.

In subgroup analyses, a benefit of consolidation and maintenance on progression-free survival was observed across most subgroups of participants (figure 3). Significant heterogeneity was observed within the subgroups defined by response after re-induction therapy (HR 0·97 [95% CI 0·54–1·72] for ≥VGPR; 0·41 [0·26–0·63] for <VGPR; $p_{heterogeneity}$= 0·011). No significant heterogeneity was observed within the subgroups defined by time to progression after first autologous HSCT (HR 0·19 [95% CI 0·04–0·90] for time to progression of <18 months; 0·35 [0·14–0·90] for time to progression of 18–24 months; 0·65 [0·44–0·97] for time to progression >24 months; $p_{heterogeneity}$= 0·055) or response after salvage HSCT (0·71 [0·46–1·11] for ≥VGPR; 0·44 [0·26–0·76] for <VGPR; $p_{heterogeneity}$= 0·151). No significant heterogeneity was identified within the subgroup defined by genetic risk (0·62 [0·33–1·15] for standard risk; 0·87 [0·35–2·19] for high risk; 0·11 [0·02–0·80] for ultra-high risk; $p_{heterogeneity}$=0·570). However, participants with ultra-high risk disease seemed to gain greater benefit in terms of progression-free survival from consolidation and maintenance than did patients with standard risk and high-risk disease (appendix pp 12–13).

At the time of interim analysis, 16 (16%) of 103 participants in the observation group and nine (9%) of 103 participants in the consolidation and maintenance group had died. Median overall survival was not reached in either group. 6-month overall survival estimates are in the appendix (p 16). The 2-year overall survival was 92·0% (95% CI 83·0–96·3) in the observation group and 91·1% (82·1–95·7) in the consolidation and maintenance group.

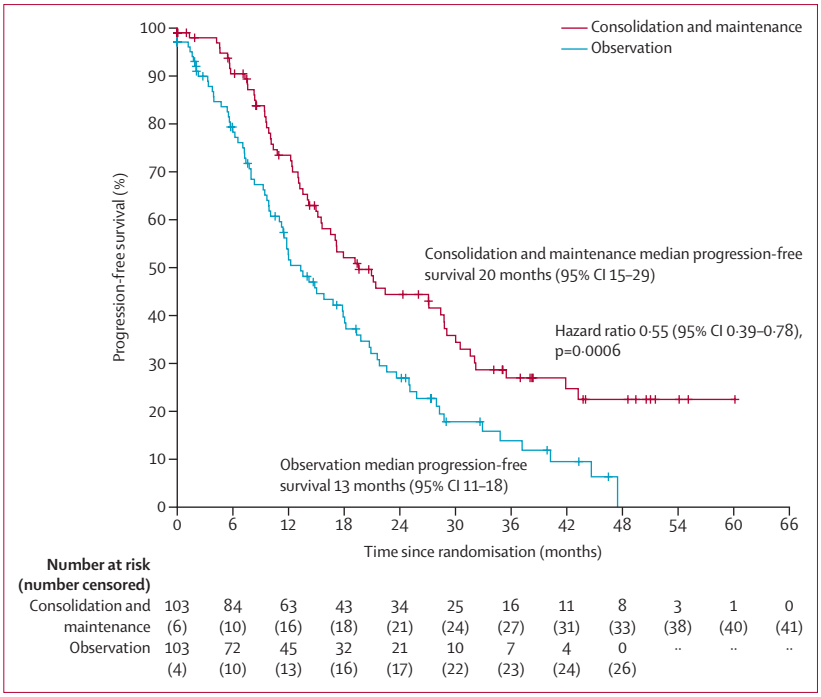

Figure 2: **Progression-free survival by allocated treatment**

No significant difference was observed between the observation and consolidation and maintenance groups for overall survival (HR 0·48 [95% CI 0·21–1·09]; figure 4A).

8 weeks after randomisation, 11 (11%) of 103 participants were negative for measurable residual disease in the observation group and seven (7%) of 103 participants were negative for measurable residual disease in the consolidation and maintenance group. The attained measurable residual disease results are in the appendix (p 16). One (1%; 95% CI 0·02–5·29) of 103 participants in the observation group had an upgraded minimal residual disease response, compared with three (3%; 0·60–8·28) of 103 participants in the consolidation and maintenance group.

27 (26%) of 103 participants in the observation group and 18 (17%) of 103 participants in the consolidation and maintenance group had a second disease progression or died. Median progression-free survival 2 was 44 months (95% CI 36 to NR) in the observation group and was not reached in the consolidation and maintenance group. 6-month second progression-free survival estimates are in the appendix (p 17). The 2-year progression-free survival 2 was 79·0% (95% CI 67·8 to 86·6) in the observation group and 89·8% (80·5 to 94·8) in the consolidation and maintenance group. The difference in progression-free survival 2 observed between the observation and consolidation and maintenance groups was not statistically significant (HR 0·56 [95% CI 0·30 to 1·01]; p=0·055; figure 4B).

53 (51%) of 103 participants in the observation group and 40 (39%) of 103 participants in the consolidation and

	Consolidation and maintenance		Observation		Hazard ratio (95% CI)	$p_{heterogeneity}$
	n/N	2-year progression-free survival estimate (95% CI)	n/N	2-year progression-free survival estimate (95% CI)		
Age, years						0·738
≥65	48/77	38·4% (26·3–50·3)	46/61	20·9% (10·7–33·4)	0·60 (0·40–0·91)	
>65	14/26	60·7% (37·9–77·4)	31/42	34·9% (19·9–50·3)	0·52 (0·27–1·00)	
Sex						0·839
Male	49/75	40·6% (28·6–52·2)	52/68	26·0% (15·5–37·8)	0·60 (0·40–0·89)	
Female	13/28	55·6% (31·3–74·3)	25/35	28·1% (12·9–45·5)	0·45 (0·22–0·93)	
International staging system stage						0·152
1	40/64	43·7% (30·0–56·6)	47/65	31·9% (19·9–44·4)	0·69 (0·45–1·05)	
2 or 3	19/32	43·4% (24·7–60·7)	24/31	18·5% (6·2–36·0)	0·51 (0·28–0·95)	
Missing	3/7	60·0% (12·6–88·2)	6/7	16·7% (0·8–51·7)	0·29 (0·05–1·72)	
ECOG performance status						0·645
0	48/73	45·8% (33·1–57·7)	58/73	26·9% (16·6–38·3)	0·58 (0·40–0·86)	
1 or 2	14/29	40·4% (20·5–59·5)	19/29	25·2% (9·8–44·2)	0·60 (0·30–1·22)	
Time to progression after first HSCT, months						0·055
<18	8/11	11·4% (0·6–39·4)	6/7	0	0·19 (0·04–0·90)	
18–24	8/12	45·5% (16·7–70·7)	19/22	12·1% (2·2–31·0)	0·35 (0·14–0·90)	
>24	46/80	48·8% (36·2–60·2)	52/74	33·9% (22·3–45·9)	0·65 (0·44–0·97)	
Risk status						0·570
Standard	18/29	51·4% (31·3–68·2)	23/31	41·5% (22·9–59·2)	0·62 (0·33–1·15)	
High	8/11	13·9% (0·7–45·2)	17/21	15·9% (3·9–35·1)	0·87 (0·35–2·19)	
Ultra-high	6/7	42·9% (9·8–73·4)	4/4	0	0·11 (0·02–0·80)	
Cytogenetics not fully performed	30/56	46·5% (31·3–60·4)	33/47	24·6% (12·0–39·6)	0·52 (0·31–0·87)	
Lenalidomide maintenance after first autologous HSCT						0·548
Yes	6/11	34·3% (8·2–63·3)	4/5	40·0% (5·2–75·3)	0·81 (0·22–3·02)	
No	56/92	45·5% (34·0–56·3)	73/98	26·1% (17·0–36·2)	0·61 (0·43–0·87)	
Proteasome inhibitor exposed in first-line						0·157
Exposed	38/59	35·6% (22·1–49·4)	46/66	25·5% (14·5–38·1)	0·75 (0·49–1·16)	
Not exposed	24/44	55·4% (38·4–69·5)	31/37	30·1% (15·8–45·7)	0·46 (0·27–0·79)	
Response after ixazomib, thalidomide, and dexamethasone re-induction						0·011
≥VGPR	22/36	48·8% (30·0–65·3)	26/41	37·7% (21·3–54·0)	0·97 (0·54–1·72)	
<VGPR	40/67	41·7% (28·5–54·3)	51/62	19·3% (10·0–30·9)	0·41 (0·26–0·63)	
Response after salvage HSCT						0·151
≥VGPR	41/68	47·0% (33·7–59·2)	39/60	30·8% (18·2–44·3)	0·71 (0·46–1·11)	
<VGPR	21/35	38·7% (20·7–56·5)	38/43	20·8% (9·8–34·6)	0·44 (0·26–0·76)	
Haematopoietic cell transplantation comorbidity index score						0·921
0	49/80	39·2% (27·5–50·8)	58/76	23·5% (13·9–34·6)	0·62 (0·42–0·91)	
1	8/16	64·3% (34·3–83·3)	8/14	39·7% (13·0–65·8)	0·44 (0·15–1·31)	
≥2	5/6	60·0% (12·6–88·2)	11/13	34·6% (10·9–60·2)	0·76 (0·24–2·43)	
Lactate dehydrogenase						0·893
≤ULN	51/80	42·0% (30·1–53·4)	65/83	26·9% (17·0–37·7)	0·57 (0·39–0·82)	
>ULN	3/10	75·0% (31·5–93·1)	8/13	27·8% (6·7–54·5)	0·45 (0·10–1·98)	
Unable to determine category	8/13	45·5% (16·7–70·7)	4/7	33·3% (4·6–67·6)	0·89 (0·24–3·31)	
Corrected serum calcium						0·885
<2·6 mmol/L	57/96	46·8% (35·5–57·3)	73/98	28·2% (18·8–38·2)	0·57 (0·40–0·80)	
≥2·6 mmol/L	4/5	0	4/5	0	0·14 (0·01–1·59)	
t(4:14) translocation						0·288
Detected	8/11	40·0% (12·3–67·0)	5/7	0	0·12 (0·02–0·63)	
Not detected	41/75	45·0% (32·0–57·2)	60/80	32·2% (21·5–43·3)	0·57 (0·38–0·86)	
No result available	13/17	44·1% (20·1–65·9)	12/16	8·7% (0·5–31·9)	0·54 (0·22–1·29)	
17p deletion						0·610
Detected	4/4	25·0% (0·9–66·5)	7/9	0	0·29 (0·06–1·54)	
Not detected	47/82	42·5% (30·3–54·1)	59/79	32·8% (21·9–44·1)	0·64 (0·44–0·94)	
No result available	11/17	56·7% (30·0–76·6)	11/15	9·3% (0·6–33·7)	0·44 (0·17–1·14)	
1q gain						0·748
Detected	12/22	39·7% (16·9–61·9)	24/30	19·4% (7·1–36·0)	0·57 (0·28–1·17)	
Not detected	39/65	43·0% (29·5–55·7)	42/59	36·3% (23·0–49·8)	0·65 (0·42–1·01)	
No result available	11/16	53·8% (26·8–74·8)	11/14	8·7% (0·5–32·1)	0·45 (0·18–1·14)	
Overall	**62/103**	**44·4% (33·6–54·6)**	**77/103**	**26·9% (18·0–36·7)**	**0·58 (0·41–0·81)**	

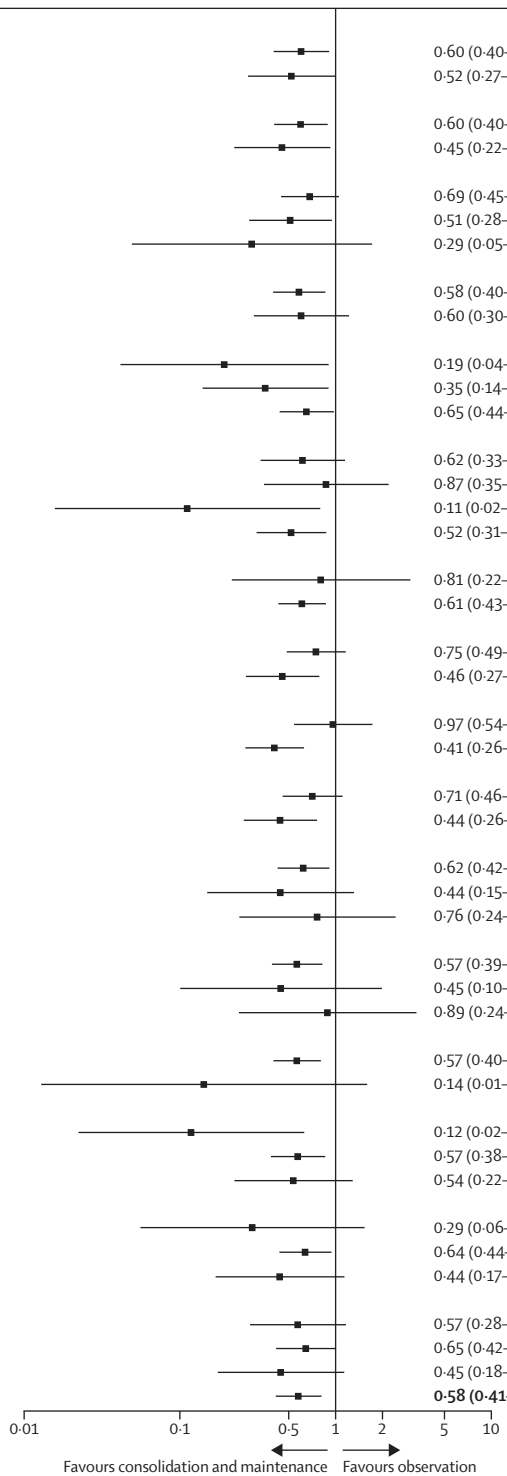

Figure 3: **Progression-free survival subgroup analysis**
n=number of events. N=number of participants. ECOG=Eastern Cooperative Oncology Group. HSCT=haematopoietic stem-cell transplantation. VGPR=very good partial response. ULN=upper limit of normal.

maintenance group commenced next-line treatment or died. Median time to next treatment was 22 months (95% CI 15–30) in the observation group and was 33 months (23 to NR) in the consolidation and maintenance group. 6-month time to next treatment estimates are in the appendix (p 17). The time to next treatment estimate at 2 years was 46·9% (95% Cl 35·3 to 57·7) in the observation group and 59·7% (47·7 to 69·8) in the consolidation and maintenance group. A significant difference in time to next treatment was observed between the groups: the median time to next treatment was longer in the consolidation and maintenance group than the observation group (HR 0·53 [95% CI 0·35 to 0·80]; p=0·0030; appendix p 15).

35 participants received treatment after progression in the consolidation and maintenance group compared with 52 participants in the observation group (appendix p 19). The majority of participants in both groups received lenalidomide-containing treatment as a third-line treatment (appendix p 19). 15 (19%) of 77 participants in the observation group subsequently received ixazomib-containing treatment.

Of 25 participants who died, the most common cause of death was myeloma (ten [63%] of 16 participants in the observation group; five [56%] of nine participants in the consolidation and maintenance group; appendix p 17). Four participants in the observation group and five participants in the consolidation and maintenance group (including one case of COVID-19) died of infection. One participant in the consolidation and maintenance group had a cardiac cause of death. In the observation group, one participant died of a second malignancy, one participant of respiratory illness, and one participant of a neurological illness.

Four participants in the observation group and five participants in the consolidation and maintenance group were diagnosed with a second primary malignancy (appendix pp 17–18). The 2-year cumulative incidence of second primary malignancies was similar between treatment groups (3·6% [95% CI 1·1–10·9] in the observation group *vs* 2·3% [0·6–8·9] in the consolidation and maintenance group). No significant difference was observed in time to first second primary malignancy between the observation and consolidation and maintenance groups (HR 1·43 [95% CI 0·39–5·21]; p=0·59). The overall incidence of second primary malignancy per 100 patient-years was 1·85 (95% CI 0·69–4·93) in observation group and 2·72 (95% CI 1·22–6·05) in the consolidation and maintenance group.

91 (88%) of 103 patients in the consolidation and maintenance group commenced ITD consolidation. One participant chose not to receive consolidation due to the COVID-19 pandemic and went straight to maintenance treatment. The median time from consolidation and maintenance randomisation to start of ITD consolidation was 7 days (range 0–97). Dose modifications consisting of reductions and omissions were applied to

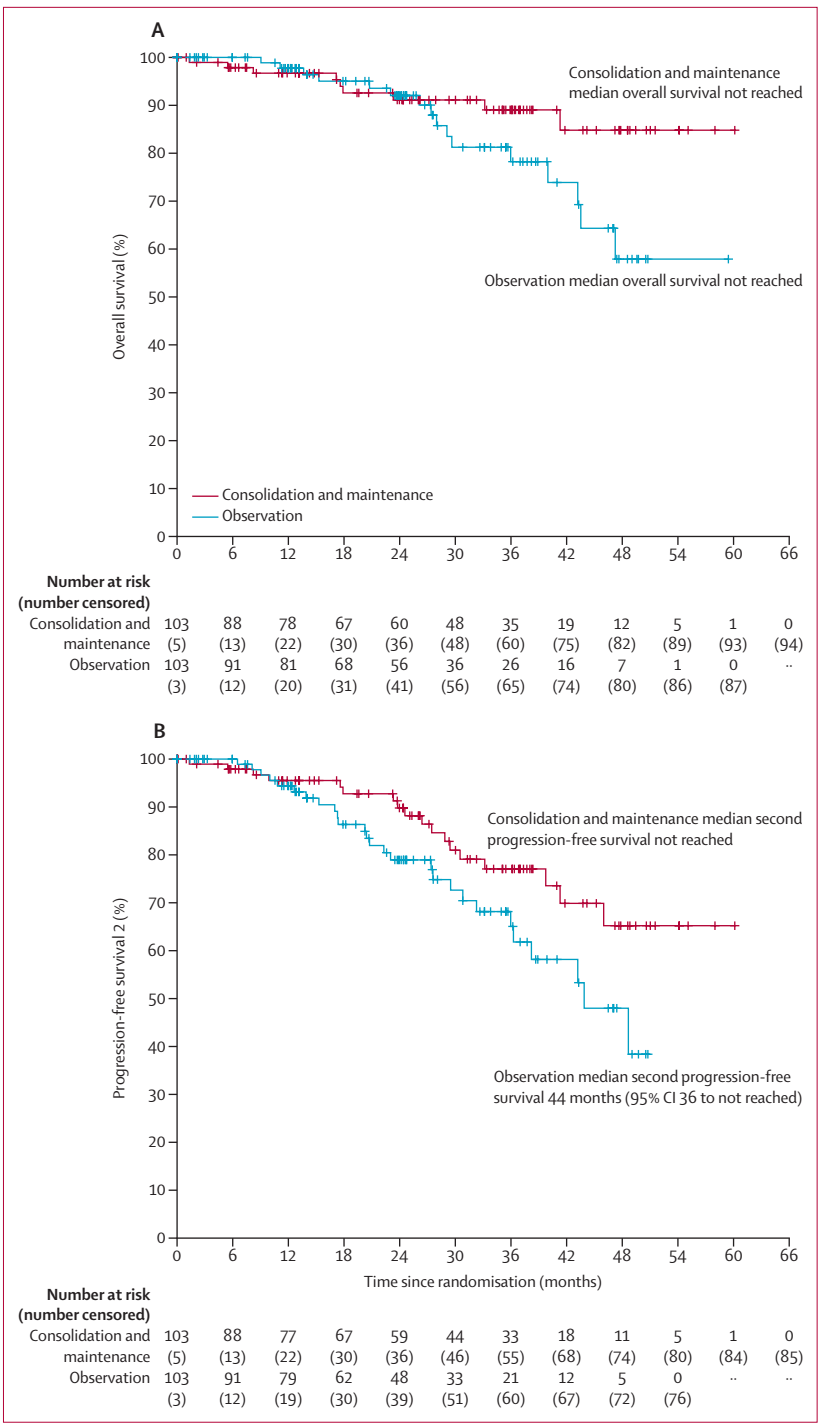

Figure 4: **Overall survival (A) and progression-free survival 2 (B) by treatment group**

27 (26%) of 103 participants allocated to ITD consolidation. 90 (87%) of 103 participants completed two cycles of ITD consolidation. Of these 90 participants, 85 (94%) continued to receive at least one cycle of maintenance treatment. The median time from consolidation and maintenance randomisation to start of maintenance was

	Grade 1–2	Grade 3	Grade 4	Grade 5
Peripheral sensory neuropathy	52 (57%)	0	0	0
Fatigue	41 (45%)	0	0	0
Upper respiratory infection	34 (37%)	7 (8%)	0	0
Platelet count decreased	27 (29%)	2 (2%)	3 (3%)	0
Constipation	27 (29%)	0	0	0
Nausea	24 (26%)	0	0	0
Back pain	21 (23%)	0	0	0
Diarrhoea	20 (22%)	1 (1%)	0	0
Cough	20 (22%)	0	0	0
Anaemia	18 (20%)	0	1 (1%)	0
Pain in extremity	15 (16%)	0	0	0
Rash maculo-papular	15 (16%)	0	0	0
Vomiting	14 (15%)	0	0	0
Dyspnoea	13 (14%)	0	0	0
Lymphocyte count decreased	12 (13%)	3 (3%)	0	0
Lung infection	11 (12%)	2 (2%)	0	1 (1%)
Dizziness	11 (12%)	0	0	0
Headache	11 (12%)	0	0	0
Insomnia	11 (12%)	0	0	0
Fever	10 (11%)	1 (1%)	0	0
Oedema limbs	8 (9%)	1 (1%)	0	0
Alanine aminotransferase increased	8 (9%)	0	1 (1%)	0
Neutrophil count decreased	7 (8%)	3 (3%)	0	0
White blood cell decreased	7 (8%)	1 (1%)	0	0
Urinary tract infection	4 (4%)	2 (2%)	0	0
Tooth infection	4 (4%)	1 (1%)	0	0
Toothache	3 (3%)	1 (1%)	0	0
Hypertension	1 (1%)	1 (1%)	0	0
Mucositis oral	1 (1%)	1 (1%)	0	0
Epistaxis	1 (1%)	1 (1%)	0	0
Syncope	0	1 (1%)	0	0
Gastrointestinal disorders-other	0	1 (1%)	0	0
Sepsis	0	0	1 (1%)	0

Grade 1–2 occurring in ≥10% of participants and any grade 3–5 event occurring in the safety population. Adverse events of all grades were collected only in the consolidation and maintenance group.

Table 2: **Adverse events in the consolidation and maintenance group (n=92)**

69·5 days (range 7·0–156·0). The median number of maintenance cycles was 15 (range 1–57). Dose modifications consisting of reductions, delays, and omissions were required for 36 (35%) of 103 participants in the consolidation and maintenance safety population (appendix p 18). Reasons for discontinuation of maintenance treatment are detailed in the appendix (p 19); two (2%) of 103 participants discontinued due to adverse events.

16 serious adverse events were reported in seven (7%) of 103 participants in observation compared with 42 serious adverse events in 29 (32 %) of 92 participants receiving consolidation and maintenance (appendix p 19). The most common MedDRA System Organ Class for serious adverse events occurring after randomisation was infections and infestations in both the observation and consolidation and maintenance groups. Adverse events were assessed in the 92 participants who received any dose of consolidation and maintenance treatment. The most common grade 3, 4, or 5 adverse events were upper respiratory infection (seven [8%] of 92 participants) and thrombocytopenia (five [5%] participants; table 2). Common adverse events of any grade were peripheral sensory neuropathy (52 [57%] of 92 participants in the consolidation and maintenance group), fatigue (41 [45%] participants), and upper respiratory infection (41 [45%] participants; table 2).

Discussion

The efficacy of salvage HSCT for managing relapse after a previous autologous HSCT in multiple myeloma has been established.[3] However, the durability of response is less than that observed when autologous HSCT is used in the first-line setting where with post-HSCT maintenance, the median progression-free survival has been extended to more than 5 years.[22] The use of post-salvage HSCT maintenance has been relatively unexplored in prospective trials, with the only published data from real-world registry-based retrospective analyses where both pre-salvage and post-salvage HSCT therapy were heterogeneous, limiting clinical practice-changing conclusions. The UK-MRA ACCoRD trial is, to the best of our knowledge, the largest study to assess salvage HSCT in relapsed multiple myeloma, and specifically consolidation and maintenance treatment after salvage HSCT. We have shown that progression-free survival, the primary endpoint of this study, is superior for consolidation and maintenance treatment versus observation. The findings are consistent with the results of studies in the front-line setting, which have demonstrated improved progression-free survival from consolidation and maintenance strategies,[22,23] including when ixazomib is used as a maintenance strategy.[9] This interim analysis demonstrates the enhanced durability of response from consolidation and maintenance is consistent across subgroups, without compromising disease response or durability at later lines of treatment (second progression-free survival), or overall survival. Analysis of time to next treatment showed an even greater benefit for consolidation and maintenance over observation, highlighting the importance of deeper disease control. The effect of consolidation and maintenance on health-related quality of life will be examined at a later pre-planned analysis for long-term follow-up. When overall survival is sufficiently mature, rank-preserving structural failure time methods will be used to test if the allocated treatment effect on overall survival was affected by treatment switching.

What is the role for salvage autologous HSCT in the modern therapeutic landscape in first relapse multiple myeloma? The benefit of a salvage HSCT over a

chemotherapy-based non-transplant, fixed duration consolidation is evident from the UK National Cancer Research Institute Myeloma X trial, where improved durability of response was associated with an overall survival benefit.[4] However, the role of salvage HSCT in the era of continuous novel agent therapy, and the utility of post-transplant consolidation and maintenance, well-proven in the front-line setting, have yet to be defined. The GMMG ReLApsE study was a randomised open-label phase 3, in which salvage HSCT plus lenalidomide maintenance was compared with continuous treatment with lenalidomide and corticosteroids;[24] on an intention-to-treat basis, no progression-free survival or overall survival advantage was observed, although it should be noted that with randomisation occurring at baseline in that study almost a third of participants did not receive the designated salvage HSCT after lenalidomide-dexamethasone re-induction, due to disease progression, adverse events, or withdrawal. The two trials examined different populations, with the ReLApsE study including patients receiving both second-line and third-line treatment and 38% of participants having received a tandem autologous HSCT in the first-line setting. In contrast, in our trial, all patients were receiving second-line treatment and none had received a tandem autologous HSCT in the first-line setting. Furthermore, the median progression-free survival in the GMMG trial was similar to the that reported in the autologous HSCT group of the NCRI Myeloma X trial,[3] where no post-salvage HSCT was delivered, whereas the median progression-free survival reported here for patients receiving post-salvage HSCT maintenance was longer than that reported in either the GMMG or Myeloma X trials.

A number of key novel agent combination trials in patients who had received 1–3 previous lines of therapy have reported durable responses, and within these trials, subgroups of patients who had received one previous line of treatment (not dissimilar to our trial population) have been reported. When making comparisons with such studies it is important to note that progression-free survival reported in our manuscript is from the post-salvage HSCT consolidation and maintenance randomisation in the study; progression-free survival measured from the initiation of relapse therapy was 25 months for the observation group and 30 months for the consolidation and maintenance group. Although a meta-analysis has not been performed, in the subgroup of patients with first relapse, the median progression-free survival reported across these studies of continuous novel agent regimens is in the range of 18–53 months. For example, for patients with one previous line of therapy, progression-free survival of 30 months was reported for carfilzomib-lenalidomide-dexamethasone in ASPIRE,[25] 27 months for daratumumab-bortezomib-dexamethasone in CASTOR,[26] and 53 months for daratumumab-lenalidomide-dexamethasone in POLLUX[27] (appendix p 19); with the exception of daratumumab, lenalidomide and dexamethasone,[27] the reported progression-free survival was similar, if not inferior to that reported in our trial where salvage autologous HSCT was maintained with ixazomib, a single oral agent. The combination of daratumumab-lenalidomide-dexamethasone might be unsuitable for patients relapsing on lenalidomide maintenance after first-line autologous HSCT. Moreover, clear advantages are that disease progression from the maintenance schedule in our trial is only on a single agent, as opposed to multi-agent refractoriness with key novel agent combinations in these trials, the regimen is steroid free, reducing long-term infective and metabolic challenges for patients, and delivery of a single agent is likely to be economically viable.

Since the inception of the ACCoRD trial, a number of new agents for treatment of relapsed and refractory myeloma have become accessible in routine clinical practice, including a number of immunotherapies targeting B-cell maturation antigen, G protein–coupled receptor class C group 5 member D, and other antigens, and evolutions of existing classes of agents such as immunomodulatory drugs. In parallel, it must be acknowledged that the standard of care first-line therapies used for myeloma have evolved since the start of our trial. Importantly, the compelling evidence base and widespread adoption of lenalidomide maintenance after first-line transplantation renders that agent unsuitable as a component of consolidation and maintenance after salvage HSCT. While lenalidomide was not used in the ACCORD trial, the expansion of the treatment armamentarium means that thalidomide use is also no longer likely to be optimal, which is likely to account for the rates of progressive disease observed before the start of consolidation in the study. An alternative all-oral combination, ixazomib, lenalidomide, and dexamethasone, has been evaluated as a response-adapted maintenance in the front-line setting, but did not improve progression-free survival significantly over lenalidomide–dexamethasone[28] and is not suitable for lenalidomide-refractory patients. Our data indicate for the first time an evidence base to support consolidation and maintenance as a valid strategy in the context of salvage autologous transplantation and show this can be achieved with an all-oral regime. An ongoing role for salvage autologous HSCT in the treatment landscape is therefore demonstrated, but the evolving therapeutic landscape means the most suitable agents to employ in this approach in the future remains a priority question to be addressed over the coming years.

Considering the heterogeneity of patients with multiple myeloma, predefined subgroup analysis is key to understanding which patients will benefit the most from an intervention while acknowledging results should be interpreted with caution. Although much research attention has focused on the molecular aberrations of myeloma, there is growing understanding that

host biology also has a central role in defining subgroups of patients.[29] In our study, age did not affect outcomes, nor did performance status, including stem-cell transplantation fitness (haematopoetic cell transplantation comorbidity index) or disease stage. Neither the durability of response from the initial autologous HSCT nor previous proteasome inhibitor exposure affected the outcome of maintenance with ixazomib. Durability of response is likely to reflect the importance of selecting for salvage autologous HSCT in only those patients with good duration of response to first autologous HSCT, a key inclusion criterion of our study. Analysis of the effect of cytogenetic aberrations on the impact of maintenance suggests that patients with ultra-high-risk disease gain a clear advantage from prolonged anti-myeloma maintenance therapy; the effect for high-risk and standard risk is less clear and did not reach nominal statistical significance. When the impact of response to re-induction or salvage autologous HSCT is examined, it is patients who reached less than VGPR who benefit most from post-salvage HSCT consolidation and maintenance, which might highlight the importance of consolidating sub optimal responses with agents to which a patient's disease is known to be sensitive.

A successful maintenance strategy after autologous HSCT in myeloma should be effective, easy to deliver, and tolerable for the patients in the long-term.[30] As the treatment landscape evolves the optimal personalised maintenance approach for any given patient is becoming more complex, especially considering factors such as genetically-defined high-risk disease and response-adapted strategies that reflect the evolving treatment paradigm. In our study, consolidation with ITD followed by ixazomib monotherapy maintenance was well tolerated with predictable haematological toxicity as the most frequent treatment-emergent adverse event. Low grade fatigue and infections were reported commonly, as were mild gastrointestinal disturbance and peripheral neuropathy, although grade 3 upper respiratory tract infections were the only notable clinically significant toxicities observed. It is worth noting that only patients who tolerated ixazomib (in combination with thalidomide and dexamethasone) during the re-induction phase were eligible for the randomisation of ixazomib-containing maintenance. The current follow-up is relatively short, and assessment of long-term toxicities such as second primary malignancies, cardiotoxicity, and infections is ongoing.

The sample size was smaller than the preplanned size at the design stage, which was due to greater attrition during the trial than anticipated. However, considering that statistical power in trials such as this are determined through the number of primary endpoint events rather than the number of participants randomly assigned, this did not impact the results.

Randomised controlled trials that report early for efficacy can overestimate the effect size.[31] The effect size we observed is larger, and is based on slightly shorter progression-free survival, than we hypothesised at the design stage. However, when a stringent, predefined stopping rule is in place[32] and 50% of required events have been reported, reporting early has been suggested to have a negligible impact on estimated effect sizes.[33] This study had planned interim analyses included in the protocol for this comparison with an appropriate stopping rule. The primary endpoint analysis was undertaken when 139 (72%) of the required events had been reported, suggesting that the estimated effect could be at most minimally inflated. Nonetheless, these findings need to be interpreted with caution while the results of the final long-term follow-up analysis are awaited.

In conclusion, the ACCoRD trial demonstrates that consolidation and maintenance treatment with ixazomib after salvage autologous HSCT is superior to observation in terms of progression-free survival. Current follow-up is insufficient to determine differences in progression-free survival 2 or overall survival.

Contributors

GC was chief investigator. GC, DC, AH, and MC designed the trial and developed the protocol. DC and ES developed and carried out the statistical analysis plan. GC, AJA, JDC, JS, MTD, KY, MG, KB, HS, SG, MC, and CP participated in recruitment of patients. RdT, RO, and MTD coordinated the central laboratory investigations. CO, AH, JR, and SG coordinated the data collection and regulatory and governance requirements. GC, ES, DC, and CP interpreted the data. GC, ES, DC, and CP developed the first draft of the manuscript. ES and DC have accessed and verified all the data in the study. All authors had access to all the data reported in the study. All authors contributed to the review and amendments of the manuscript for important intellectual content and approved this final version for submission.

Declaration of interests

GC reports research funding from Janssen, Takeda Oncology, Amgen, and BMS/Celgene; and consultancy fees from Janssen, Takeda, Sanofi, Oncopeptides, Karyopharm, Pfizer, Roche, and BMS/Celgene.
AJA reports speaker fees and participation on advisory boards for Janssen and participation on advisory boards for Takeda. ES reports receipt of unrestricted educational grants to his institution from Takeda Oncology, Celgene Corporation, Merck, Amgen, and Sanofi. CO reports receipt of unrestricted educational grants to her institution from Takeda Oncology, Celgene Corporation, Merck, Amgen, and Sanofi. AH reports receipt of unrestricted educational grants to his institution from Takeda Oncology, Celgene Corporation, Merck, Amgen, and Sanofi; and speaker fees from Abbvie. JR reports receipt of unrestricted educational grants to her institution from Takeda Oncology, Celgene Corporation, Merck, Amgen and Sanofi. JS reports speaker fees from Janssen, Jazz, Mallinckrodt, and Sanofi; participation on advisory boards for Medac and Vertex; and Independent Data Monitoring Committee membership for a Kiadis Pharma clinical trial. MG reports participation on advisory boards for Amgen, Sanofi, Celgene, Stemline therapeutics, Janssen, and Novartis; research grants from Janssen; speaker honoraria from Janssen, Amgen and Alnylam; and travel expenses to attend educational meetings from Novartis, Janssen, and Takeda. KB reports participation on advisory boards at Takeda, Janssen, and Celgene/BMS; speaker honoraria from Janssen, Sanofi, and Celgene/BMS; and travel expenses to attend educational meetings from Janssen, GSK, and Takeda. SG reports receipt of unrestricted educational grants to her institution from Takeda Oncology, Celgene Corporation, Merck, Amgen, and Sanofi.
DAC reports receipt of unrestricted educational grants to his institution from Takeda Oncology, Celgene Corporation, Merck, Amgen, and Sanofi; payment to their institution for educational lectures from Janssen; participation on a Data Safety Monitoring Board for a multiple myeloma study; and personal payment for meeting attendance from European

Myeloma Network, Rotterdam. LR is a patient and public contributor. CP reports speaker honoraria from Janssen, Amgen, and Novartis; and participation on advisory boards at Pfizer and Sanofi. All other authors declare no competing interests.

Data sharing

De-identified participant data will be made available when all trial primary and secondary endpoints have been met. Any requests for trial data and supporting material (data dictionary, protocol, and statistical analysis plan) will be reviewed by the trial management group in the first instance. Only requests that have a methodologically sound proposal and whose proposed use of the data has been approved by the independent trial steering committee will be considered. Proposals should be directed to the corresponding author in the first instance; to gain access, data requestors will need to sign a data access agreement.

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