Mezigdomide, carfilzomib, and dexamethasone versus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma (SUCCESSOR-2): a phase 3, open-label, randomised controlled trial

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Summary

Background A growing number of patients with multiple myeloma are anti-CD38 antibody-exposed and lenalidomide-exposed at first relapse, subsequently limiting their treatment options. Mezigdomide, a potent cereblon E3 ligase modulator, induces maximal, rapid Ikaros and Aiolos degradation, resulting in enhanced myeloma cell cytotoxicity and immune stimulation versus immunomodulatory drugs. The SUCCESSOR-2 trial evaluates the efficacy and safety of mezigdomide in combination with carfilzomib and dexamethasone versus carfilzomib plus dexamethasone.

Methods This phase 3, open-label, randomised controlled trial was conducted at 160 hospital-based sites in 26 countries using a two-stage, inferentially seamless design. Eligible adult patients had measurable multiple myeloma, had received at least one previous regimen (including anti-CD38 antibodies and lenalidomide) on which they had achieved minimal response or better, and documented disease progression during or after their most recent treatment. Interactive response technology was used to randomly assign patients, stratified by age (≤70 years or >70 years), number of previous lines of therapy (≤2 or >2), and International Staging System stage (I, II, or III). Patients received oral mezigdomide (days 1–21 of each 28-day cycle) plus intravenous carfilzomib (56 mg/m² weekly) and oral or intravenous dexamethasone (40 mg weekly) or carfilzomib (56 mg/m² twice weekly or 70 mg/m² weekly) and dexamethasone (20 mg twice weekly or 40 mg weekly). In stage 1, mezigdomide dosing across three levels was optimised. In stage 2, patients were randomly assigned to the selected mezigdomide dose (1·0 mg) plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. The primary endpoint was progression-free survival (PFS) evaluated in patients who received 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone across both study stages. No imputation was planned for missing efficacy endpoint values or missing safety evaluations. The trial is registered with ClinicalTrials.gov (NCT05552976) and EUClinicalTrials.eu (EUCT number 2022–500861–29–00). The trial is active but not recruiting.

Findings Between Feb 3, 2023, and Nov 28, 2025, 762 patients were assessed for eligibility, of which 606 patients were enrolled and 479 were included in the analyses (288 patients in the mezigdomide–carfilzomib–dexamethasone group and 191 patients in the carfilzomib–dexamethasone group). 252 (53%) patients were male, 411 (86%) were anti-CD38 antibody-refractory, and 363 (76%) were lenalidomide-refractory, with a median of two previous lines of therapy (IQR 2–4). At 10·6 months median follow-up, mezigdomide–carfilzomib–dexamethasone significantly improved PFS compared with carfilzomib–dexamethasone (median 18·0 months *vs* 8·3 months; hazard ratio 0·48 [95% CI 0·36–0·63]; p<0·0001). Grade 3 or 4 adverse events were observed in 241 (84%) patients receiving mezigdomide–carfilzomib–dexamethasone versus 105 (56%) patients receiving carfilzomib–dexamethasone, including neutropenia (176 [61%] *vs* 17 [9%]) and infections (98 [34%] *vs* 29 [16%]). Eight (3%; 95% CI 1–5) and one (1%; 95% CI 0–3) treatment-related grade 5 adverse events were reported with mezigdomide–carfilzomib–dexamethasone and with carfilzomib–dexamethasone, respectively (rate difference 2%; 95% CI −1 to 5). Deaths occurred in 62 (22%) patients in the mezigdomide–carfilzomib–dexamethasone group and 51 (27%) patients in the carfilzomib–dexamethasone group, mainly due to disease progression.

Interpretation Mezigdomide–carfilzomib–dexamethasone provided a significant PFS benefit compared with carfilzomib–dexamethasone alone, with higher rates of grade 3 or 4 adverse events, including infections, which were mostly manageable with standard clinical practice and supportive care. These findings support mezigdomide–carfilzomib–dexamethasone as a clinically meaningful treatment option as early as first relapse in predominantly triple-class-exposed, anti-CD38 antibody-refractory and lenalidomide-refractory patients, a growing population with substantial unmet need.

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Introduction

Multiple myeloma is characterised by repeated relapse and the development of increasing therapeutic resistance and shorter progression-free survival (PFS), with most patients ultimately experiencing treatment-refractory disease. The widespread adoption of frontline anti-CD38 antibodies and lenalidomide has resulted in deep and durable remissions in a substantial proportion of patients with newly diagnosed multiple myeloma.[1,2] However, this success has resulted in a growing population of patients who are exposed or refractory to these agents as early as first relapse, thereby limiting subsequent treatment options and contributing to poor clinical outcomes.[1–3] This population has not been thoroughly investigated and prospective evidence is currently scarce. Several novel therapeutic approaches have shown significant PFS benefit and expanded treatment options for patients with relapsed or refractory multiple myeloma, including chimeric antigen receptor (CAR) T-cell therapies, bispecific antibodies, and antibody-drug conjugates.[4–8]

Research in context

Evidence before this study

We searched PubMed, with no language restrictions, for articles published between Jan 1, 2016, and April 22, 2026. Specific search terms included "multiple myeloma", "relapsed", "refractory", "mezigdomide", "lenalidomide", and "CD38". This approach identified clinical trials and real-world analyses evaluating treatments for relapsed or refractory multiple myeloma, including in patients exposed to anti-CD38 antibodies or lenalidomide. Real-world evidence showed that exposure or refractoriness to anti-CD38 antibodies and lenalidomide is associated with poor outcomes in this population. Despite anti-CD38 antibody-based and lenalidomide-based therapies being standards of care in frontline and early-relapse settings, no published prospective studies specifically focused on patients universally exposed to both agents as early as first relapse. Clinical trials in this setting are ongoing, including those evaluating T-cell-redirecting therapies. Real-world data showed heterogeneous treatment patterns, with carfilzomib plus dexamethasone among the most frequently used combinations, and median progression-free survival (PFS) of only 6·3 months across treatment regimens, highlighting a substantial unmet need for effective, accessible regimens with differentiated mechanisms of action suitable for routine clinical use. Mezigdomide is an oral cereblon E3 ligase modulator, specifically optimised for maximal and rapid degradation of Ikaros and Aiolos target proteins, leading to increased myeloma cell killing and superior immunostimulatory activity when compared with immunomodulatory drugs. Phase 1/2 data have shown that mezigdomide has promising activity in the relapsed or refractory setting, including in combination with carfilzomib–dexamethasone, supporting further prospective evaluation.

Added value of this study

SUCCESSOR-2 is the first phase 3 randomised trial specifically designed to evaluate mezigdomide–carfilzomib–dexamethasone versus carfilzomib–dexamethasone in patients with relapsed or refractory multiple myeloma who were universally exposed to both anti-CD38 antibodies and lenalidomide. Its inferentially seamless design enabled prospective, randomised dose optimisation within a single confirmatory trial. Carfilzomib–dexamethasone was selected as the comparator as an approved, guideline-recommended option in early relapse; furthermore, it is among the most frequently used regimens in patients previously treated with anti-CD38 antibodies and lenalidomide in real-world practice. The addition of mezigdomide to carfilzomib–dexamethasone allowed for evaluation of the specific contribution of mezigdomide to the efficacy and safety of the combination. After a median follow-up of 10·6 months, mezigdomide–carfilzomib–dexamethasone showed superior efficacy versus carfilzomib–dexamethasone, reducing the risk of progression or death by 52%, with the median PFS more than doubled. Mezigdomide–carfilzomib–dexamethasone induced deep responses, doubling the very good partial response or better rate and tripling the complete response or better rate of carfilzomib–dexamethasone. The safety profile of mezigdomide–carfilzomib–dexamethasone was consistent with previous mezigdomide studies, with neutropenia being the most common grade 3 or 4 adverse event, and with the known toxicity profile of carfilzomib.

Implications of all the available evidence

Taken together with previous real-world evidence and data from early-phase clinical trials, the results of SUCCESSOR-2 showed that mezigdomide–carfilzomib–dexamethasone substantially improves outcomes versus carfilzomib–dexamethasone in a growing and under-studied population of patients with relapsed or refractory multiple myeloma who are predominantly refractory to anti-CD38 antibodies and lenalidomide. These findings address a major evidence gap in early relapse and support mezigdomide–carfilzomib–dexamethasone as a potent, differentiated combination that addresses distinct clinical needs in the evolving relapsed or refractory multiple myeloma treatment paradigm at early relapse. Mezigdomide is under active investigation across additional combinations and multiple myeloma populations.

However, most patients with multiple myeloma are treated in the community setting,[9] where implementation of these therapies can be constrained by operational and logistical challenges.[10,11] Consequently, broader implementation in community practice remains limited, highlighting the need for effective regimens that are easily adoptable in all treatment settings to address the needs of individual patients.

Mezigdomide is an oral cereblon E3 ligase modulator (CELMoD) in clinical development for relapsed or refractory multiple myeloma.[12,13] Relative to lenalidomide and pomalidomide, mezigdomide engages cereblon in a distinct and more effective manner, resulting in rapid and complete proteasomal degradation of transcription factors Ikaros and Aiolos.[14,15] Mezigdomide was rationally designed based on structure–function relationships and as a single enantiomer to maximise cereblon binding and target degradation, with the goal of enhancing antitumour potency and potentially minimising off-target effects.[14] These molecular properties translate into increased myeloma cell cytotoxicity and superior immunostimulatory activity characterised by enhanced mitigation of immune cell dysfunction compared with immunomodulatory agents.[14,16–18] Notably, Ikaros degradation also results in reversible neutrophil maturation arrest, which in preclinical studies was mitigated with an approximately 5-day drug washout.[12,19–21]

In a phase 1/2 study, mezigdomide plus dexamethasone showed efficacy in heavily pretreated relapsed or refractory multiple myeloma in a largely triple-class refractory population that included those exposed to anti-B-cell maturation antigen (BCMA) agents. The safety profile was characterised primarily by neutropenia, with few treatment-related or infection-related deaths, despite the highly exposed and refractory population.[12] The 1·0 mg mezigdomide dosing regimen induced a robust pharmacodynamic response, including a significant increase in proliferating T cells and a shift towards an activated or effector memory phenotype.[12] Furthermore, preclinical studies have shown synergistic anti-tumour activity between mezigdomide and proteasome inhibitors,[22] a finding supported by phase 1/2 data in which the combination of mezigdomide, carfilzomib, and dexamethasone yielded promising efficacy and a manageable safety profile.[13]

We designed the phase 3 SUCCESSOR-2 trial to identify the recommended dose of mezigdomide in combination with carfilzomib and dexamethasone and to evaluate the efficacy and safety of mezigdomide–carfilzomib–dexamethasone compared with carfilzomib–dexamethasone in patients with relapsed or refractory multiple myeloma who had received at least one previous line of therapy, including anti-CD38 antibodies and lenalidomide. Carfilzomib–dexamethasone is approved, efficacious, and one of the most frequently used standards of care in this patient population.[2] Here, we report the results of the prespecified interim efficacy analysis.

Methods

Study design

SUCCESSOR-2, a phase 3, multicentre, open-label, randomised controlled trial, uses an inferentially seamless design with an initial mezigdomide dose-optimisation stage.[23] Patients were recruited at 160 hospital-based sites in 26 countries (appendix pp 3–11). In stage 1, patients were randomly assigned to one of three mezigdomide doses in combination with carfilzomib and dexamethasone or to carfilzomib–dexamethasone alone. Based on the totality of data, an independent data monitoring committee selected the recommended stage 2 dose. In stage 2, additional patients were randomly assigned to mezigdomide–carfilzomib–dexamethasone at the recommended mezigdomide dose and to carfilzomib–dexamethasone (appendix p 12).[23] Patients assigned to the carfilzomib–dexamethasone group were not permitted to cross over.

The trial has been conducted in accordance with international guidelines, including the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and country-specific regulations. The local independent ethics committee or institutional review board at each study site approved the protocol. Patients and the public were not involved in the design, conduct, or reporting of the trial. The authors had full access to all trial data, contributed to data interpretation, and directed the drafting and revision of the manuscript. The SUCCESSOR-2 trial is registered with ClinicalTrials.gov (NCT05552976) and EUClinicalTrials.eu (EUCT number 2022–500861–29–00). The trial status is active but not recruiting.

Participants

Eligible adult patients (≥18 years) had measurable multiple myeloma, an Eastern Cooperative Oncology Group performance status score of 0–2, and one or more previous line of antimyeloma therapy (no maximum), including anti-CD38 antibodies and lenalidomide. Patients were required to have reached a minimal response or better to at least one previous line of antimyeloma therapy and documented disease progression during or after their most recent treatment. Patients previously treated with carfilzomib or mezigdomide were excluded. Patients were required to sign a written informed consent form in accordance with regulatory, local, and institutional guidelines. Full eligibility and exclusion criteria are reported in the appendix (pp 13–15).

Randomisation and masking

Patients were randomly assigned with an interactive response technology based on the permuted-block

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See **Online** for appendix

method. In stage 1, patients were randomly assigned (3:3:3:2) to mezigdomide 0·3 mg, 0·6 mg, or 1·0 mg in combination with carfilzomib and dexamethasone or to carfilzomib–dexamethasone using three blocks: one block had a size of 3 in a 1:1:1 ratio to the three mezigdomide doses evaluated; the other two blocks had a block size of 4 in a 1:1:1:1 ratio to the three evaluated mezigdomide doses or to the carfilzomib–dexamethasone group. The block order for every three blocks was randomised. In stage 2, patients were randomly assigned in a 3:2 ratio to mezigdomide at the selected dose plus carfilzomib and dexamethasone or to carfilzomib–dexamethasone alone, for a block size of 5. Patients were stratified by age (≤70 or >70 years), number of previous lines of therapy (≤2 or >2), and International Staging System stage at screening (stage I, II, or III).

As this was an open-label study, investigators and enrolled patients were not masked to treatment assignment. However, any review of aggregate study data by the sponsor study team and personnel was masked, before the planned treatment unblinding. Further details are available in the appendix (p 12).

Procedures

In stage 1, in the mezigdomide–carfilzomib–dexamethasone group, oral mezigdomide was given daily at 0·3 mg, 0·6 mg, or 1·0 mg on days 1–21 of each 28-day cycle with intravenous weekly carfilzomib at 20 mg/m² on day 1 of cycle 1; then at 56 mg/m² on days 8 and 15 of cycle 1; days 1, 8, and 15 of cycles 2–12; and days 1 and 15 of cycles 13 or later; and oral or intravenous weekly dexamethasone at 40 mg on days 1, 8, 15, and 22 of each cycle. In the carfilzomib–dexamethasone group, treatment was originally administered as intravenous twice-weekly carfilzomib at 20 mg/m² on days 1 and 2 of cycle 1; then at 56 mg/m² on days 8, 9, 15, and 16 of cycle 1, and days 1, 2, 8, 9, 15, and 16 in cycles 2 or later; plus oral or intravenous dexamethasone at 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23. As of July 2023, a once-weekly carfilzomib–dexamethasone regimen option was made available to reflect approved standard of care in many countries, which includes intravenous carfilzomib at 20 mg/m² on day 1 of cycle 1; then at 70 mg/m² on days 8 and 15 of cycle 1, and days 1, 8, and 15 of cycles 2 or later; plus oral or intravenous dexamethasone at 40 mg on days 1, 8, 15, and 22 of cycles 1–9, and days 1, 8, and 15 of cycles 10 or later. The carfilzomib–dexamethasone regimen used was per investigator's choice at randomisation.

In stage 2, patients received mezigdomide at the selected dose plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone, administered in 28-day cycles as described. Investigators had the option of halving the starting dose of dexamethasone for patients who were older than 75 years, underweight (defined as having a BMI <18·5 kg/m²), had poorly controlled diabetes, or had a previous intolerance to steroid therapy. For these patients, dexamethasone could be administered at 20 mg to patients receiving mezigdomide–carfilzomib–dexamethasone and those receiving the once-weekly carfilzomib–dexamethasone regimen, and at 10 mg to patients receiving the twice-weekly carfilzomib–dexamethasone regimen.

Patients were treated until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Evaluation of safety assessments of adverse events and second primary malignancy surveillance were monitored continuously starting after informed consent. Assessment of response was performed on day 1 of each cycle starting in cycle 2.

In the event of predefined toxicity, dose modifications were permitted as described in the appendix (pp 16–19). Antiviral prophylaxis was recommended against herpes zoster reactivation. Immunoglobulin infusions were administered as per local institutional guidelines. Required supportive care in both treatment groups included thromboembolism prophylaxis, hepatitis B virus (HBV) prophylaxis (for hepatitis B surface antigen-positive and HBV DNA-negative patients), and, from December 2024, *Pneumocystis jirovecii* pneumonia prophylaxis and granulocyte colony-stimulating factor (GCSF) prophylaxis (for patients with grade 4 neutropenia or grade 3 or 4 febrile neutropenia). Further details are available in the appendix (pp 15–16).

Outcomes

The primary endpoint was PFS, as assessed by an independent review committee. The key secondary endpoint was overall survival. Additional secondary endpoints included PFS after subsequent therapy; complete response or better, very good partial response or better, and overall response per the International Myeloma Working Group uniform response criteria[24] (analysed centrally); time to response; time to progression; time to next treatment; minimal residual disease negativity (analysed centrally); duration of response; health-related quality of life; and safety assessments. A secondary endpoint in stage 1 was determining the dose of mezigdomide in combination with carfilzomib–dexamethasone to continue in stage 2, and mezigdomide plasma concentrations. Adverse events were collected from the time of signing the consent up to 28 days after discontinuation of study treatment dosing. Thereafter, new adverse events deemed related to study treatment and any second primary malignancies were captured. Adverse events were coded using Medical Dictionary for Regulatory Activities version 25.0 or higher and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 whenever possible. Endpoint definitions and details of all secondary endpoints are included in the appendix (pp 19–21). A prespecified subgroup analysis was performed to evaluate the effect of baseline characteristics on the primary endpoint outcome.

Statistical analysis

Reported analyses were performed following dose selection and evaluated in the confirmatory analysis group, defined as all patients randomised to the selected mezigdomide–carfilzomib–dexamethasone group and the carfilzomib–dexamethasone group in both study stages, with safety analyses evaluated in patients who received at least one dose of study treatment. In total, 455 patients were planned for inclusion in the confirmatory analysis group. With an assumed 33·3% risk reduction (hazard ratio [HR] 0·667) with mezigdomide, 273 PFS events provided approximately 89% power to detect improved treatment effect under the exponential distribution assumption of PFS (one-sided alpha 0·025); this calculation was adjusted for three preplanned interim analyses: mezigdomide dose selection, PFS futility (at 30% of events), and PFS superiority (at 75% of events, reported herein; appendix pp 21–22).

A prespecified multiplicity strategy was implemented to adjust for multiple comparisons and to control the overall type I error rate for the primary endpoint PFS at one-sided alpha level of 0·025. A rank-based single-step Dunnett's adjustment method was used for p value adjustment to control for potential type I error inflation due to dose selection in stage 1.[25–27] The weighted inverse normal p value combination method was applied to combine p values across the two stages. A group sequential alpha spending method using Lan-DeMets functions with O'Brien–Fleming boundaries was employed to allow for interim analyses while controlling type I error rate (appendix pp 21–24).[28]

The Kaplan–Meier method was used to estimate survival distribution functions for time-to-event analyses and compared between treatment groups using a log-rank test stratified by baseline stratification factors. We used a stratified Cox proportional hazards model to estimate HRs and 95% CIs, with treatment as the only explanatory variable. The proportional hazards assumption was evaluated by visually examining the Kaplan–Meier curve. When the proportional hazards assumption did not hold, the HR was interpreted as an average treatment effect over time, and a prespecified analysis of restricted mean survival time was performed. The stratified Miettinen–Nurminen test was used to test treatment differences in response assessment. No adjustments were made for multiplicity for secondary endpoints, which are presented as point estimates with 95% CIs. The confidence interval widths have not been adjusted for multiplicity; the interpretation of these results is intended to be descriptive and should not be substituted for formal hypothesis testing. The binomial exact method was used for 95% CIs for the proportion of patients with grade 5 adverse events and the exact method based on score statistics for the 95% CI of the rate difference. Statistical analyses were performed using SAS (version 9.4). An independent data monitoring committee regularly reviewed all safety data

	Mezigdomide–carfilzomib–dexamethasone (n=288)	Carfilzomib–dexamethasone (n=191)	All patients (N=479)
Age, years	68 (61–75)	67 (61–74)	68 (61–75)
Age group, years			
<65	102 (35%)	79 (41%)	181 (38%)
65 to <75	111 (39%)	67 (35%)	178 (37%)
≥75	75 (26%)	45 (24%)	120 (25%)
Sex*			
Male	146 (51%)	106 (55%)	252 (53%)
Female	142 (49%)	85 (45%)	227 (47%)
Race			
American Indian or Alaska Native	10 (3%)	3 (2%)	13 (3%)
Asian	90 (31%)	57 (30%)	147 (31%)
Black or African American	11 (4%)	13 (7%)	24 (5%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	162 (56%)	114 (60%)	276 (58%)
Not collected, unknown, or missing	15 (5%)	4 (2%)	19 (4%)
Region			
Asia	88 (31%)	56 (29%)	144 (30%)
Europe	109 (38%)	72 (38%)	181 (38%)
USA	27 (9%)	26 (14%)	53 (11%)
Rest of world	64 (22%)	37 (19%)	101 (21%)
Time since initial diagnosis, years	4·6 (2·5–7·1)	4·5 (2·6–7·5)	4·5 (2·5–7·3)
ECOG performance status score			
0	116 (40%)	74 (39%)	190 (40%)
1	154 (53%)	103 (54%)	257 (54%)
2	16 (6%)	14 (7%)	30 (6%)
3	2 (1%)†	0	2 (<1%)†
Derived International Staging System stage at study entry			
I	149 (52%)	96 (50%)	245 (51%)
II	87 (30%)	59 (31%)	146 (30%)
III	52 (18%)	36 (19%)	88 (18%)
Presence of soft-tissue plasmacytomas	66 (23%)	52 (27%)	118 (25%)
Extramedullary	25 (9%)	20 (10%)	45 (9%)
Paraskeletal	51 (18%)	34 (18%)	85 (18%)
Cytogenetic abnormality‡			
High risk	74 (26%)	62 (32%)	136 (28%)
Standard risk	178 (62%)	102 (53%)	280 (58%)
Not evaluable or data missing	36 (13%)	27 (14%)	63 (13%)
Number of previous lines of antimyeloma therapy, range; IQR	2·0 (1–9); 2·0–3·5	2·0 (1–8); 2·0–4·0	2·0 (1–9); 2·0–4·0
One previous line	43 (15%)	33 (17%)	76 (16%)
Two previous lines	109 (38%)	68 (36%)	177 (37%)
Three previous lines	64 (22%)	35 (18%)	99 (21%)
Four or more previous lines	72 (25%)	55 (29%)	127 (27%)
Therapy exposure			
Anti-CD38 antibody	288 (100%)	191 (100%)	479 (100%)
Immunomodulatory drug	288 (100%)	191 (100%)	479 (100%)
Lenalidomide	288 (100%)	191 (100%)	479 (100%)
Pomalidomide	114 (40%)	64 (34%)	178 (37%)

(Table 1 continues on next page)

	Mezigdomide–carfilzomib–dexamethasone (n=288)	Carfilzomib–dexamethasone (n=191)	All patients (N=479)
(Continued from previous page)			
Proteasome inhibitor (triple-class exposed)	265 (92%)	176 (92%)	441 (92%)
BCMA-targeted therapy§	23 (8%)	12 (6%)	35 (7%)
T-cell engager	12 (4%)	9 (5%)	21 (4%)
CAR T cell therapy	9 (3%)	3 (2%)	12 (3%)
Antibody-drug conjugate	5 (2%)	3 (2%)	8 (2%)
T-cell-redirecting therapy	28 (10%)	12 (6%)	40 (8%)
Refractory status¶			
Anti-CD38 antibody	248 (86%)	163 (85%)	411 (86%)
Immunomodulatory agent	247 (86%)	154 (81%)	401 (84%)
Lenalidomide	220 (76%)	143 (75%)	363 (76%)
Pomalidomide	99 (34%)	56 (29%)	155 (32%)
Proteasome inhibitor	138 (48%)	102 (53%)	240 (50%)
Triple-class refractory‖	111 (39%)	75 (39%)	186 (39%)
Refractory to last line of therapy	264 (92%)	181 (95%)	445 (93%)

Data are median (IQR) or n (%), unless indicated otherwise. Percentages might not total 100% due to rounding. In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. BCMA=B-cell maturation antigen. CAR=chimeric antigen receptor. ECOG=Eastern Cooperative Oncology Group. *Sex was self-reported by patients. †Eligibility required an ECOG performance status score of 0–2 at screening; these two patients had an ECOG performance status score of 1 during screening and an ECOG performance status score of 3 at baseline, the timepoint shown in this table. ‡High risk is defined as presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16); standard risk is defined as absence of del(17p), translocation t(4;14), and translocation t(14;16). §Some patients might have received more than one BCMA-targeted therapy before being randomly assigned in SUCCESSOR-2. ¶Refractory is defined as disease that is non-responsive on therapy (did not reach minimal response or development of progressive disease while on therapy) or progresses within 60 days of the last dose. ‖Triple-class refractory is defined as refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody.

Table 1: **Demographic and disease characteristics of patients at baseline**

and interim analysis results. Details on the subgroup analyses are provided in the appendix (pp 22–23).

Role of the funding source

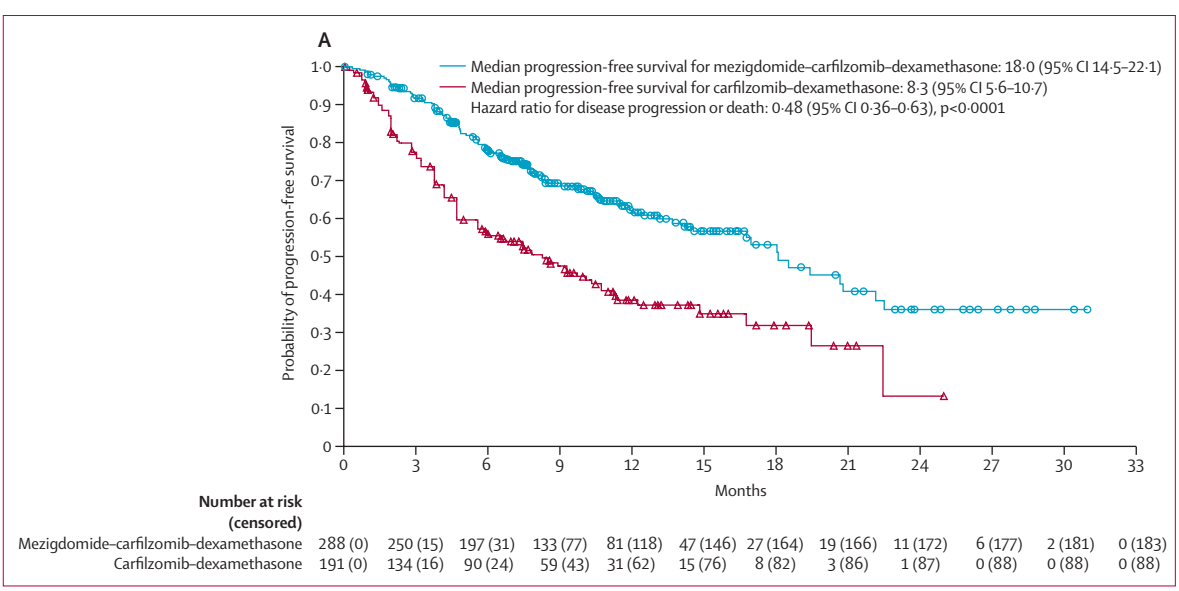
The funder of the study supplied mezigdomide and had a role in the study design, data collection, data analysis, data interpretation, and writing of the report, including in the decision to submit and funding for medical writing support.

Results

Between Feb 3, 2023, and Nov 28, 2025, 762 patients were assessed for eligibility, and 606 patients were randomly assigned to either stage 1 of the trial (n=235) or stage 2 of the trial (n=371; appendix p 25).

In stage 1, 190 patients received mezigdomide–carfilzomib–dexamethasone at one of three doses, and 45 patients received carfilzomib–dexamethasone. Based on the totality of data, 1·0 mg was the recommended mezigdomide dose for stage 2.

In total, 479 patients were randomly assigned across stages 1 and 2 as part of the confirmatory analysis group; 288 were assigned to mezigdomide–carfilzomib–dexamethasone at 1·0 mg mezigdomide, of whom all received treatment, and 191 were assigned to carfilzomib–dexamethasone, of whom 186 received treatment. In the carfilzomib–dexamethasone group, 130 patients received the once-weekly regimen. Overall, 120 (25%) of 479 patients were aged 75 years or older, median time since diagnosis was 4·5 years (IQR 2·5–7·3), the median number of previous lines of therapy was 2 (IQR 2–4; range 1–9), and 127 (27%) patients received four or more previous lines of therapy. 136 (28%) patients had high-risk cytogenetics at baseline (defined as presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16);



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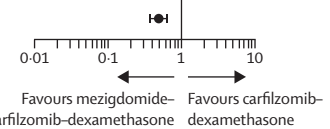
appendix p 36), and 118 (25%) had soft-tissue plasmacytomas. All patients had anti-CD38 antibody and lenalidomide exposure, 441 (92%) were triple-class exposed, and most were refractory to anti-CD38 antibodies (411 [86%]) or lenalidomide (363 [76%]); 445 (93%) were refractory to their last line of therapy. In total, 178 (37%) and 35 (7%) patients had previous exposure to pomalidomide and BCMA-targeted therapy, respectively. Baseline demographics and patient characteristics were generally balanced between treatment groups (table 1).

At data cutoff (Jan 15, 2026), 151 (52%) of 288 patients in the mezigdomide–carfilzomib–dexamethasone group and 60 (31%) of 191 in the carfilzomib–dexamethasone group

B

	Total number of patients	Mezigdomide–carfilzomib–dexamethasone	Carfilzomib–dexamethasone	Hazard ratio (95% CI)
		Number of events / number of patients	Number of events / number of patients	
Overall	**479**	**105/288**	**103/191**	**0·49 (0·37–0·64)**
Age, years				
<65	181	40/102	44/79	0·52 (0·34–0·80)
65 to <75	178	41/111	38/67	0·43 (0·27–0·67)
≥75	120	24/75	21/45	0·52–0·29–0·94)
Sex				
Female	227	50/142	44/85	0·48 (0·32–0·73)
Male	252	55/146	59/106	0·48 (0·33–0·70)
Race				
Asian	147	36/90	28/57	0·61 (0·37–1·00)
Black or African American	24	3/11	6/13	0·50 (0·13–2·01)
White	276	58/162	67/114	0·44 (0·31–0·63)
Other, not collected, or unknown	31	8/25	2/6	0·45 (0·09–2·26)
Missing	1	0/0	0/1	
Region				
USA	53	3/27	9/26	0·28 (0·08–1·05)
Europe	181	39/109	42/72	0·49 (0·32–0·76)
Asia	144	34/88	28/56	0·58 (0·35–0·96)
Rest of the world	101	29/64	24/37	0·40 (0·23–0·70)
Renal function				
<45 mL/min	64	18/36	16/28	0·56 (0·28–1·12)
45 to <60 mL/min	83	25/49	23/34	0·36 (0·20–0·66)
60 to <90 mL/min	208	38/128	41/80	0·46 (0·30–0·72)
≥90 mL/min	124	24/75	23/49	0·52 (0·29–0·92)
ISS staging at study entry				
Stage I	245	45/149	50/96	0·42 (0·28–0·64)
Stage II	146	32/87	31/59	0·51 (0·31–0·84)
Stage III	88	28/52	22/36	0·60 (0·34–1·05)
Cytogenetic risk				
High risk	136	32/74	36/62	0·49 (0·30–0·80)
Standard risk	280	58/178	50/102	0·51 (0·35–0·74)
Not evaluable or data missing	63	15/36	17/27	0·44 (0·22–0·90)
Functional high-risk disease*				
Yes	166	32/98	38/68	0·36 (0·22–0·58)
No	313	73/190	65/123	0·57 (0·41–0·80)
Presence of soft-tissue plasmacytomas				
Yes	118	32/66	42/52	0·34 (0·21–0·54)
No	361	73/222	61/139	0·58 (0·42–0·82)
Presence of extramedullary plasmacytomas*				
Yes	45	14/25	18/20	0·33 (0·16–0·67)
No	434	91/263	85/171	0·51 (0·38–0·69)



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C

	Total number of patients	Mezigdomide–carfilzomib–dexamethasone	Carfilzomib–dexamethasone	Hazard ratio (95% CI)
		Number of events / number of patients	Number of events / number of patients	
Overall	**479**	**105/288**	**103/191**	**0·49 (0·37–0·64)**
Number of previous lines of therapy				
≤2	253	53/152	50/101	0·54 (0·37–0·80)
>2	226	52/136	53/90	0·44 (0·30–0·64)
Previous proteasome inhibitor exposure (triple-class exposed)				
Yes	441	97/265	95/176	0·49 (0·37–0·65)
No	38	8/23	8/15	0·55 (0·20–1·48)
Previous pomalidomide exposure				
Yes	178	51/114	39/64	0·49 (0·32–0·75)
No	301	54/174	64/127	0·45 (0·31–0·65)
Refractory to anti-CD38 antibody therapy				
Yes	411	93/248	89/163	0·48 (0·36–0·64)
No	68	12/40	14/28	0·50 (0·23–1·08)
Refractory to lenalidomide				
Yes	363	89/220	80/143	0·50 (0·36–0·67)
No	116	16/68	23/48	0·40 (0·21–0·76)
Refractory to anti-CD38 antibody therapy and lenalidomide*				
Yes	326	80/199	72/127	0·47 (0·34–0·65)
No	153	25/89	31/64	0·48 (0·28–0·82)
Refractory to pomalidomide				
Yes	155	49/99	37/56	0·51 (0·33–0·78)
No	324	56/189	66/135	0·44 (0·31–0·64)

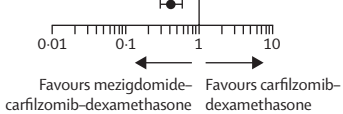

***Figure*: Progression-free survival**

(A) Kaplan–Meier estimates of progression-free survival among patients in the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. (B) Subgroup analysis by demographics and disease characteristics of progression-free survival in patients in the confirmatory analysis group. (C) Subgroup analysis by previous therapy and refractoriness of progression-free survival in patients in the confirmatory analysis group. (B) and (C) A hazard ratio of less than 1·0 indicates an advantage for mezigdomide–carfilzomib–dexamethasone versus carfilzomib–dexamethasone; hazard ratios are unstratified. Higher stages of the ISS indicate more severe disease. High-risk cytogenetics is defined as presence of del(17p), and/or translocation t(4;14), and/or translocation t(14;16); standard risk is defined as absence of del(17p), translocation t(4;14), and translocation t(14;16). ISS=International Staging System. *Subgroup analyses were prespecified unless indicated as exploratory.

were continuing treatment. The most common reason for discontinuation was disease progression (appendix p 25), occurring in 85 (30%) patients receiving mezigdomide–carfilzomib–dexamethasone and 93 (49%) receiving carfilzomib–dexamethasone. At a median follow-up of 10·6 months (IQR 7·2–15·3), the median duration of mezigdomide–carfilzomib–dexamethasone treatment was longer than for carfilzomib–dexamethasone (8·9 months [5·6–13·1] *vs* 6·2 months [3·2–10·5]); 83 (29%) patients receiving mezigdomide–carfilzomib–dexamethasone had at least 1 year of treatment, versus 36 (19%) of 186 receiving carfilzomib–dexamethasone. Median relative dose intensity was 83% (64–94) for mezigdomide and 87% (74–97) and 94% (81–100) for carfilzomib in the mezigdomide–carfilzomib–dexamethasone and carfilzomib–dexamethasone groups, respectively (appendix p 37). Reduction of mezigdomide dose was reported for 122 (42%) patients, with a median of 1·0 dose reduction (1·0–2·0).

The risk of disease progression or death was significantly lower for patients receiving mezigdomide–carfilzomib–dexamethasone versus carfilzomib–dexamethasone, with the p value crossing the prespecified superiority boundary at the interim analysis. At data cutoff, 208 events of disease progression or death had been recorded (105 [36%] of 288 patients in the mezigdomide–carfilzomib–dexamethasone group; 103 [54%] of 191 patients in the carfilzomib–dexamethasone group). PFS was significantly longer with mezigdomide–carfilzomib–dexamethasone than with carfilzomib–dexamethasone (median 18·0 months [95% CI 14·5–22·1] *vs* 8·3 months [5·6–10·7]; HR for disease progression or death, 0·48 [0·36–0·63]; p<0·0001; figure A). In subgroup analyses, the PFS benefit with mezigdomide–carfilzomib–dexamethasone was consistently observed across prespecified subgroups, including patients with high-risk cytogenetics, soft-tissue plasmacytomas, anti-CD38 antibody or lenalidomide refractoriness, age 75 years or older, and more than

two previous lines of therapy (figure B, C). In an exploratory analysis, the benefit of mezigdomide–carfilzomib–dexamethasone was also observed for patients with functional high-risk disease (defined as progressive disease within 18 months of first-line therapy;[29,30] figure B), and those with individual and two or more cytogenetic abnormalities (appendix p 36). Notably, the median PFS for patients with one previous line of therapy receiving mezigdomide–carfilzomib–dexamethasone was not reached (NR) versus 6·4 months with carfilzomib–dexamethasone. The median time to progression was 20·7 months (95% CI 18·0–NR) for mezigdomide–carfilzomib–dexamethasone versus 9·2 months (6·2–11·3) for carfilzomib–dexamethasone (HR 0·40 [95% CI 0·30–0·55]; appendix p 26). PFS2, defined as the time from randomisation to documented disease progression on the next-line therapy after study therapy, or death from any cause, whichever occurs first, was also prolonged for patients receiving mezigdomide–carfilzomib–dexamethasone (23·6 months [95% CI 18·2–NR]) versus carfilzomib–dexamethasone (13·0 months [10·8–18·1]; HR 0·53 [95% CI 0·39–0·72]; appendix p 27). More patients in the carfilzomib–dexamethasone group than in the mezigdomide–carfilzomib–dexamethasone group received subsequent therapy (95 [50%] of 191 *vs* 69 [24%] of 288); the most common subsequent therapy in either group was bispecific antibodies (29 [10%] with mezigdomide–carfilzomib–dexamethasone; 41 [21%] with carfilzomib–dexamethasone; appendix p 27). Because only approximately a third of patients had received subsequent therapy at the time of this interim analysis, time to next treatment data were not yet mature for meaningful interpretation. A higher proportion of patients receiving mezigdomide–carfilzomib–dexamethasone versus carfilzomib–dexamethasone achieved a complete response or better (77 [27%] *vs* 17 [9%]; proportion difference, 18% [95% CI 11–24]), very good partial response or better (173 [60%] *vs* 59 [31%]; proportion difference 29% [95% CI 20–37]), and overall response (231 [80%] *vs* 102 [53%]; proportion difference 27% [95% CI 18–35]; table 2). The median time to response was 1·1 months (IQR 1·0–1·9) with mezigdomide–carfilzomib–dexamethasone and 1·1 months (IQR 1·0–1·9) with carfilzomib–dexamethasone. Acknowledging the short median follow-up, 72% (95% CI 65–78) of patients receiving mezigdomide–carfilzomib–dexamethasone continued to respond at 12 months versus 54% (95% CI 41–66) of those receiving carfilzomib–dexamethasone (appendix p 28). An analysis of minimal residual disease among patients who achieved complete response or better is ongoing and will be reported subsequently.

At this interim overall survival futility analysis, 62 (22%) deaths of 288 patients were reported in the mezigdomide–carfilzomib–dexamethasone group and 51 (27%) of 191 in the carfilzomib–dexamethasone group (HR 0·79 [95% CI 0·54–1·15]; appendix p 29). The most common cause of death was progressive disease (39 [14%] and 36 [19%] patients, respectively; appendix p 38). Three (2%) of 191 patients in the carfilzomib–dexamethasone group died before treatment initiation.

	Mezigdomide–carfilzomib–dexamethasone (n=288)	Carfilzomib–dexamethasone (n=191)	Difference*
Overall response†	231	102	..
Rate	80% (75–85)	53% (46–61)	27% (18–35)
Best response			
Stringent complete response	72 (25%)	16 (8%)	..
Complete response	5 (2%)	1 (1%)	..
Very good partial response	96 (33%)	42 (22%)	..
Partial response	58 (20%)	43 (23%)	..
Minimal response	6 (2%)	5 (3%)	..
Stable disease	38 (13%)	62 (32%)	..
Progressive disease	3 (1%)	14 (7%)	..
Not evaluable	2 (1%)	0	..
Missing	8 (3%)	8 (4%)	..
Complete response or better	77	17	..
Rate	27% (22–32)	9% (5–14)	18% (11–24)
Very good partial response or better	173	59	..
Rate	60% (54–66)	31% (24–38)	29% (20–37)
Time to response, months‡	1·1 (1·0–1·9)	1·1 (1·0–1·9)	..

Data are n, n (%), % (95% CI), or median (IQR). Percentages might not total 100% due to rounding. In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomly assigned to 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone. Best overall response was evaluated by an independent review committee. *Proportion difference with two-sided 95% CI. †Patients who had a partial response or better. ‡Time to response is defined as the time from randomisation to the first documentation of response (partial response or better).

Table 2: **Treatment response**

The most common adverse events are reported in table 3; all-grade and grade 3, 4, and 5 adverse events are reported in the appendix (pp 39–63). The most common grade 3 or 4 adverse event in the mezigdomide–carfilzomib–dexamethasone group was neutropenia, which occurred in 176 (61%) of 288 patients compared with 17 (9%) of 186 receiving carfilzomib–dexamethasone, with lower rates observed in the USA (12 [44%] of 27 patients) and Europe (50 [46%] of 109) compared with Asia (71 [81%] of 88; appendix p 64). Grade 3 or 4 febrile neutropenia was observed in 23 (8%) patients receiving mezigdomide–carfilzomib–dexamethasone and none receiving carfilzomib–dexamethasone. The median duration of grade 3 or 4 neutropenia, including febrile neutropenia, was 10 days for both mezigdomide–carfilzomib–dexamethasone (IQR 6–15) and carfilzomib–dexamethasone (IQR 6–14). Dose delay or pause of mezigdomide due to neutropenia or febrile neutropenia occurred for 111 (39%) patients in the mezigdomide–carfilzomib–dexamethasone group. Carfilzomib dosing was delayed or paused for the same reason in 98 (34%) patients in the mezigdomide–carfilzomib–dexamethasone group versus one (1%) patient in the carfilzomib–dexamethasone group. Grade 3 or 4 thrombocytopenia

	Mezigdomide–carfilzomib–dexamethasone (n=288)		Carfilzomib–dexamethasone (n=186)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Patients with an adverse event	286 (99%)	241 (84%)	178 (96%)	105 (56%)
Haematological				
Neutropenia*	199 (69%)	176 (61%)	32 (17%)	17 (9%)
Thrombocytopenia†	174 (60%)	113 (39%)	77 (41%)	42 (23%)
Anaemia	149 (52%)	75 (26%)	66 (35%)	28 (15%)
White blood cell count decrease	67 (23%)	54 (19%)	23 (12%)	7 (4%)
Non-haematological				
Diarrhoea	112 (39%)	10 (3%)	33 (18%)	1 (1%)
Upper respiratory tract infection	79 (27%)	13 (5%)	31 (17%)	3 (2%)
Fatigue	67 (23%)	9 (3%)	39 (21%)	7 (4%)
Cough	66 (23%)	1 (<1%)	22 (12%)	0
Pneumonia	58 (20%)	45 (16%)	21 (11%)	11 (6%)
Dyspnoea	58 (20%)	11 (4%)	26 (14%)	5 (3%)
Hypertension	31 (11%)	11 (4%)	40 (22%)	17 (9%)
Patients with a serious adverse event	188 (65%)	157 (55%)	63 (34%)	52 (28%)
Pneumonia	44 (15%)	38 (13%)	12 (6%)	10 (5%)
Acute kidney injury	14 (5%)	13 (5%)	3 (2%)	3 (2%)
Thrombocytopenia†	13 (5%)	13 (5%)	3 (2%)	3 (2%)
Febrile neutropenia	13 (5%)	13 (5%)	0	0
Neutropenia*	11 (4%)	11 (4%)	0	0
Upper respiratory tract infection	11 (4%)	9 (3%)	0	0

Data are n (%). Reported here are the treatment-emergent adverse events of any grade that occurred in ≥20% of patients and grade 3 or 4 treatment-emergent adverse events that occurred in ≥10% of patients in either treatment group, and serious treatment-emergent adverse events (any grade) that occurred in ≥4% of patients in either treatment group in the confirmatory analysis group of the safety population, defined as all patients from stages 1 and 2 randomly assigned to 1·0 mg mezigdomide plus carfilzomib and dexamethasone or carfilzomib–dexamethasone alone who received at least one dose of study treatment. Adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. *Includes Medical Dictionary for Regulatory Activities preferred terms of neutropenia and neutrophil count decreased. †Includes preferred terms of thrombocytopenia and platelet count decreased.

Table 3: **Most common adverse events and serious adverse events**

occurred in 113 (39%) patients receiving mezigdomide–carfilzomib–dexamethasone, with lower rates in the USA (three [11%] of 27 patients) and Europe (23 [21%] of 109) than Asia (57 [65%] of 88). One (<1%) patient discontinued treatment due to neutropenia in the mezigdomide–carfilzomib–dexamethasone group and none in the carfilzomib–dexamethasone group. GCSF was administered to most patients with grade 3 or 4 neutropenia during each treatment cycle (appendix p 30).

Serious adverse events were reported in 188 (65%) patients receiving mezigdomide–carfilzomib–dexamethasone and 63 (34%) receiving carfilzomib–dexamethasone; the most common was pneumonia (44 [15%] and 12 [6%] patients, respectively; appendix pp 65–66). The most common adverse events leading to dose delay or reduction were infections, haematological toxicities, and general disorders in both groups (appendix pp 67–68). Discontinuation due to an adverse event occurred in 28 (10%) patients in the mezigdomide–carfilzomib–dexamethasone group and 11 (6%) in the carfilzomib–dexamethasone group. Infections were reported in 210 (73%) patients in the mezigdomide–carfilzomib–dexamethasone group and 100 (54%) in the carfilzomib–dexamethasone group (appendix p 69); upper respiratory tract infection was the most frequent, occurring in 79 (27%) and 31 (17%) patients, respectively. In the mezigdomide–carfilzomib–dexamethasone group, 98 (34%) patients had grade 3 or 4 infections (82 [28%] patients had a worst grade of 3 and 16 [6%] had a worst grade of 4), versus 29 (16%) in the carfilzomib–dexamethasone group (28 [15%] with a worst grade of 3 and one [1%] with a worst grade of 4); regional variation in infection rates was observed with mezigdomide–carfilzomib–dexamethasone, with lower incidence of grade 3 or 4 infections reported in the USA (none) and Europe (28 [26%] of 109) compared with Asia (43 [49%] of 88; appendix p 64). The median time to onset of grade 3 or 4 infections with mezigdomide–carfilzomib–dexamethasone was 73 days (IQR 20–155) and with carfilzomib–dexamethasone was 114 days (IQR 37–232). The most common grade 3 or 4 infection was pneumonia (45 [16%] with mezigdomide–carfilzomib–dexamethasone; 11 [6%] with carfilzomib–dexamethasone). Infections concurrent with grade 3 or higher neutropenia occurred in 66 (31%) of 210 patients treated with mezigdomide–carfilzomib–dexamethasone and in two (2%) of 100 patients treated with carfilzomib–dexamethasone alone. Fatal infections occurred in seven (2%) of 288 patients and two (1%) of 186 patients, respectively. In the mezigdomide–carfilzomib–dexamethasone group, discontinuation due to infection was infrequent (<2·5%). The frequencies of *P jirovecii* pneumonia and cytomegalovirus infection were low (appendix p 69). Most cases occurred before the implementation of reinforced protocol-specified *P jirovecii* pneumonia prophylaxis. In total, 91 (32%) and 39 (21%) patients, respectively, received one or more doses of immunoglobulin therapy. Antiviral prophylaxis adherence was high in all patients.

Cardiovascular adverse events were similar between treatment groups (cardiac events: 52 [18%] patients with mezigdomide–carfilzomib–dexamethasone and 30 [16%] with carfilzomib–dexamethasone; and vascular events: 64 [22%] with mezigdomide–carfilzomib–dexamethasone and 55 [30%] with carfilzomib–dexamethasone). The most common cardiac adverse event in both groups was cardiac failure (eight [3%] patients with mezigdomide–carfilzomib–dexamethasone and seven [4%] with carfilzomib–dexamethasone), and the most common vascular event was hypertension (31 [11%] with mezigdomide–carfilzomib–dexamethasone and 40 [22%] with carfilzomib–dexamethasone). Second primary malignancies were reported in seven (2%) patients receiving mezigdomide–carfilzomib–dexamethasone and four (2%) receiving carfilzomib–dexamethasone (appendix p 70). Additional safety results are reported in the appendix (p 24).

Deaths were reported in 62 (22%) of 288 patients in the mezigdomide–carfilzomib–dexamethasone group and 51 (27%) of 191 patients in the carfilzomib–dexamethasone group, mainly due to disease progression, adverse events, and the category termed other (appendix p 38). The number of deaths from adverse events and other reasons was 19 (7%) in the mezigdomide–carfilzomib–dexamethasone group and 15 (8%) in carfilzomib–dexamethasone group. Deaths in the other category were primarily cardiac or infectious events. Of the deaths from adverse events, the investigator determined that the event was related to a trial treatment in eight (3% [95% CI 1–5]) patients receiving mezigdomide–carfilzomib–dexamethasone and one (1% [95% CI 0–3]) patient receiving carfilzomib–dexamethasone (rate difference 2% [95% CI –1 to 5]; appendix p 71).

Health-related quality of life was generally maintained in the mezigdomide–carfilzomib–dexamethasone group compared with the carfilzomib–dexamethasone group. The EORTC QLQ-C30 questionnaire scores for global health status and functional domains remained relatively stable during on-treatment visits, with mean changes from baseline remaining below the prespecified thresholds for meaningful change in both treatment groups (appendix pp 31–32). Similar findings were observed for disease-specific domains measured by the EORTC QLQ-MY20 questionnaire, including disease symptoms, side effects of treatment, body image, and future perspectives (appendix pp 33–35).

Discussion

This prespecified interim efficacy analysis reports results of SUCCESSOR-2, a phase 3 trial employing an inferentially seamless two-stage design that enabled prospective, randomised dose optimisation of mezigdomide in relapsed or refractory multiple myeloma. Patients who had received at least one previous therapy, including anti-CD38 antibodies and lenalidomide, and received mezigdomide–carfilzomib–dexamethasone had a statistically significant and clinically meaningful improvement in PFS compared with patients who received carfilzomib–dexamethasone alone. Benefit was observed as early as first relapse and was consistent across key prespecified subgroups, irrespective of previous lines of therapy, age, cytogenetic risk, or presence of soft-tissue plasmacytomas. Moreover, this benefit was maintained in patients with functional high-risk disease, suggesting benefit with mezigdomide–carfilzomib–dexamethasone in a population with a particularly high unmet need. Finally, the observed efficacy of mezigdomide–carfilzomib–dexamethasone following lenalidomide exposure, and in patients exposed to pomalidomide, suggests a differentiated mechanism of action and superior activity for mezigdomide versus immunomodulatory drugs.

Patients with relapsed or refractory multiple myeloma increasingly present with multidrug-refractory disease following frontline treatment with anti-CD38 antibody-containing and lenalidomide-containing regimens.[1,2] Real-world data indicate poor outcomes among patients refractory to both agents, with median PFS ranging from approximately 4 months to 6 months.[2,31] Although several agents have shown clinical activity in relapsed or refractory multiple myeloma,[4–7,32] prospective evidence remains scarce in patients who are exposed or refractory to both anti-CD38 antibodies and lenalidomide. In the KarMMa-3 trial, median PFS was 13·8 months for idecabtagene vicleucel versus 4·4 months for standard regimens (daratumumab–pomalidomide–dexamethasone, daratumumab–bortezomib–dexamethasone,carfilzomib–dexamethasone,elotuzumab–pomalidomide–dexamethasone, and ixazomib–lenalidomide–dexamethasone).[5] In the daratumumab-exposed subgroup of the CARTITUDE-4 trial, median PFS was 19·3 months for ciltacabtagene autoleucel versus 4·5 months with pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone.[6] The phase 2 single-arm SELECT study (N=52), which enrolled patients with one or two previous lines of treatment (77% exposed to anti-CD38 antibodies and 100% to lenalidomide), established a median PFS of 11·1 months for patients receiving carfilzomib–pomalidomide–dexamethasone.[32] Several phase 3 trials investigating bispecific antibodies in similar populations to SUCCESSOR-2 are currently ongoing (ie, NCT06208150, NCT05572515, and NCT06152575). Of note, the BCMA-targeted bispecific antibody teclistamab monotherapy improved PFS (not reached *vs* 8·2 months) and overall survival compared with carfilzomib–dexamethasone or pomalidomide–bortezomib–dexamethasone in patients who had received one to three previous lines of therapy.[8] Cross trials comparisons should be interpreted with caution because of differences in trial design, patient populations, and follow-up time.

Multidrug-refractory disease following first-line relapse represents an evolving and critical unmet medical need, with key questions remaining around optimal treatment sequencing and combination approaches. BCMA-targeted therapies have shown PFS improvements over triplet regimens in patients with previous anti-CD38 antibody and lenalidomide exposure.[5,6] However, multiple factors associated with resistance to BCMA-targeted therapies, such as high tumour burden, elevated soluble BCMA levels, immune and T-cell fitness, high-risk disease, and presence of soft-tissue plasmacytomas, underscore the need for differentiated treatment approaches for individual patients.[33] In addition, BCMA-targeted therapies and other T-cell-redirecting therapies are associated with complex safety considerations (eg, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, opportunistic infections, or ocular toxicity)[4–7] that require specialised management, and therefore might not be appropriate for all patients and

treatment settings. The clinical benefit observed with the novel triplet mezigdomide–carfilzomib–dexamethasone expands available treatment options in relapsed or refractory multiple myeloma by providing a differentiated mechanism of action that might address limitations of current therapies. Although additional investigation is required to define the optimal sequencing of available treatments, preliminary data offer some insights. Mezigdomide promotes T-cell and natural killer cell activation and proliferation and mitigates T-cell exhaustion,[17,18] creating an immunologically favourable environment that amplifies the effectiveness of BCMA-targeted agents.[34] In addition, its differentiated mechanism of action might be associated with non-overlapping resistance mechanisms, suggesting that patients could derive benefit from subsequent BCMA-targeted therapies following mezigdomide–carfilzomib–dexamethasone treatment. As a practical and readily adoptable treatment option, mezigdomide–carfilzomib–dexamethasone could also be used before cell therapy. With preliminary efficacy observed in patients previously exposed to BCMA-targeted therapy and CAR T-cell or T-cell engagers,[12] together with its immunomodulatory activity, mezigdomide-based regimens might represent a valid therapeutic option between sequential T-cell-redirecting therapies. Finally, mezigdomide in combination with T-cell-redirecting therapies represents a promising therapeutic strategy that is undergoing additional investigation as maintenance or combination partner (eg, NCT06121843 and NCT06988488).

The results of our trial indicate that mezigdomide–carfilzomib–dexamethasone has substantial activity in patients with myeloma at first and subsequent relapses; importantly, the PFS benefit was maintained regardless of previous treatment (number of previous lines of therapy, refractory status to anti-CD38 therapy or other treatments), age, cytogenetic status, or the presence of soft-tissue plasmacytomas. Additionally, the oral nature of mezigdomide, combined with the well established carfilzomib–dexamethasone standard of care supports the use of this regimen across diverse treatment settings, including community practice. This represents a potential practical advantage over BCMA-targeting therapies and other T-cell-redirecting therapies, which require specialised centres for administration and significant operational and logistical considerations.

Carfilzomib–dexamethasone is an effective, guideline-recommended treatment option for patients with early relapsed or refractory multiple myeloma.[35] With the well characterised risk–benefit profile of carfilzomib–dexamethasone, the addition of mezigdomide to the approved regimen allowed for evaluation of the specific contribution of mezigdomide to the efficacy and safety of the combination. The shorter PFS observed in the carfilzomib–dexamethasone group as compared with earlier studies[36,37] reflects the high degree of drug exposure and refractoriness in this population, which is more representative of current clinical practice.[2] Indeed, the PFS results observed for carfilzomib–dexamethasone in SUCCESSOR-2 are in line with that observed for patients receiving carfilzomib–dexamethasone or pomalidomide–bortezomib–dexamethasone (8·2 months) as part of the control group in the MajesTEC-9 trial, where 70% received carfilzomib–dexamethasone, in a population with a similar universal exposure to anti-CD38 antibodies and lenalidomide.[8] In this setting, the magnitude of benefit observed with mezigdomide–carfilzomib–dexamethasone is notable, as it more than doubles the median PFS of carfilzomib–dexamethasone. In addition, real-world data show that carfilzomib–dexamethasone is one of the most commonly used regimens in patients with previous anti-CD38 antibody and lenalidomide exposure,[2] highlighting its relevance in the SUCCESSOR-2 trial population. Of note, other ongoing phase 3 trials investigating the same patient population include carfilzomib–dexamethasone in their control group (eg, NCT05572515, NCT06152575, and NCT06413498). At the time the SUCCESSOR-2 trial was designed, treatment options at first relapse that were both anti-CD38 antibody-free and lenalidomide-free were limited to a small number of approved regimens (ie, pomalidomide–bortezomib–dexamethasone and selinexor–bortezomib–dexamethasone), which have shown median PFS of 11·2–13·9 months across studies.[38,39] Other combinations such as elotuzumab–pomalidomide–dexamethasone and carfilzomib–pomalidomide–dexamethasone[32] were either restricted to later lines of therapy or not approved in this setting.[35] In this context, carfilzomib–dexamethasone showed consistent efficacy across phase 3 studies in patients with similar previous treatment exposure (one to three previous lines), with median PFS ranging from 15·8 to 18·7 months.[36,37] The ongoing SUCCESSOR-1 trial (NCT05519085), comparing mezigdomide–bortezomib–dexamethasone versus pomalidomide–bortezomib–dexamethasone, will provide an informative head-to-head comparison of a mezigdomide triplet regimen versus an established triplet regimen containing an immunomodulatory drug.

The safety profile of mezigdomide–carfilzomib–dexamethasone was consistent with findings from early-phase mezigdomide studies;[12,13] no new or unexpected adverse events were identified. As a known, reversible on-target effect of mezigdomide treatment, neutropenia was the most common grade 3 or 4 adverse event. An increased incidence of infections was observed with mezigdomide–carfilzomib–dexamethasone compared with carfilzomib–dexamethasone, with regional variation noted, including lower rates in the USA and Europe compared with Asia. Most infections occurred in the absence of concurrent grade 3 or 4

neutropenia. The incidence of fatal infections with mezigdomide–carfilzomib–dexamethasone (2%) was comparable with that reported in other studies of similar populations.[5–7,37] Despite higher rates of neutropenia and infections with mezigdomide–carfilzomib–dexamethasone, patient-reported quality of life remained similar between the three-drug and two-drug regimens. After implementation of reinforced protocol-specified management strategies in December 2024, including enhanced GCSF support and mandatory *P jirovecii* pneumonia prophylaxis, alongside ongoing measures such as dose modifications, immunoglobulin replacement, and antiviral prophylaxis, a reduction in neutropenia and infections was observed. A notable reduction in grade 3 or 4 hypertension was observed, potentially associated with the lower carfilzomib dose in the mezigdomide–carfilzomib–dexamethasone group.

Grade 5 treatment-emergent adverse events, which included those related to myeloma progression, occurred more frequently during treatment with mezigdomide–carfilzomib–dexamethasone than with carfilzomib–dexamethasone, whereas overall mortality was lower with mezigdomide–carfilzomib–dexamethasone, driven by fewer deaths attributed to disease progression.

A distinguishing feature of this trial is the inferentially seamless two-stage design, in which stage 1 data informed enrolment into stage 2 within a single, fully randomised protocol, enabling dose optimisation while preserving the rigour of randomisation. Considering the different carfilzomib–dexamethasone dosing schedules between the treatment groups and the known on-target toxicity of neutropenia for mezigdomide, double-masking was not possible. The open-label design might have introduced performance or reporting bias; the primary and key secondary efficacy endpoints were objective (PFS and overall survival) and clinical responses were evaluated by an independent review committee to mitigate potential bias.

A limitation of this prespecified interim analysis is the relatively short follow-up of 10·6 months, thus overall survival evaluation is ongoing; furthermore, duration of response was affected by substantial censoring due to ongoing responses at the time of data cutoff, with responses expected to deepen with longer follow-up. Additionally, exclusion of patients with previous carfilzomib exposure might limit the generalisability of these results to this patient population. The definition of high-risk cytogenetics was based on criteria established at the time of trial design and does not reflect updated International Myeloma Society and International Myeloma Working Group risk stratification frameworks.[40]

In conclusion, mezigdomide–carfilzomib–dexamethasone showed a significant PFS benefit as early as first relapse in a growing population with substantial unmet medical need that is predominantly refractory to anti-CD38 antibodies and lenalidomide. Although grade 3 or 4 adverse events, including infections, occurred more frequently with mezigdomide–carfilzomib–dexamethasone, adverse events were mostly manageable through standard clinical practice and supportive care. Oral mezigdomide plus intravenous carfilzomib and oral or intravenous dexamethasone offers an outpatient treatment option with potential implementation across diverse care settings, including community practice. These findings support mezigdomide–carfilzomib–dexamethasone as a potent, differentiated, easily adoptable potential new standard of care for relapsed or refractory multiple myeloma.

Contributors

MAD, FS, PM, BY, AR, PKo, JKa, and PGR participated in the conception and design of the study. JG and ZZ did the data analysis. MAD, FS, CFu, MAH-B, CG, DR, GM, OA, CP, EdQC, KG, HI, DW, RG, CL, C-JL, HQ, YW, CC, CFo, VH, PKa, VG, PJH, MK-H, YLK, ML, AM, OM, CN, SVSSP, MSR, GV, EvdH, ZX, PAO, AO, JY, JKu, and PGR contributed to data acquisition. All authors contributed to data interpretation. MAD, JG, ZZ, PM, BY, AR, PKo, JKa, and PGR accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The Bristol Myers Squibb policy on data sharing can be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Bristol Myers Squibb will honour legitimate requests for our clinical trial data from qualified researchers with a clearly defined scientific objective. Data considered for sharing might include non-identifiable patient-level and study-level clinical trial data, full clinical study reports and protocols from trials completed on or after Jan 1, 2008, with primary results published in peer-reviewed journals.

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