Article:
Dimopoulos, M.A., Schjesvold, F., Fu, C. et al. (2026) 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. The Lancet. ISSN: 0140-6736

https://doi.org/10.1016/s0140-6736(26)01088-3

The Lancet

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

--Manuscript Draft--

Manuscript Number:	
Article Type:	Fast Track (Randomised Controlled Trial)
Keywords:	
Corresponding Author:	Meletios A Dimopoulos, MD National and Kapodistrian University of Athens Athens, GREECE
First Author:	Meletios A Dimopoulos, MD
Order of Authors:	Meletios A Dimopoulos, MD
	Fredrik Schjesvold
	Chengcheng Fu
	Monique Hartley-Brown
	Cesar Gomez
	Donna Reece
	Gabor Mikala
	Omar Alkharabsheh
	Christopher Parrish
	Edvan Crusoe
	Kenny Galvez
	Henry Idrobo
	Darrell White
	Ridhi Gupta
	Cindy Lee
	Chia-Jen Liu
	Hang Quach
	Yafei Wang
	Claudio Cerchione
	Cecily Forsyth
	Vania Hungria
	Pritam Kalaskar
	Vasko Grakanlov
	Phoebe Joy Ho
	Maika Klaiber-Hakimi
	Yok Lam Kwong
	Martha Louzada
	Amitabha Mazumder

	Oliver Miles
	Chandramouli Nagarajan
	Sripada V.S.S. Prasad
	Marc S Raab
	Gergely Varga
	Eyck von der Heyde
	Zhongjun Xia
	Paola Andrea Ochoa
	Albert Oriol
	Junichiro Yuda
	Junya Kuroda
	Jing Gong
	Zehua Zhou
	Paulo Maciag
	Brian Yu
	Alberto Rocci
	Phillip Koo
	Jessica Katz
	Paul G Richardson
Manuscript Region of Origin:	UNITED STATES OF AMERICA
Abstract:	Background A growing number of patients with multiple myeloma are anti-CD38 antibody- and lenalidomide-exposed at first relapse, subsequently limiting their treatment options. Mezigdomide, a potent cereblon E3 ligase modulator, induces maximal, rapid Ikaros/Aiolos degradation, resulting in enhanced myeloma cell cytotoxicity and immune stimulation versus immunomodulatory drugs. Methods This phase 3, open-label, randomised controlled trial (ClinicalTrials.gov NCT05552976; active, not recruiting) was conducted at 160 hospital-based sites in 26 countries using a two-stage, inferentially seamless design. Eligible adult patients had measurable multiple myeloma, ≥1 prior 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 randomise patients, stratified by age (≤70 or >70 years), number of prior 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/intravenous dexamethasone (40 mg weekly) (MeziKd) or carfilzomib (56 mg/m2 twice weekly or 70 mg/m2 weekly) and dexamethasone (20 mg twice weekly or 40 mg weekly) (Kd). Stage 1 optimised mezigdomide dosing across three levels. Stage 2 randomised patients to the selected mezigdomide dose (1·0 mg) plus Kd or Kd alone. The primary endpoint was progression-free survival evaluated in patients who received 1·0 mg mezigdomide plus Kd or Kd alone across both study stages. No imputation was planned for missing efficacy endpoint values or missing safety evaluations. Findings Between 3 February 2023 and 28 November 2025, 606 patients were enrolled and 479 (MeziKd, n=288; Kd, n=191) were included in the analyses: 252 (53%) were male, 411 (86%) anti-CD38 antibody-refractory, and 363 (76%) lenalidomide-refractory, with a median of 2 prior lines of therapy (IQR, 2–4). At 10·6 months median follow-up, MeziKd significantly improved progression-free survival compared with Kd (median, 18·0 vs 8·3 months; HR, 0·48; 95% CI, 0·36–0·63; p<0·0001). Grade 3/4 adverse events were observed in 241 (84%) MeziKd patients versus 105 (56%) for Kd, including

	neutropenia (176 [61%] vs 17 [9%]) and infections (98 [34%] vs 29 [16%]). Eight (3%) and one (1%) treatment-related grade 5 adverse events were reported with MeziKd and with Kd, respectively. Interpretation MeziKd significantly improved progression-free survival, with a predictable, manageable safety profile, as early as first relapse in a predominantly triple-class-exposed, anti-CD38 antibody- and lenalidomide-refractory population, supporting MeziKd as a clinically meaningful treatment option for this growing population with substantial unmet need. Funding Bristol Myers Squibb

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

Meletios A. Dimopoulos, Fredrik Schjesvold, Chengcheng Fu, Monique A. Hartley-Brown, Cesar Gomez, Donna Reece, Gabor Mikala, Omar Alkharabsheh, Christopher Parrish, Edvan de Queiroz Crusoé, Kenny Gálvez, Henry Idrobo, Darrell White, Ridhi Gupta, Cindy Lee, Chia-Jen Liu, Hang Quach, Yafei Wang, Claudio Cerchione, Cecily Forsyth, Vania Hungria, Pritam Kalaskar, Vasko Graklanov, Phoebe Joy Ho, Maika Klaiber-Hakimi, Yok Lam Kwong, Martha Louzada, Amitabha Mazumder, Oliver Miles, Chandramouli Nagarajan, Sripada V.S.S. Prasad, Marc S. Raab, Gergely Varga, Eyck von der Heyde, Zhongjun Xia, Paola Andrea Ochoa, Albert Oriol, Junichiro Yuda, Junya Kuroda, Jing Gong, Zehua Zhou, Paulo Maciag, Brian Yu, Alberto Rocci, Phillip Koo, Jessica Katz, Paul G. Richardson, on behalf of the SUCCESSOR-2 Trial Investigators

Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece (Prof MA Dimopoulos MD); Department of Medicine, Korea University College of Medicine, Seoul, Republic of Korea (Prof MA Dimopoulos); Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway (F Schjesvold MD PhD); The First Affiliated Hospital of Soochow University, Jiangsu Institute of Hematology, Suzhou, China (C Fu MD PhD); Dana-Farber Cancer Institute, Boston, MA, USA (MA Hartley-Brown MD, Prof PG Richardson MD); Department of Haematology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, United Kingdom (C Gomez MD PhD); Department of Medical Oncology and Hematology, The Princess Margaret Cancer Centre, Toronto, ON, Canada (Prof D Reece MD); Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary (G Mikala MD PhD, G Varga MD); USA Health Mitchell Cancer Institute, University of South Alabama, Mobile, AL, USA (O Alkharabsheh MD); Department of Haematology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom (C Parrish MD); D'Or Institute for Research and Education, Salvador, Brazil and Department of Internal Medicine, Federal University of

Bahia, Salvador, Brazil (E de Queiroz Crusoé MD PhD); Hospital Pablo Tobón Uribe, Medellín, Colombia (K Gálvez MD); Julián Coronel Medical Center, Cali, Colombia (H Idrobo MD); Division of Hematology, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada (Prof D White MD); Department of Oncology, Montefiore Medical Center and Albert Einstein College of Medicine, New York, NY, USA (R Gupta MD); Department of Haematology, Royal Adelaide Hospital, Adelaide, SA, Australia (C Lee MBBS); Division of Transfusion Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (C-J Liu, MD PhD); Department of Haematology, St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, VIC, Australia (Prof H Quach MD MBBS); Department of Hematology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin's Clinical Research Center for Cancer, Tianjin, China (Y Wang MD); Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy (C Cerchione MD); Department of Haematology, Gosford Hospital, Gosford, NSW, Australia (C Forsyth MBBS); Clinica São Germano, São Paulo, Brazil (V Hungria MD PhD); Mumbai Oncocare Centre, Thane, India (P Kalaskar, MD DM); Department of Clinical Hematology, University Hospital "Sveti Georgi," Medical University of Plovdiv, Plovdiv, Bulgaria (V Graklanov MD PhD); Institute of Haematology, Royal Prince Alfred Hospital and University of Sydney, Sydney, NSW, Australia (Prof PJ Ho MBBS DPhil); Clinic for Hematology, Oncology and Palliative Care, Marien Hospital Düsseldorf, Düsseldorf, Germany (M Klaiber-Hakimi MD); Division of Haematology, Oncology, and Bone Marrow Transplantation, Department of Medicine, School of Clinical Medicine, University of Hong Kong, Hong Kong, China (Prof YL Kwong MD); London Regional Cancer Center, London, ON, Canada (M Louzada MD); The Oncology Institute of Hope & Innovation, Glendale, CA, USA (Prof A Mazumder MD); Department of Haematology, Musgrove Park Hospital, Taunton, United Kingdom (O Miles MBBS); Department of Haematology, Singapore General Hospital and National Cancer Centre Singapore, Singapore, Singapore (C Nagarajan MD); Department of Hematology and Medical Oncology, Apollo Hospitals, Hyderabad, India (SVSS Prasad MBBS MD DM); Heidelberg Myeloma Center, Department of Medicine V, University Hospital Heidelberg, Heidelberg, Germany (Prof MS Raab MD); Onkologische Schwerpunktpraxis Dres. Ingo Zander und Eyck von der Heyde, Hanover, Germany (E von der

Heyde MD); Department of Hematologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China (Z Xia MD); Instituto Alexander Fleming, Buenos Aires, Argentina (PA Ochoa MD); Catalan Institute of Oncology and Josep Carreras Institute, Hospital Germans Trias i Pujol, Badalona, Spain (A Oriol MD PhD); Department of Hematology, National Cancer Center Hospital East, Chiba, Japan (J Yuda MD PhD); [39]Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan (Prof J Kuroda MD PhD); [40]Bristol Myers Squibb, Princeton, NJ, USA (J Gong PhD, Z Zhou PhD, P Maciag MD PhD, B Yu PharmD, P Koo PharmD, J Katz MD PhD); [41]Celgene International Sàrl, a Bristol-Myers Squibb Company, Boudry, Switzerland (A Rocci MD PhD)

Correspondence to: Prof Meletios A. Dimopoulos, Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens,11528, Athens, Greece
mdimop@med.uoa.gr

Journal: *The Lancet*

Article Type: Article

Abstract word count: 414

Article word count: 4165

References: 32

Figures/Tables: 4

Supplementary Material: Supplementary Appendix

Summary

Background

A growing number of patients with multiple myeloma are anti-CD38 antibody- and lenalidomide-exposed at first relapse, subsequently limiting their treatment options. Mezigdomide, a potent cereblon E3 ligase modulator, induces maximal, rapid Ikaros/Aiolos degradation, resulting in enhanced myeloma cell cytotoxicity and immune stimulation versus immunomodulatory drugs.

Methods

This phase 3, open-label, randomised controlled trial (ClinicalTrials.gov NCT05552976; active, not recruiting) was conducted at 160 hospital-based sites in 26 countries using a two-stage, inferentially seamless design. Eligible adult patients had measurable multiple myeloma, ≥1 prior 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 randomise patients, stratified by age (≤70 or >70 years), number of prior 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/m^2 weekly) and oral/intravenous dexamethasone (40 mg weekly) (MeziKd) or carfilzomib (56 mg/m^2 twice weekly or 70 mg/m^2 weekly) and dexamethasone (20 mg twice weekly or 40 mg weekly) (Kd). Stage 1 optimised mezigdomide dosing across three levels. Stage 2 randomised patients to the selected mezigdomide dose (1·0 mg) plus Kd or Kd alone. The primary endpoint was progression-free survival evaluated in patients who received 1·0 mg mezigdomide plus Kd or Kd alone across both study stages. No imputation was planned for missing efficacy endpoint values or missing safety evaluations.

Findings

Between 3 February 2023 and 28 November 2025, 606 patients were enrolled and 479 (MeziKd, n=288; Kd, n=191) were included in the analyses: 252 (53%) were male, 411 (86%) anti-CD38 antibody-refractory, and 363 (76%) lenalidomide-refractory, with a median of 2 prior lines of therapy (IQR, 2–4).

At 10·6 months median follow-up, MeziKd significantly improved progression-free survival compared with Kd (median, 18·0 *vs* 8·3 months; HR, 0·48; 95% CI, 0·36–0·63; p<0·0001). Grade 3/4 adverse events were observed in 241 (84%) MeziKd patients versus 105 (56%) for Kd, including neutropenia (176 [61%] *vs* 17 [9%]) and infections (98 [34%] *vs* 29 [16%]). Eight (3%) and one (1%) treatment-related grade 5 adverse events were reported with MeziKd and with Kd, respectively.

Interpretation

MeziKd significantly improved progression-free survival, with a predictable, manageable safety profile, as early as first relapse in a predominantly triple-class-exposed, anti-CD38 antibody- and lenalidomide-refractory population, supporting MeziKd as a clinically meaningful treatment option for this growing population with substantial unmet need.

Funding Bristol Myers Squibb

Research in Context

Evidence before this study

We searched PubMed, with no language restrictions, for articles published between 1 January 2016, and 22 April 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/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- 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 (Kd) among the most frequently used combinations, and median progression-free survival 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 (CELMoD), 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/refractory setting, including in combination with Kd, supporting further prospective evaluation.

Added value of this study

SUCCESSOR-2 is the first phase 3 randomised trial specifically designed to evaluate MeziKd versus Kd in patients with relapsed/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. Kd 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 Kd 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, MeziKd demonstrated superior efficacy versus Kd, reducing the risk of progression or death by 52%, with the median progression-free survival more than doubled. MeziKd achieved deep responses, doubling the very good partial response or better rate and tripling the complete response or better rate of Kd. The safety profile of MeziKd was consistent with previous mezigdomide studies, with neutropenia being the most common grade 3/4 adverse event, and with the known toxicity profile of carfilzomib.

Implications of all the available evidence

This study addresses an important evidence gap. The results of SUCCESSOR-2 demonstrate that MeziKd substantially improves outcomes in a growing and under-studied population of patients with relapsed/refractory multiple myeloma who are predominantly refractory to anti-CD38 antibodies and lenalidomide. These findings establish MeziKd as a clinically meaningful, broadly accessible treatment option, and provide evidence for a differentiated approach in this setting. Mezigdomide is under active investigation across additional combinations and multiple myeloma populations.

Introduction

Multiple myeloma is characterised by repeated relapse and the development of increasing therapeutic resistance and shorter progression-free survival, with most patients ultimately experiencing treatment-refractory disease. The widespread adoption of frontline anti-CD38 antibodies and lenalidomide has substantially improved outcomes and meaningfully extended survival.[1,2] However, this success has resulted in a growing population of patients who are exposed and/or refractory to these agents as early as first relapse, thereby limiting subsequent treatment options and contributing to poor clinical outcomes.[1-3]

Several novel therapeutic approaches have expanded treatment options for patients with relapsed/refractory multiple myeloma, including chimeric antigen receptor T-cell therapies, bispecific antibodies, and antibody-drug conjugates. Despite the clinical benefits of such approaches, constraints related to access and tolerability may limit their use in broader practice settings, highlighting the ongoing need for effective oral or outpatient-compatible therapies.[4-7]

Mezigdomide is an oral cereblon E3 ligase modulator (CELMoD) in clinical development for relapsed/refractory multiple myeloma.[8,9] Relative to lenalidomide and pomalidomide, mezigdomide engages cereblon in a distinct and more effective manner, resulting in more rapid and complete proteasomal degradation of transcription factors Ikaros and Aiolos.[10,11] These molecular effects translate into increased myeloma cell cytotoxicity and superior immunostimulatory activity characterized by enhanced mitigation of immune cell dysfunction compared to immunomodulatory agents.[10,12-14]

In a phase 1/2 study, mezigdomide plus dexamethasone demonstrated efficacy in heavily pretreated relapsed/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- or infection-related deaths, despite the high-risk population studied.[8] The 1·0 mg mezigdomide dosing regimen induced a robust pharmacodynamic response, including a significant increase in proliferating T cells and a shift toward an activated or effector memory phenotype.[8]

Furthermore, preclinical studies have demonstrated synergistic anti-tumour activity between mezigdomide and proteasome inhibitors,[15] a finding supported by phase 1/2 data in which the combination of mezigdomide, carfilzomib, and dexamethasone (MeziKd) yielded promising efficacy and a manageable safety profile.[9]

We designed the phase 3 SUCCESSOR-2 trial to identify the recommended dose of mezigdomide in combination with carfilzomib and dexamethasone (Kd) and to evaluate the efficacy and safety of MeziKd compared with Kd, in patients with relapsed/refractory multiple myeloma who had received ≥1 prior line of therapy, including anti-CD38 antibodies and lenalidomide. Kd is an approved, efficacious, and one of the most frequently used standards of care in this patient population.[2] Here, we report the results of a 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.[16] Patients were recruited at 160 hospital-based sites in 26 countries (appendix pp 2–6). In stage 1, patients were randomised to one of three mezigdomide doses in combination with Kd or to Kd alone. Based on the totality of data, an independent data monitoring committee selected the recommended stage 2 dose. In stage 2, additional patients were randomised to MeziKd at the recommended mezigdomide dose and to Kd (appendix p 7).[16]

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. 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 at

ClinicalTrials.gov (NCT05552976; registered September 2022) and EUClinicalTrials.eu (EUCT number 2022-500861-29-00); status is active, not recruiting.

Participants

Eligible adult patients (≥18 years) had measurable multiple myeloma, an Eastern Cooperative Oncology Group performance status score of 0–2, and ≥1 prior line of antimyeloma therapy (no maximum), including anti-CD38 antibodies and lenalidomide. Patients were required to have achieved minimal response or better to ≥1 prior 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 8–10).

Randomisation and masking

Patients were randomised using interactive response technology based on the permuted-block method. In stage 1, patients were randomised 3:3:3:2 to mezigdomide 0·3, 0·6, or 1·0 mg in combination with Kd or to Kd and 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 Kd arm. The block order for every three blocks was randomised. In stage 2, patients were randomised in a 3:2 ratio to mezigdomide at the selected dose plus Kd or to Kd alone, for a block size of 5. Patients were stratified by age (≤70 or >70 years), number of prior 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 blinded to treatment assignment. However, any review of aggregate study data by the sponsor study team and personnel was blinded, prior to the planned treatment unblinding. Further details are available in the appendix (p 7).

Procedures

In stage 1, in the MeziKd arm, oral mezigdomide was given daily at 0·3, 0·6, or 1·0 mg on days 1–21 of each 28-day cycle with intravenous weekly carfilzomib at 20 mg/m^2 on day 1 of cycle 1; then at 56 mg/m^2 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; and oral or intravenous weekly dexamethasone at 40 mg on days 1, 8, 15, and 22 of each cycle. In the Kd arm, treatment was originally administered as intravenous twice-weekly carfilzomib at 20 mg/m^2 on days 1 and 2 of cycle 1; then at 56 mg/m^2 on days 8, 9, 15, and 16 of cycle 1, and days 1, 2, 8, 9, 15, and 16 in cycles ≥2; 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 Kd regimen option was made available, which includes intravenous carfilzomib at 20 mg/m^2 on day 1 of cycle 1; then at 70 mg/m^2 on days 8 and 15 of cycle 1, and days 1, 8, and 15 of cycles ≥2; 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. The Kd regimen used was per investigator's choice at randomisation.

In stage 2, patients received mezigdomide at the selected dose plus Kd or Kd alone, administered in 28-day cycles as described.

Investigators had the option of halving the starting dose of dexamethasone for patients who were over 75 years of age, underweight (defined as having a body mass index <18·5 kg/m^2), had poorly controlled diabetes, or had prior intolerance to steroid therapy. For these patients, dexamethasone could be administered at 20 mg to patients receiving MeziKd and those receiving the once-weekly Kd regimen, and at 10 mg to patients receiving the twice-weekly Kd regimen.

Patients were treated until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Safety assessments of adverse event evaluation 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 11–14). Required supportive care included thromboembolism prophylaxis, hepatitis B virus (HBV) prophylaxis (for hepatitis B surface antigen-positive/HBV DNA-negative patients), and, from December

2024, *Pneumocystis jirovecii* pneumonia prophylaxis and granulocyte colony-stimulating factor (G-CSF) prophylaxis (for patients with grade 4 neutropenia or grade 3/4 febrile neutropenia). Antiviral prophylaxis was recommended against herpes zoster reactivation. Immunoglobulin infusions were administered as per local institutional guidelines. Further details are available in the appendix (pp 10–11).

Outcomes

The primary endpoint was progression-free survival, as assessed by an independent review committee. The key secondary endpoint was overall survival. Additional secondary endpoints included progression-free survival after subsequent therapy; complete response or better, very good partial response or better, and overall response per International Myeloma Working Group uniform response criteria[17] (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 Kd to continue in stage 2, and mezigdomide plasma concentrations. Adverse events were collected from the time of signing the consent through 28 days after discontinuation of study treatment dosing, and were coded using Medical Dictionary for Regulatory Activities (MedDRA) 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 14–16). A prespecified subgroup analysis was performed to evaluate the impact 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 MeziKd arm and the Kd arm in both study stages, with safety analyses evaluated in patients who received ≥1 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, 0·667) with mezigdomide, 273 progression-free survival events provided

approximately 89% power to detect improved treatment effect under the exponential distribution assumption of progression-free survival (1-sided alpha, 0·025); this calculation was adjusted for three preplanned interim analyses: mezigdomide dose selection, progression-free survival futility (at 30% of events), and progression-free survival superiority (at 75% of events, reported herein) (appendix pp 16–17).

The Kaplan–Meier method was used to estimate survival distribution functions for time-to-event analyses and compared between treatment arms using a log-rank test stratified by baseline stratification factors. We used a stratified Cox proportional hazard model to estimate hazard ratios and 95% confidence intervals (CIs), with treatment as the only explanatory variable. 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 CI 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. Statistical analyses were performed using SAS (version 9.4; 2023). An independent data monitoring committee regularly reviewed all safety data and interim analysis results. Details on the subgroup analyses, as well as controlling of type 1 error between trial stages, are provided in the appendix (pp 17–19).

Role of the funding source

This study was funded by Bristol Myers Squibb. The funder of the study supplied mezigdomide and had a role in the study design, data analysis, data interpretation, and writing of the report, including funding for medical writing support.

Results

Altogether, 606 patients were randomised between 3 February 2023, and 28 November 2025 (appendix p 20); 235 into stage 1 and 371 into stage 2 of the trial.

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

In total, 479 patients were randomised across stages 1 and 2 as part of the confirmatory analysis group; 288 to receive MeziKd at 1·0 mg mezigdomide and 191 to receive Kd, of whom 288 and 186, respectively, received treatment. In the Kd arm, 130 patients received the once-weekly regimen. Overall, 120 (25%) patients were ≥75 years of age, the median number of prior lines of therapy was 2 (interquartile range [IQR], 2–4), 136 (28%) had high-risk cytogenetics at baseline, and 118 (25%) had extramedullary disease. 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%) had previous exposure to pomalidomide and anti-BCMA therapy, respectively. Baseline demographics and patient characteristics were generally balanced between treatment arms (table 1).

At data cutoff (15 January 2026), 151 (52%) patients in the MeziKd group and 60 (31%) in the Kd group were continuing treatment. The most common reason for discontinuation was disease progression (appendix p 20), occurring in 85 (30%) patients receiving MeziKd and 93 (49%) receiving Kd. At a median follow-up of 10·6 months (IQR, 7·2–15·3), the median duration of MeziKd treatment was longer than for Kd (8·9 months [IQR, 5·6–13·1] *vs* 6·2 months [IQR, 3·2–10·5]); 83 (29%) patients receiving MeziKd had ≥1 year of treatment, versus 36 (19%) receiving Kd. Median relative dose intensity was 83% (IQR, 64–94) for mezigdomide and 87% (IQR, 74–97) and 94% (IQR, 81–100) for carfilzomib in the MeziKd and Kd groups, respectively (appendix p 25). Reduction of mezigdomide dose was reported for 122 (42%) patients, with a median of 1·0 dose reduction (IQR, 1·0–2·0).

The risk of disease progression or death was significantly lower for patients receiving MeziKd versus Kd, 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%] patients in the MeziKd group; 103 [54%] patients in the Kd group). Progression-free survival was significantly longer with MeziKd than

with Kd (median, 18·0 months [95% CI, 14·5–22·1] *vs* 8·3 months [95% CI, 5·6–10·7]; hazard ratio for disease progression/death, 0·48 [95% CI, 0·36–0·63]; p<0·0001; figure 1A). In prespecified subgroup analyses, the progression-free survival benefit with MeziKd was consistently observed across prespecified subgroups, including patients with high-risk cytogenetics, extramedullary disease, anti-CD38 antibody or lenalidomide refractoriness, age ≥75 years, and >2 prior lines of therapy (figure 1B). Notably, the median progression-free survival for patients with one prior line of therapy receiving MeziKd was not reached as of data cutoff. Patients receiving MeziKd also had prolonged PFS2 versus those receiving Kd (appendix p 21).

A higher proportion of patients receiving MeziKd versus Kd 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 MeziKd and 1·1 months (IQR, 1·0–1·9) with Kd. In the MeziKd group, 72% (95% CI, 65–78) of patients continued to respond at 12 months versus 54% (95% CI, 41–66) of patients receiving Kd (appendix p 22). An analysis of minimal residual disease among patients who achieved complete response or better will be reported subsequently.

At this interim overall survival futility analysis, 62 (22%) deaths were reported in the MeziKd group and 51 (27%) in the Kd group, with an overall survival trend in favour of MeziKd (hazard ratio, 0·79 [95% CI, 0·54–1·15]; appendix p 23). The most common cause of death was progressive disease (39 [14%] and 36 [19%] patients, respectively; appendix p 26). Three (2%) patients in the Kd group died prior to treatment initiation.

The most common adverse events are reported in table 3, and exposure-adjusted incidence rates in the appendix (p 27). The most common grade 3/4 adverse event in the MeziKd group was, as expected, neutropenia, which occurred in 176 (61%) patients receiving MeziKd and 17 (9%) receiving Kd. Grade 3/4 febrile neutropenia was observed in 23 (8%) patients receiving MeziKd and none receiving Kd. The

median duration of grade 3/4 neutropenia or febrile neutropenia was 10 days for both MeziKd (IQR, 6–15) and Kd (IQR, 6–14). G-CSF was administered to most patients with grade 3/4 neutropenia during each treatment cycle (appendix p 24). Neutropenia and febrile neutropenia resulted in the dose delay/pause of mezigdomide and carfilzomib for 111 (39%) and 98 (34%) patients, respectively, in the MeziKd arm versus one (1%) patient for carfilzomib in the Kd arm.

Serious adverse events were reported in 188 (65%) patients receiving MeziKd and 63 (34%) receiving Kd; the most common was pneumonia (44 [15%] and 12 [6%] patients, respectively; appendix pp 28–29). Adverse events resulting in dose modifications of each treatment drug are reported in the appendix (pp 30–32). Discontinuation of mezigdomide due to an adverse event occurred in 19 (7%) patients; for carfilzomib, adverse events led to discontinuation in 40 (14%) patients receiving MeziKd and six (3%) receiving Kd. Grade 5 adverse events occurred in 21 (7%) and eight (4%) patients, respectively; eight (3%) and one (1%), respectively, were considered related to study treatment (appendix p 33).

Infections were reported in 210 (73%) patients in the MeziKd group and 100 (54%) in the Kd group (appendix pp 34–35); upper respiratory tract infection was the most frequent, occurring in 79 (27%) and 31 (17%) patients, respectively. In the MeziKd group, 98 (34%) patients had grade 3/4 infections (82 [28%] patients had a worst grade of 3 and 16 [6%] had a worst grade of 4), versus 29 (16%) in the Kd group (28 [15%] with a worst grade of 3 and one [1%] with a worst grade of 4); the median time to onset of grade 3/4 infections with MeziKd was 73 days (IQR, 20–155). The most common grade 3/4 infection was pneumonia (45 [16%] MeziKd; 11 [6%] Kd). A minority of those with infections had concurrent grade ≥3 neutropenia (66/210 [31%] MeziKd; 2/100 [2%] Kd). The incidence of fatal infections was very low, at 3% (seven patients) and 1% (two patients), respectively. In total, 91 (32%) and 39 (21%) patients, respectively, received immunoglobulin replacement therapy.

Cardiac adverse events were similar between treatment groups (52 [18%] MeziKd, 30 [16%] Kd; exposure-adjusted rate per 100 person-years, 24·2 MeziKd, 28·1 Kd). Second primary malignancies were reported in seven (2%) patients receiving MeziKd and four (2%) receiving Kd; three (1%) and one (1%),

respectively, were non-melanoma skin cancers (appendix p 36). Additional safety results are reported in the appendix (p 19).

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/refractory multiple myeloma. Patients who had received ≥1 prior therapy, including anti-CD38 antibodies and lenalidomide, and received MeziKd experienced a statistically significant and clinically meaningful improvement in progression-free survival compared with those who received Kd alone. Benefit was observed as early as first relapse and was consistent across key prespecified subgroups, irrespective of prior lines of therapy, age, cytogenetic risk, or presence of extramedullary disease.

Patients with relapsed/refractory multiple myeloma increasingly present with multidrug-refractory disease following frontline anti-CD38 antibody- and lenalidomide-containing regimens.[1,2] Real-world data indicate poor outcomes among patients refractory to both agents, with median progression-free survival ranging from approximately 4–6 months.[2,18] The patients enrolled in SUCCESSOR-2 were universally exposed to anti-CD38 antibodies and lenalidomide, with most patients refractory to both, reflecting the evolving clinical reality of guideline-recommended early exposure.[2,19] The shorter progression-free survival observed in the Kd arm as compared with earlier studies[20,21] likely reflects the high degree of drug exposure and refractoriness in this population, which is more representative of current clinical practice.[2] In this setting, the magnitude of benefit observed with MeziKd is notable, as it more than doubles the median progression-free survival of Kd. Several agents have shown clinical activity in relapsed/refractory multiple myeloma[4,6,7]; however, prospective evidence remains limited in patients who are exposed or refractory to both anti-CD38 antibodies and lenalidomide. In the CARTITUDE-4 trial (daratumumab-exposed subgroup), the median progression-free survival was 19·3 months with cilta-cel, compared with 4·5 months with daratumumab combined with dexamethasone plus pomalidomide (DPd)

or bortezomib (DVd).[6] In the KarMMa-3 trial, median progression-free survival was 13·8 months with ide-cel and 4·4 months with standard regimens.[5] In the single-arm SELECT trial, carfilzomib combined with pomalidomide and dexamethasone was associated with a median progression-free survival of 11·1 months.[22] Emerging evidence from ongoing trials in patients with prior anti-CD38 antibody and lenalidomide exposure, including our findings and trials investigating T-cell engagers, will further inform the treatment options for this population.

With expanding use of T-cell–redirecting therapies[5-7] and immune fitness being an important determinant of their outcomes and toxicity,[23–25] the need for enhanced immunoactivity and more effective regimens with differing mechanisms of action is becoming increasingly important. Mezigdomide promotes T-cell and natural killer cell activation and proliferation and mitigates T-cell exhaustion,[13,14] supporting the use of mezigdomide-based therapy in this setting. In addition, mezigdomide in combination with T-cell–redirecting therapies represents a promising therapeutic strategy that is undergoing additional investigation (NCT06121843; NCT06988488). Of note, the efficacy of MeziKd after lenalidomide treatment, and in patients exposed to pomalidomide, suggests a differentiated mechanism of action when compared with immunomodulatory drugs. The ongoing SUCCESSOR-1 trial (NCT05519085), comparing mezigdomide plus bortezomib and dexamethasone (MeziVd) versus pomalidomide plus Vd (PVd), will provide an informative head-to-head comparison of mezigdomide versus an immunomodulatory drug.

Kd is an effective, guideline-recommended treatment option for patients with early relapsed/refractory multiple myeloma.[19] With the well-characterised risk–benefit profile of Kd, 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. In addition, real-world data show that Kd is one of the most commonly used regimens in patients with prior 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 Kd in their control arm (e.g., MajesTEC-9

[NCT05572515], MagnetisMM-32 [NCT06152575], iMMagine-3 [NCT06413498]). At the time the SUCCESSOR-2 trial was designed, treatment options at first relapse that were both anti-CD38 antibody- and lenalidomide-free were limited to a small number of approved regimens (i.e., PVd; selinexor-bortezomib-dexamethasone [SVd]), which have shown median progression-free survival of 11·2–13·9 months across studies.[26,27] Other combinations such as elotuzumab-pomalidomide-dexamethasone (EPd) and carfilzomib-pomalidomide-dexamethasone (KPd) were either restricted to later lines of therapy[19] or not approved in this setting. In this context, Kd demonstrated consistent efficacy across phase 3 studies in patients with similar prior treatment exposure (1–3 prior lines), with median progression-free survival ranging from 15·8–18·7 months.[20,21]

The safety profile of MeziKd was consistent with findings from prior mezigdomide studies[8,9]; no previously uncharacterised adverse events were identified. Neutropenia was the most common grade 3/4 adverse event and there was an increased incidence of infections (including pneumonia) compared with Kd alone. As a known, reversible on-target effect of mezigdomide treatment, neutropenia was generally manageable with the protocol-specified adverse event management strategies for mezigdomide, including dose delay/pause and G-CSF support. The majority of infections were not associated with grade 3/4 neutropenia and less than half of patients in the MeziKd group experienced a dose delay/pause due to neutropenia. Antimicrobial infection prophylaxis was recommended. Cardiac adverse events occurred at expected rates.[28,29] A notable reduction in grade 3/4 hypertension was observed, potentially associated with the lower carfilzomib dose in the MeziKd arm. The manageable safety profile, outpatient administration, and lack of specialised infrastructure or hospitalisation requirements support the use of MeziKd across diverse treatment settings, including real-world community oncology practice.[30]

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 rigor of randomisation. This prespecified interim analysis is limited by the relatively short follow-up of 10·6 months, thus overall survival evaluation is ongoing. The open-label design may

have introduced performance or reporting bias; however, the primary and key secondary efficacy endpoints were objective (progression-free survival and overall survival) and clinical responses were evaluated by an independent review committee to mitigate potential bias. Exclusion of patients with prior carfilzomib exposure may limit the generalisability of these results to this patient population. Overall, the demographics of patients enrolled in SUCCESSOR-2 were broadly consistent with those reported in relapsed/refractory multiple myeloma in real-world and clinical trial settings,[1,2,31,32] including median age (68 years) and representation of older patients (25% aged ≥ 75 years). Furthermore, patients were enrolled across multiple regions worldwide, suggesting a globally representative population and supporting generalisability of the findings across diverse settings.

In conclusion, MeziKd demonstrated a significant progression-free survival 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. Together with the predictable and manageable safety profile, these findings support MeziKd as a readily accessible potential new standard of care for relapsed/refractory multiple myeloma across multiple treatment settings.

Acknowledgments

This study was supported by Celgene, a Bristol-Myers Squibb Company. Professional medical writing and editorial assistance was provided by Sarah Spaeh, PhD, and Mauro Locati, PhD, of the Publications Division of Omnicom Health Medical Communications, and was funded by Bristol Myers Squibb. The authors are fully responsible for all content of this manuscript.

Data sharing statement

The Bristol Myers Squibb policy on data sharing may 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 may include non-identifiable patient-level and study-level clinical trial data, full clinical study reports and protocols from trials completed on or after 1 January 2008 with primary results published in peer-reviewed journals.

Contributions

MAD, FS, PM, BY, AR, PK, JK, and PGR participated in the conception and design of the study. JG and ZZ performed the data analysis. MAD, FS, CF, MAH-B, CG, DR, GM, OA, CP, EdQC, KG, HI, DW, RG, CL, C-JL, HQ, YW, CC, CF, VH, PK, VG, PJH, MK-H, YLK, ML, AM, OM, NC, SVSSP, MSR, GV, EvdH, ZX, PAO, AO, JY, JK, and PGR contributed to data acquisition. All authors contributed to data interpretation. MAD, JG, ZZ, PM, BY, AR, PK, JK, 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

All authors received support for the current study from Bristol Myers Squibb.

MAD reports receiving consulting fees from Amgen, AstraZeneca, Beigene, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Menarini, Regeneron, Sanofi, Swixx, and Takeda; honoraria from Amgen, Astra Zeneca, Beigene, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Menarini, Regeneron, Sanofi, Swixx, and Takeda; and travel support from Amgen, Bristol Myers Squibb, Janssen, and Takeda.

FS reports receiving consulting fees from Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Johnson & Johnson, Kite Pharma, Menarini, Oncopeptides, and Regeneron; and honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Johnson & Johnson, Kite Pharma, Menarini, Pfizer, and Sanofi.

CFu reports receiving research support from Beigene and Johnson & Johnson; consulting fees from Beigene, Bristol Myers Squibb, Glaxo Smith Kline, and Johnson & Johnson; and honoraria from Beigene, Bristol Myers Squibb, Glaxo Smith Kline, and Johnson & Johnson.

MAH-B reports receiving grants from Bristol Myers Squibb, Glaxo Smith Kline, Karyopharm Therapeutics, Sanofi, and Takeda; consulting fees and honoraria from Glaxo Smith Kline; and travel support from Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Karyopharm Therapeutics, and Sanofi.

CG reports nothing to disclose.

DR reports receiving research support from Bristol Myers Squibb, Janssen, ORIC, and Sanofi; consulting fees from Bristol Myers Squibb, Glaxo Smith Klein, Janssen, Pfizer, and Sanofi; honoraria from Bristol Myers Squibb, Janssen, Pfizer, and Takeda; payment for expert testimony from Janssen; and participation on a data safety monitoring board for Bristol Myers Squibb.

GM reports nothing to disclose.

OA reports receiving research support from Bristol Myers Squibb/Celgene, Loxo/Lilly, and Seagen; consulting fees from Agios, Amgen, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Genentech, Incyte, and NCODA; honoraria from Curio Science; and travel support from Bristol Myers Squibb.

CP reports receiving consulting fees from Sanofi; honoraria and travel support from Amgen, Bristol Myers Squibb, Johnson & Johnson, Pfizer, and Sanofi.

EdQC reports receiving consulting fees from Glaxo Smith Kline, Johnson & Johnson, Sanofi, and Takeda; honoraria from AbbVie, Amgen, The Binding Site, Bristol Myers Squibb, Glaxo Smith Kline, Johnson & Johnson, Sanofi, and Takeda; and participation on an advisory board for Amgen, Bristol Myers Squibb, Glaxo Smith Kline, Johnson & Johnson, Sanofi, and Takeda.

KG reports nothing to disclose.

HI reports [TBC]

DW reports receiving honoraria from Amgen, Antengene, Apobiologix, Bristol Myers Squibb, Forus, Glaxo Smith Kline, Karyopharm, Pfizer, and Sanofi.

RG reports receiving consulting fees and participation on an advisory board for Johnson & Johnson; and honoraria from the Academy for Continued Healthcare Learning.

CL reports [TBC]

C-JL reports nothing to disclose.

HQ reports receiving research support from AbbVie, Antengene, Bristol Myers Squibb, Glaxo Smith Kline, and Karyopharm; consulting fees from Bristol Myers Squibb, Glaxo Smith Kline, Johnson & Johnson, Pfizer, and Regeneron; honoraria from AbbVie, Bristol Myers Squibb, Glaxo Smith Kline, and Johnson & Johnson; and payment for expert testimony from Pfizer.

YW reports [TBC]

CC reports receiving grants, consulting fees, honoraria, and travel support from AbbVie, Amgen, Astellas, Beigene, Bristol Myers Squibb, Curis, Glycomimetics, Glaxo Smith Kline, Immunogen, Janssen, Jazz Pharmaceuticals, Karyopharm Therapeutics, Menarini, Novartis, Oncopeptides, Pfizer, Sanofi, Servier, SkylineDx, Stemline, and Takeda.

CFo reports participation on an advisory board for Glaxo Smith Kline.

VH reports receiving consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Glaxo Smith Kline, Johnson & Johnson, Pfizer, Regeneron, Roche, Sanofi, and Takeda; and honoraria from AbbVie, Amgen, Bristol Myers Squibb, Glaxo Smith Kline, Janssen-Cilag, Pfizer, Sanofi, and Takeda.

PKa reports [TBC]

VG reports [TBC]

PJH reports [TBC]

MK-H reports nothing to disclose.

YLK reports research support from Bristol Myers Squibb, Merck, and Novartis; and consulting fees from Amgen, Astellas, Bayer, Beigene, Bristol Myers Squibb, Celgene, Janssen, Merck, Novartis, Roche, and Takeda.

ML reports [TBC]

AM reports nothing to disclose.

OM reports [TBC]

CN reports [TBC]

SVSSP reports [TBC]

MSR reports receiving research support from Sanofi; consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Oncopeptides, Pfizer, Roche, and Sanofi; honoraria from AbbVie, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, and Sanofi; travel support from AbbVie, Bristol Myers Squibb, Glaxo Smith Kline, Janssen, Oncopeptides, and Sanofi; and receipt of materials or other services from Sanofi.

GV reports nothing to disclose.

EvdH reports receiving consulting fees from AstraZeneca, Bristol Myers Squibb, Lilly, and Novartis; honoraria from AstraZeneca, Bristol Myers Squibb, and Novartis; payment for expert testimony from BeOne Medicine, Bristol Myers Squibb, Lilly, and Novartis; travel support from Lilly; and participation on an advisory board for AstraZeneca, Bristol Myers Squibb, Lilly, and Novartis.

ZX reports [TBC]

PAO reports [TBC]

AO reports receiving consulting fees from Amgen, Bristol Myers Squibb/Celgene, Glaxo Smith Kline, Janssen, Pfizer, and Sanofi; and honoraria from Amgen, Bristol Myers Squibb/Celgene, Glaxo Smith Kline, Janssen, and Sanofi.

JY reports receiving research support from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, BrightPath Bio, Celaid Therapeutics, Chugai, Daiichi Sankyo, Genmab, Incyte, Janssen, Mitsubishi Tanabe, MSD, Novartis, Sanofi, Sumitomo Pharma, and Takeda; and participation on an advisory board for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Genmab, Incyte, Janssen, Mitsubishi Tanabe, MSD, Novartis, Sanofi, Sumitomo Pharma, and Takeda.

JKu reports receiving grant and research support from AbbVie, Bristol Myers Squibb, Chugai Pharmaceutical, Glaxo Smith Kline, Gilead, Janssen, Kyowa Kirin, Meiji Seika, Novartis, Ohara Pharmaceutical, Ono Pharmaceutical, Otsuka Pharmaceutical, Parexel, Pfizer, Taiho Pharmaceutical, and Tanabe Pharma; consulting fees from BeOne Medicine, Bristol Myers Squibb, Janssen, and Pfizer; honoraria from AbbVie, BeOne Medicine, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Genmab, Janssen, Nippon Shinyaku, Novartis, Ono Pharmaceutical, Pfizer, and Sanofi; and receipt of materials from Taiho Pharmaceutical.

JG reports previous employment by and owning stock in Bristol Myers Squibb.

ZZ reports being employed by and owning stock in Bristol Myers Squibb.

PM reports being employed by, owning stock in, and receiving travel support from Bristol Myers Squibb.

BY reports being employed by and owning stock in Bristol Myers Squibb.

AR reports employment (self or immediate family) with Bristol Myers Squibb, Galapagos, and Novartis; and owning stock (self or immediate family) in Bristol Myers Squibb and Novartis.

PKo reports being employed by Bristol Myers Squibb; and owning stock in Bristol Myers Squibb and Novartis.

JKa reports being employed by and owning stock in Bristol Myers Squibb.

PGR reports receiving research support from Oncopeptides; consulting fees from Bristol Myers Squibb/Celgene, Glaxo Smith Kline, Karyopharm, Oncopeptides, Regeneron, and Sanofi; and being employed by Dana Farber Cancer Institute.

References

1. Mancuso K, Barbato S, Di Raimondo F, et al. Forcing ahead: second-line treatment options for lenalidomide-refractory multiple myeloma. *Cancers (Basel)* 2025; **17**: 1168.
2. Ramasamy K, Vij R, Kuter D, et al. Real-world treatment patterns and clinical outcomes in patients with multiple myeloma previously treated with lenalidomide and an anti-CD38 monoclonal antibody. C*lin Lymphoma Myeloma Leuk* 2025; **5**: 337–48. e2.
3. Cavo M, Bringhen S, Buda G, et al. Addressing unmet needs in relapsed/refractory multiple myeloma: an Italian Delphi consensus on current challenges and emerging therapies. *Front Oncol* 2026; **16**: 1756247.
4. Dimopoulos MA, Beksac M, Pour L, et al. Belantamab mafodotin, pomalidomide, and dexamethasone in multiple myeloma. *N Engl J Med* 2024; **391**: 408–21.
5. Ailawadhi S, Arnulf B, Patel K, et al. Ide-cel vs standard regimens in triple-class-exposed relapsed and refractory multiple myeloma: updated KarMMa-3 analyses. *Blood* 2024; **144**: 2389– 401.
6. Einsele H, San-Miguel J, Dhakal B, et al. Cilta-cel in lenalidomide-refractory multiple myeloma (CARTITUDE-4): an updated analysis including overall survival from an open-label, multicentre, randomised, phase 3 trial. *Lancet Onc*ol 2026; **27**: 254–68.
7. Costa LJ, Bahlis NJ, Perrot A, et al. Teclistamab plus daratumumab in relapsed or refractory multiple myeloma. *N Engl J Med* 2026; **394**: 739–52.
8. Richardson PG, Trudel S, Popat R, et al. Mezigdomide plus dexamethasone in relapsed and refractory multiple myeloma. *N Engl J Med* 2023; **389**: 1009–22.
9. Sandhu I, Richardson PG, Oriol A, et al. Mezigdomide (MEZI) plus dexamethasone (DEX) and bortezomib (BORT) or carfilzomib (CFZ) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated results from the CC-92480-MM-002 trial. *Blood* 2024; **144** (suppl 1): 1025 (abstr).
10. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 ligase modulator CC-92480 for the treatment of relapsed and refractory multiple myeloma. *J Med Chem* 2020; **63**: 6648–76.

11. Watson ER, Novick S, Matyskiela ME, et al. Molecular glue CELMoD compounds are regulators of cereblon conformation. *Science* 2022; **378**: 549–53.
12. Lopez-Girona A, Havens CG, Lu G, et al. CC-92480 is a novel cereblon E3 ligase modulator with enhanced tumoricidal and immunomodulatory activity against sensitive and resistant multiple myeloma cells. *Blood* 2019; **134** (suppl 1): 1812 (abstr).
13. Chiu H, Zhao J, Ortiz Estevez M, Hagner PR, Gandhi AK. Mezigdomide reverses T-cell exhaustion through degradation of Aiolos/Ikaros and reinvigoration of cytokine production pathways. *Blood* 2023; **142** (suppl 1): 335 (abstr).
14. Chen LY, Van Oekelen O, Amatangelo M, et al. Mezigdomide treatment in relapsed-refractory myeloma patients shifts bone marrow NK and T cell populations from exhaustion to activation. Poster presentation at the American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA. Abstract 4686.
15. Bjorklund CC, Larrayoz M, Kang J, et al. Mezigdomide combined with bortezomib disrupts the cell cycle and elicits superior antitumor effects in multiple myeloma. *Blood Neoplasia* 2025; **3**: 100179.
16. Richardson PG, Amatangelo M, Berenson JR, et al. A phase 3, two-stage, randomized study of mezigdomide, carfilzomib, and dexamethasone (MeziKd) versus carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): SUCCESSOR-2. Poster presentation at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. Abstract TPS8070.
17. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; **17**: e328-46.
18. Kastritis E, Theodorakakou F, Ntanasis-Stathopoulos I, et al. Management and outcomes of anti-CD38 refractory patients: the impact of retreatment and of subsequent therapies. *HemaSphere* 2023; **7**: e975.

19. Dimopoulos MA, Terpos E, Boccadoro M, et al. EHA–EMN evidence-based guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. *Nat Rev Clin Oncol* 2025; **22**: 680–700.
20. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17**: 27–38.
21. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020; **396**: 18–97.
22. Perrot A, Delimpasi S, Spanoudakis E, et al. An open-label phase 2 study treating patients with first or second relapse of multiple myeloma with carfilzomib, pomalidomide, and dexamethasone (KPd): SELECT study. *Leuk Lymphoma* 2024; **65**: 833–42.
23. Lee H, Durante M, Skerget S, et al. Impact of soluble BCMA and non–T-cell factors on refractoriness to BCMA-targeting T-cell engagers in multiple myeloma. *Blood* 2024; **144**: 2637–51.
24. Rade M, Fandrei D, Kreuz M, et al. A longitudinal single-cell atlas to predict outcome and toxicity after BCMA-directed CAR T cell therapy in multiple myeloma. *Cancer Cell* 2026; **44**: 586–603.
25. van de Donk NWCJ, Chari A, Mateos MV. Mechanisms of resistance against T-cell engaging bispecific antibodies in multiple myeloma: implications for novel treatment strategies. *Lancet Haematol* 2024; **11**: e693–707.
26. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2019; **20**: 781-94.
27. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet* 2020; **396**: 1563–73.

28. Chari A, Stewart AK, Russell SD, et al. Analysis of carfilzomib cardiovascular safety profile across relapsed and/or refractory multiple myeloma clinical trials. *Blood Adv* 2018; **2**: 1633–44.
29. Waxman AJ, Clasen S, Hwang W-T, et al. Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis. *JAMA Oncol* 2018; **4**: e174519.
30. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. *Blood Cancer J* 2018; **8**: 109.
31. Dhakal B, Einsele H, Schecter JM, et al. Real-world treatment patterns and outcomes in relapsed/refractory multiple myeloma (1-3 prior lines): Flatiron database. *Blood Adv* 2024; **8**: 5062–71.
32. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. Lyon, France: International Agency for Research on Cancer. 2024 (https://gco.iarc.who.int/today).

Tables

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

	MeziKd (n=288)	Kd (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%)
Male sex	146 (51%)	106 (55%)	252 (53%)
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%)
United States	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)	4·6 (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 ISS 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 extramedullary plasmacytomas	66 (23%)	52 (27%)	118 (25%)
Extraosseous	25 (9%)	20 (10%)	45 (9%)
Paraosseous	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/missing	36 (13%)	27 (14%)	63 (13%)
Prior antimyeloma therapy			
Number of prior lines of therapy	2·0 (2·0–3·5)	2·0 (2·0–4·0)	2·0 (2·0–4·0)
1 prior line	43 (15%)	33 (17%)	76 (16%)
2 prior lines	109 (38%)	68 (36%)	177 (37%)
3 prior lines	64 (22%)	35 (18%)	99 (21%)

	MeziKd (n=288)	Kd (n=191)	All patients (N=479)
>3 prior 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%)
Proteasome inhibitor (triple-class exposed)	265 (92%)	176 (92%)	441 (92%)
BCMA-targeted therapy	23 (8%)	12 (6%)	35 (7%)
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 (%). Percentages may not total 100 due to rounding. BCMA=B-cell maturation antigen. ECOG=Eastern Cooperative Oncology Group. ISS=International Staging System. Kd=carfilzomib and dexamethasone. MeziKd=mezigdomide plus carfilzomib and dexamethasone. [*]In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomised to 1·0 mg mezigdomide plus Kd or Kd alone. [†]Eligibility required an ECOG performance status score of 0 to 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). [§]Refractory is defined as disease that is nonresponsive on therapy (failure to achieve 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 2: **Treatment response**[*]

	MeziKd (n=288)	**Kd (n=191)**
Overall response[†]	231	102
Rate	80% (75–85)	53% (46–61)
Difference[‡]	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)
Difference[‡]	18% (11–24)	
Very good partial response or better	173	59
Rate	60% (54–66)	31% (24–38)
Difference[‡]	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 may not total 100 due to rounding. CI=confidence interval. Kd=carfilzomib and dexamethasone. MeziKd=mezigdomide plus carfilzomib and dexamethasone. *In the confirmatory analysis group, defined as all patients from stages 1 and 2 randomised to 1·0 mg mezigdomide plus Kd or Kd alone. Best overall response was evaluated by an independent review committee. [†]Patients who achieved partial response or better. [‡]Proportion difference with two-sided 95% CI. [§]Time to response is defined as the time from randomisation to the first documentation of response (partial response or better).

Table 3: **Most common adverse events**[*]

	MeziKd (n=288)		Kd (n=186)	
	Any grade	**Grade 3/4**	**Any grade**	**Grade 3/4**
Patients with an adverse event	286 (99%)	241 (84%)	178 (96%)	105 (56%)
Haematologic				
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-haematologic				
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%)

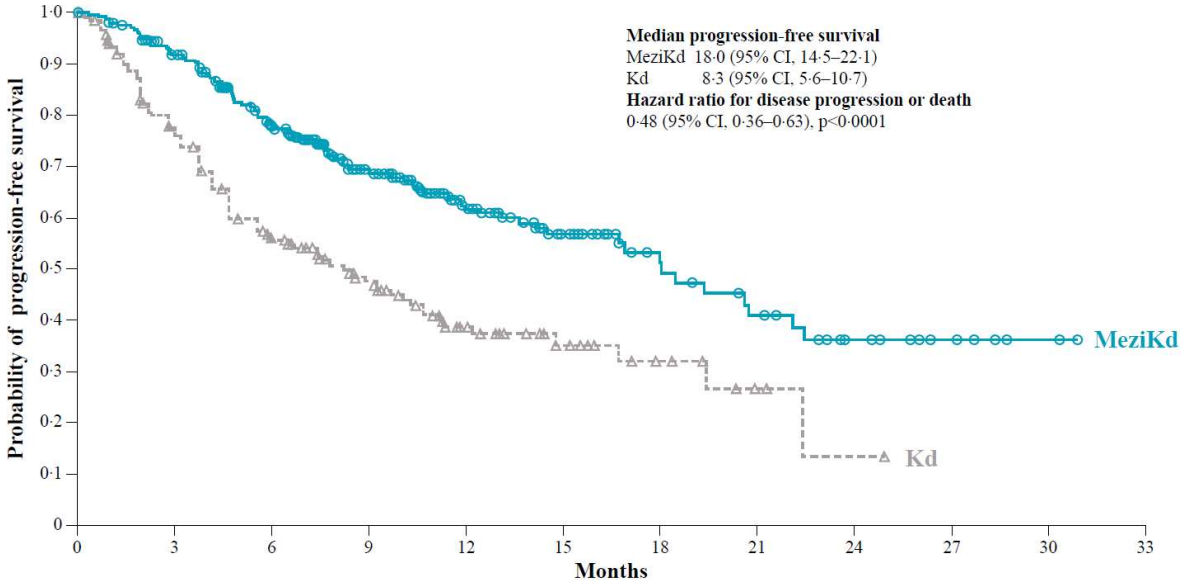
Data are n (%). Kd=carfilzomib and dexamethasone. MeziKd=mezigdomide plus carfilzomib and dexamethasone.

[*]Includes treatment-emergent adverse events of any grade that occurred in ≥20% of patients and grade 3/4 treatment-emergent adverse events that occurred in ≥10% of patients in either treatment arm in the confirmatory analysis group of the safety population, defined as all patients from stages 1 and 2 randomised to 1·0 mg mezigdomide plus Kd or Kd alone who received ≥1 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.

Figures

Figure 1: **Progression-free survival**

A



Number at risk

MeziKd	288	250	197	133	81	47	27	19	11	6	2	0
Kd	191	134	90	59	31	15	8	3	1	0	0	0

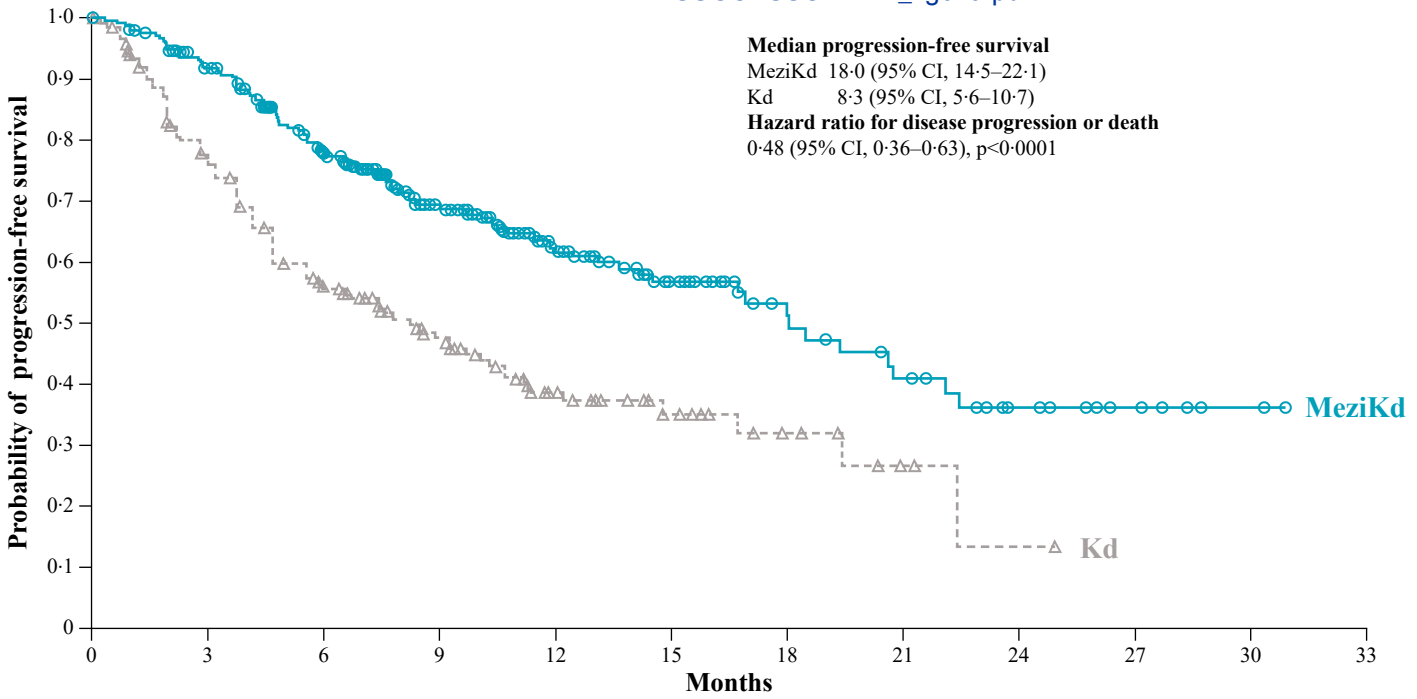
B

	Total number of patients	MeziKd	Kd	Hazard ratio (95% CI)
		number of events/number of patients		
Overall	479	105/288	103/191	0·49 (0·37–0·64)
Age				
<65 years	181	40/102	44/79	0·52 (0·34–0·80)
65 to <75 years	178	41/111	38/67	0·43 (0·27–0·67)
≥75 years	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				
United States	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 world	101	29/64	24/37	0·40 (0·23–0·70)
Number of prior 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 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 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)
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)
Previous proteasome inhibitor exposure				
Yes	441	97/265	95/176	0·49 (0·37–0·65)
No	38	8/23	8/15	0·55 (0·20–1·48)
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)
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/Missing	63	15/36	17/27	0·44 (0·22–0·90)
Presence of extramedullary 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)

(A) Kaplan–Meier estimates of progression-free survival among patients in the confirmatory analysis group, defined as all patients from stages 1 and 2 randomised to 1·0 mg mezigdomide plus Kd or Kd alone. Progression-free survival was assessed by an independent review committee. Symbols indicate censored observations. (B) Select subgroups from the prespecified subgroup analysis of progression-free survival in patients in the confirmatory analysis group. Baseline disease and demographic characteristics were used to determine subgroups. A hazard ratio of <1·0 indicates an advantage for MeziKd versus Kd. 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). The presence of extramedullary plasmacytomas includes both extraosseous and paraosseous plasmacytomas. CI=confidence interval. ISS=International Staging System. Kd=carfilzomib and dexamethasone. MeziKd=mezigdomide plus carfilzomib and dexamethasone.

Figure 1a

Click here to access/download;Figure;Dimopoulos (Lancet) SUCCESSOR-2 IA_fig01a.pdf



Number at risk

MeziKd	288	250	197	133	81	47	27	19	11	6	2	0
Kd	191	134	90	59	31	15	8	3	1	0	0	0

Figure 1b

Click here to access/download;Figure;Dimopoulos (Lancet) SUCCESSOR-2 IA_fig01b.pdf

	Total number of patients	MeziKd	Kd	Hazard ratio (95% CI)
		number of events/number of patients		
Overall	479	105/288	103/191	0·49 (0·37–0·64)
Age				
<65 years	181	40/102	44/79	0·52 (0·34–0·80)
65 to <75 years	178	41/111	38/67	0·43 (0·27–0·67)
≥75 years	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				
United States	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 world	101	29/64	24/37	0·40 (0·23–0·70)
Number of prior 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 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 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)
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)
Previous proteasome inhibitor exposure				
Yes	441	97/265	95/176	0·49 (0·37–0·65)
No	38	8/23	8/15	0·55 (0·20–1·48)
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)
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/Missing	63	15/36	17/27	0·44 (0·22–0·90)
Presence of extramedullary 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)