ORIGINAL ARTICLE

Mezigdomide plus Dexamethasone in Relapsed and Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

Despite recent progress, multiple myeloma remains incurable. Mezigdomide is a novel cereblon E3 ubiquitin ligase modulator with potent antiproliferative and tumoricidal activity in preclinical models of multiple myeloma, including those resistant to lenalidomide and pomalidomide.

METHODS

In this phase 1–2 study, we administered oral mezigdomide in combination with dexamethasone to patients with relapsed and refractory myeloma. The primary objectives of phase 1 (dose-escalation cohort) were to assess safety and pharmacokinetics and to identify the dose and schedule for phase 2. In phase 2 (dose-expansion cohort), objectives included the assessment of the overall response (partial response or better), safety, and efficacy of mezigdomide plus dexamethasone at the dose and schedule determined in phase 1.

RESULTS

In phase 1, a total of 77 patients were enrolled in the study. The most common dose-limiting toxic effects were neutropenia and febrile neutropenia. On the basis of the phase 1 findings, investigators determined the recommended phase 2 dose of mezigdomide to be 1.0 mg, given once daily in combination with dexamethasone for 21 days, followed by 7 days off, in each 28-day cycle. In phase 2, a total of 101 patients received the dose identified in phase 1 in the same schedule. All patients in the dose-expansion cohort had triple-class–refractory multiple myeloma, 30 patients (30%) had received previous anti–B-cell maturation antigen (anti-BCMA) therapy, and 40 (40%) had plasmacytomas. The most common adverse events, almost all of which proved to be reversible, included neutropenia (in 77% of the patients) and infection (in 65%; grade 3, 29%; grade 4, 6%). No unexpected toxic effects were encountered. An overall response occurred in 41% of the patients (95% confidence interval [CI], 31 to 51), the median duration of response was 7.6 months (95% CI, 5.4 to 9.5; data not mature), and the median progression-free survival was 4.4 months (95% CI, 3.0 to 5.5), with a median follow-up of 7.5 months (range, 0.5 to 21.9).

CONCLUSIONS

The all-oral combination of mezigdomide plus dexamethasone showed promising efficacy in patients with heavily pretreated multiple myeloma, with treatment-related adverse events consisting mainly of myelotoxic effects. (Funded by Celgene, a Bristol-Myers Squibb Company; CC-92480-MM-001 ClinicalTrials.gov number, NCT03374085; EudraCT number, 2017-001236-19.)

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Despite recent advances in therapy, multiple myeloma remains incurable. Drug-class combinations of immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies are the standard of care in early lines of therapy[1]; however, nearly all the patients who receive these treatments ultimately have a relapse, refractory disease, or both. As the disease progresses, patients have increasingly shorter remission periods,[2-4] and patients with triple-class–refractory multiple myeloma (refractory to ≥1 immunomodulatory agent, 1 proteasome inhibitor, and 1 anti-CD38 monoclonal antibody) have a very poor prognosis.[5,6] Although therapies that target B-cell maturation antigen (BCMA) are newly available,[7-11] relapse will occur in most patients, and ultimately, these agents will need to be used in combination to improve outcomes. As such, alternative treatments with limited toxic effects, ease of administration, and different mechanisms of action are needed to address resistance in refractory disease and serve as backbones across established and new treatment methods.

The cereblon E3 ligase modulator compounds are a class of novel protein degraders that co-opt cereblon, the adaptor protein for the cullin-RING E3 ubiquitin ligase.[12,13] Two such agents, iberdomide (CC-220)[14] and mezigdomide (CC-92480), are being evaluated in patients with multiple myeloma because of their increased potency, selectivity for cereblon, and enhanced immune stimulation. Mezigdomide was specifically designed to achieve rapid, potent, and deep degradation of Ikaros and Aiolos, key transcription factors in hematopoietic cell development and differentiation.[15-19] Mezigdomide possesses superior potency owing to its unique cereblon-binding interactions, in which allosteric rearrangement of the cereblon-binding site to an active conformation is induced in 100% of cereblon molecules (as compared with approximately 50% induced by iberdomide), thus promoting maximal substrate-binding capacity.[20] The degradation of Ikaros and Aiolos induced by mezigdomide leads to enhanced cytotoxic effects in myeloma cells in vitro, including cells that are resistant to lenalidomide and pomalidomide and those with cereblon down-regulation, as well as to direct T-cell and natural killer–cell immune-stimulatory activities.[15,16,21] Mezigdomide also has marked synergistic effects when used in combination with dexamethasone and other myeloma therapies in vitro.[22]

On the basis of ex vivo models in which CD34+ mononuclear cells in the bone marrow differentiate and mature into neutrophils, it was anticipated that deep, sustained degradation of Ikaros and Aiolos by mezigdomide would not only induce enhanced antimyeloma activity but also increase maturation arrest of neutrophils and neutropenia relative to immunomodulatory agents.[23] Therefore, this phase 1–2, multicenter, dose-escalation and dose-expansion study evaluated multiple doses and schedules of mezigdomide plus dexamethasone in patients with heavily pretreated relapsed and refractory multiple myeloma.

METHODS

STUDY OVERSIGHT

This study was designed and analyzed by the sponsor (Celgene, a Bristol-Myers Squibb Company) in collaboration with the academic authors. The study was conducted at 40 sites in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practices guidelines, local regulations governing the conduct of clinical studies, and institutional guidelines. At each site, an institutional review board or ethics committee approved the protocol, available with the full text of this article at NEJM.org. All the patients provided written informed consent. Safety was monitored by the sponsor and the safety review committee. All the authors had access to and reviewed the data and vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. Medical writing assistance was funded by the sponsor.

PATIENTS

Patients were eligible for phase 1 (dose-escalation cohort) if they were 18 years of age or older; had an Eastern Cooperative Oncology Group performance-status score of 0 to 2 (on a 6-point scale, with higher numbers reflecting greater disability); had adequate bone marrow, renal, and cardiac function; and had received at least three previous lines of therapy, including lenalidomide, pomalidomide, a proteasome inhibitor, a glucocorticoid, and an anti-CD38 antibody. At the time of enrollment, patients must also have had progres-

sion of disease during the 60 days after the final dose of their last antimyeloma therapy. Patients in phase 2 (dose-expansion cohort) were additionally required to have disease refractory to an immunomodulatory agent (lenalidomide or pomalidomide, or both), a glucocorticoid, a proteasome inhibitor, and an anti-CD38 antibody, in accordance with the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma.[24]

STUDY DESIGN

This was an open-label, multicenter, phase 1–2 study with dose-escalation and dose-expansion cohorts. Unlike standard phase 1 study designs, this study used two initial schedules to inform the duration of the degradation of Ikaros and Aiolos needed for antimyeloma activity and the off-drug duration needed for adequate reversal of the neutropenic effects. In phase 1, four administration schedules were assessed, including two continuous schedules and two intermittent-intensive schedules in 28-day cycles. The continuous schedules, both in 28-day cycles, comprised either 10 consecutive days of treatment, followed by 4 days off, and then repeated (the 10-day schedule, repeated), or 21 consecutive days of treatment, followed by 7 days off (the 21-day schedule). The intermittent-intensive schedules, also in 28-day cycles, comprised either 3 consecutive days of treatment, followed by 11 days off, and then repeated (the 3-day schedule, repeated), or 7 consecutive days of treatment, followed by 7 days off, and then repeated (the 7-day schedule, repeated). The protocol permitted adjustments to the dose and schedule on the basis of real-time biomarker data to determine the dose and schedule for phase 2 of the study. Additional information about the study design is provided in the Supplementary Appendix, available at NEJM.org.

OBJECTIVES

The primary objectives in phase 1 were to assess safety and pharmacokinetics and to determine the maximum tolerated dose and the recommended phase 2 dose of mezigdomide when given with dexamethasone. Adverse events were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 or higher. Dose-limiting toxic effects that occurred during the first 28-day treatment cycle were used to determine the maximum tolerated dose (for definitions of dose-limiting toxic effects, see the Supplementary Appendix). The primary objective in phase 2 was to assess the efficacy of mezigdomide plus dexamethasone at the dose determined in phase 1, as measured by overall response (defined as partial response or better).

Secondary objectives included safety and additional efficacy variables, such as the duration of response and progression-free survival. Clinical benefit (minimal response or better) and disease control (stable disease or better) were also assessed. The overall response was assessed on the basis of the IMWG Uniform Response Criteria for Multiple Myeloma (Table S1 in the Supplementary Appendix).[24,25] Exploratory objectives included evaluation of the pharmacodynamic effects of Ikaros and Aiolos degradation in peripheral blood mononuclear cells. Changes in designated biomarkers were assessed and, when possible, correlated with clinical outcomes over time.

STATISTICAL ANALYSIS

In phase 1, no formal statistical power calculations were performed to determine sample size. All outcome analyses in phase 1 were descriptive, with results reported by dose and schedule. For phase 2, the sample size was calculated on the basis of a group sequential design for a one-sample binomial test with normal approximation. The null hypothesis was a response of 12% or less, and the alternative hypothesis was a response of greater than 12%. We calculated that a sample size of 101 patients would provide the study with at least 90% power, at a one-sided alpha level of 0.025, to detect a treatment benefit of an overall response of at least 24%. Two-sided 95% confidence intervals were calculated for response in both cohorts with the use of the Clopper–Pearson method. We used the Kaplan–Meier method to summarize the time-to-event end points, and applied log–log transformation to calculate the confidence intervals for time-to-event quantities. Excess toxic effects were monitored with the use of a Bayesian method on the basis of the occurrence of adverse events leading to treatment discontinuation.[26] For phase 1, the target for dose-limiting toxic effects was 20% for all schedules. For phase 2, the assumed rate of 13% for excess toxic effects leading to treatment discontinuation was determined on the basis of the phase 3

MM-003 trial, in which 9% of patients with relapsed and refractory myeloma who received a combination of pomalidomide and dexamethasone discontinued treatment due to adverse events.[27]

RESULTS

DOSE-ESCALATION COHORT

Patients

As of July 6, 2022, a total of 77 patients across 13 dose-escalation subgroups were enrolled and had received at least one dose of mezigdomide. Two continuous (the 10-day schedule, repeated, and the 21-day schedule) and two intermittent-intensive (the 3-day schedule, repeated, and the 7-day schedule, repeated) dosing schedules (see Fig. S2A) were conducted in parallel and adapted on the basis of safety and pharmacodynamic effects to determine the dose and schedule for phase 2. The median age was 65 years (range, 40 to 78), and patients had received a median of 6 (range, 2 to 13) previous lines of therapy, including stem-cell transplantation (78%) (Table 1). The median follow-up was 6.3 months (range, 0.6 to 33.1). The evaluated dose levels and observed dose-limiting toxic effects are shown in Figure S1. The most common toxic effects were neutropenia and febrile neutropenia. The maximum tolerated dose of mezigdomide was determined to be 1.0 mg given orally once daily plus dexamethasone in either the 10-day schedule, repeated, or the 21-day schedule. Higher total daily doses were associated with an acceptable adverse-effects profile among patients receiving treatment in intermittent-intensive schedules.

Safety

During phase 1 of the study, the most common cause of death was disease progression (Table S6). The reasons for treatment discontinuation are shown in Fig. S2A. At the time of data cutoff, six patients had discontinued study therapy owing to death from causes other than disease progression, including three deaths due to adverse events (one from rhinovirus pneumonia, one from influenza, and one from brain abscess associated with meningoencephalitis caused by listeria infection), two due to the malignant disease under study (although not meeting the specific criteria for disease progression per IMWG), and one due to an unknown cause. Of the three deaths due to adverse events, one was considered by investigators to be related to the study treatment (brain abscess). The most common adverse events of any grade were neutropenia (in 81% of the patients), infection (in 74%), anemia (in 61%), thrombocytopenia (in 51%), and fatigue (in 40%) (Table 2). The most common grade 3 or 4 adverse events were neutropenia (grade 3 in 23% and grade 4 in 48%), infection (grade 3 in 36% and grade 4 in 4%), and anemia (grade 3 in 38%). Serious adverse events are listed in Table S7. Overall, adverse events led to a dose reduction in 19 patients (25%).

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic data showed that exposure to mezigdomide was dose-dependent, with maximum exposure observed at approximately 1.5 to 3 hours after patients received their once-daily dose (Fig. S3A); systemic exposure increased by a factor of 1.8 after at least five consecutive doses. Maximum degradation of Aiolos in peripheral blood cells was achieved within 3 hours after the first dose, and repression of Aiolos was sustained for 24 hours after a daily dose above 0.3 mg, which indicated that twice-daily dosing was unnecessary (Fig. 1A, and Fig. S3B and S3C). Degradation of Aiolos was also observed in the tumors of the patients, with the nearly complete loss of Aiolos observed in a patient who received mezigdomide after having had a relapse while receiving pomalidomide-based therapy (Fig. 1B). An overall median decrease of approximately 70% in Aiolos levels was observed in tumor samples from patients who had received pomalidomide as their last line of therapy (data not shown).

Quick, deep, and sustained reductions in concentrations of serum free light chains were achieved with continuous schedules (the 10-day schedule, repeated, and the 21-day schedule) (Fig. 1C and Fig. S4) but fluctuated with intensive schedules (Fig. 1D), a finding that suggests that 3-day and 7-day dosing schedules were not sufficient to control the disease. Immune modulation in the peripheral blood was also more apparent with a continuous schedule; the greatest increase in proliferating T cells and the most sustained decrease in circulating B cells over the dosing period were observed among patients receiving mezigdomide at a dose of 1.0 mg on the 21-day schedule (Fig. S5A and S5B). At this dose and schedule, mezigdomide also induced a

T-cell shift toward an activated effector memory phenotype (Fig. S5C). These data were evaluated with the use of preclinical modeling, which predicted that 4 days off from treatment would be too short for neutrophil recovery; therefore, schedules with 7 days off were prioritized in the interest of safety. With regard to efficacy, serum free light-chain concentrations were dynamic with the use of a "1 week on, 1 week off" schedule, creating a see-saw effect that correlated with the dose-and-break pattern. In contrast, continuous schedules were associated with deep and sustained reductions in serum free light chains and greater immune stimulation. Considering both the efficacy and safety, investigators selected the 21-day schedule for further development.

Efficacy

An overall response was observed in 25% (95% confidence interval [CI], 16 to 36) of the patients in the dose-escalation cohort, including a complete response in 1%, a very good partial response in 12%, and a partial response in 12% (Table 3). Of the 19 patients who had a response, 16 had disease that was refractory to lenalidomide, 14 had disease refractory to pomalidomide, 9 had plasmacytomas (including extramedullary soft-tissue only and bone-based plasmacytomas with a measurable soft-tissue component), and 3 had received previous anti-BCMA therapy. The median duration of response was 6.0 months (95% CI, 1.9 to 11.1). Among the 11 patients who received 1.0 mg of mezigdomide plus dexamethasone once daily and were assigned to the 21-day schedule, the overall response was 55%, with a median duration of response of 9.2 months (95% CI, 1.0 to 12.2); similar efficacy was seen at the 1.0-mg dose among the patients who received treatment on the 10-day schedule, repeated (Table 3 and Fig. S6). On the basis of the pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data, the recommended phase 2 dose was determined to be 1.0 mg of mezigdomide plus dexamethasone once daily on the 21-day schedule.

DOSE-EXPANSION COHORT

Patients

As of September 16, 2022, a total of 101 patients were enrolled in the dose-expansion cohort and had received at least one dose of mezigdomide at the dose and schedule determined in phase 1: 1.0 mg once daily, in combination with dexamethasone, on the 21-day schedule. The median age of the patients was 67 years (range, 42 to 85) and they had received a median of 6 previous lines of therapy (range, 3 to 15), including stem-cell transplantation (77%) (Table 1). The median follow-up was 7.5 months (range, 0.5 to 21.9). All the patients had triple-class–refractory disease, 40% of the patients had plasmacytomas, and 30% had received previous anti-BCMA therapy, including antibody–drug conjugates (22%), T-cell engagers (8%), and chimeric antigen receptor (CAR) T-cell therapy (3%).

Safety

During phase 2 of the study, the most common cause of death was disease progression. The reasons for treatment discontinuation are shown in Fig. S2B. At the time of data cutoff, eight patients in the dose-expansion cohort had discontinued study therapy owing to death from causes other than disease progression, including five deaths due to adverse events (two from *Pneumocystis jirovecii* pneumonia, one from pneumonia, one from Covid-19, and one from septic shock), two due to the malignant disease under study, and one due to an unknown cause. Of the five deaths due to adverse events and one due to an unknown cause, two were considered by investigators to be related to study treatment (one due to *P. jirovecii* pneumonia and one due an unknown cause).

After a median of 4 treatment cycles (range, 1 to 20), the most common adverse events of any grade were neutropenia (in 77% of the patients), infection (in 65%), anemia (in 52%), and thrombocytopenia (in 43%), with febrile neutropenia occurring in 15% (Table 2). The most common grade 3 or 4 adverse events were neutropenia (grade 3 in 22% and grade 4 in 54%), infection (grade 3 in 29% and grade 4 in 6%), and anemia (grade 3 in 35% and grade 4 in 1%); grade 3 or 4 febrile neutropenia occurred in 13% (grade 3) and 2% (grade 4) of patients. Serious adverse events are reported in Table S8. Adverse events led to a reduction in the dose of mezigdomide in 29 patients (29%) and treatment discontinuation in 6 patients (6%); in 5 of the patients who discontinued treatment (5%), the discontinuation was considered to be related to mezigdomide. A total of 10 patients (10%) had two or more dose reductions. The median time to the

first mezigdomide dose interruption was 29 days (range, 3 to 428), and the median time to the first mezigdomide dose reduction was 59 days (range, 16 to 211). A total of 78 patients (77%) received granulocyte colony-stimulating factor (G-CSF), of whom 69 (68%) received it owing to neutropenia of any grade and 66 (65%) owing to grade 3 or 4 neutropenia; 47 patients (46%) received prophylactic G-CSF.

Efficacy

An overall response was observed in 41% (95% CI, 31 to 51) of the patients in the dose-expansion cohort, including a stringent complete response

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Dose-Escalation Cohort (N=77)	Dose-Expansion Cohort (N=101)
Median age (range) — yr	65 (40–78)	67 (42–85)
Male sex — no. (%)	45 (58)	55 (54)
Race — no. (%)†		
White	69 (90)	77 (76)
Black	3 (4)	4 (4)
Asian	1 (1)	7 (7)
Other	1 (1)	4 (4)
Not reported	3 (4)	9 (9)
Median time since initial diagnosis (range) — yr‡	7.2 (0.9–23.2)	7.4 (1.1–37.0)
ECOG performance-status score — no. (%)§		
0	21 (27)	35 (35)
1	49 (64)	57 (56)
2	7 (9)	9 (9)
ISS disease stage — no. (%)¶		
I	25 (32)	39 (39)
II	34 (44)	41 (41)
III	17 (22)	21 (21)
Missing data	1 (1)	0
Cytogenetic profile — no. (%)‖		
High risk	23 (30)	37 (37)
Standard risk	5 (6)	8 (8)
Missing data	49 (64)	56 (55)
Presence of plasmacytomas — no. (%)**	27 (35)	40 (40)
Median no. of previous lines of therapy (range)	6 (2–13)	6 (3–15)
Previous therapy — no. (%)		
Stem-cell transplantation	60 (78)	78 (77)
Proteasome inhibitor	77 (100)	101 (100)
Lenalidomide	76 (99)	101 (100)
Pomalidomide	71 (92)	101 (100)
Anti-CD38 antibody	60 (78)	101 (100)
Anti-BCMA therapy	9 (12)	30 (30)
Antibody–drug conjugate	7 (9)	22 (22)
T-cell engager	1 (1)	8 (8)
CAR T-cell therapy	1 (1)	3 (3)

Table 1. (Continued.)

Characteristic	Dose-Escalation Cohort (N=77)	Dose-Expansion Cohort (N=101)
Refractory status — no. (%)		
Immunomodulatory agent	73 (95)	101 (100)
Lenalidomide	62 (81)	89 (88)
Pomalidomide	65 (84)	97 (96)
Proteasome inhibitor	58 (75)	101 (100)
Anti-CD38 antibody	54 (70)	101 (100)
Triple-class††	43 (56)	101 (100)

* Percentages may not total 100 because of rounding. BCMA denotes B-cell maturation antigen, and CAR chimeric antigen receptor.
† Race was reported by the patient.
‡ Shown is the time between the initial diagnosis and screening for the study. The initial date of diagnosis was missing for one patient in phase 1 of the study; therefore, the value for the dose-escalation cohort was derived from 76 patients.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.
¶ The International Staging System (ISS) consists of three stages: stage I, serum β2-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and serum albumin level 3.5 g per deciliter or higher; stage II, neither stage I nor III; and stage III, serum β2-microglobulin level 5.5 mg per liter or higher (≥470 nmol per liter). Higher stages indicate more severe disease.
‖ High risk was defined as the presence of del(17p), t(4;14), t(14;16), 1q21 amplification (≥4 copies), or all these abnormalities. Standard risk was defined as the absence of all these abnormalities.
** Plasmacytomas include extramedullary soft-tissue only and bone-based plasmacytomas with a measurable soft-tissue component.
†† Triple-class–refractory disease was defined as disease that was refractory to at least one immunomodulatory agent (lenalidomide or pomalidomide), one proteasome inhibitor, and one anti-CD38 antibody.

(defined as a complete response with a normal serum free light-chain ratio and an absence of clonal plasma cells according to the IMWG response criteria) in 2%, complete response in 3%, very good partial response in 20%, and partial response in 16% (Table 3). The median duration of response was 7.6 months (95% CI, 5.4 to 9.5; data not yet mature) (Fig. 2A and 2B), and the median progression-free survival was 4.4 months (95% CI, 3.0 to 5.5) (Fig. 2C). At the time of reporting, the data on overall survival were not yet mature.

The overall response in subgroups of patients who had plasmacytomas and previous anti-BCMA therapy was 30% (95% CI, 17 to 46) and 50% (95% CI, 31 to 69), respectively (Table 3 and Fig. S7). In patients who had previous anti-BCMA therapy, the median duration of response was 6.9 months (95% CI, 4.5 to could not be estimated), and the median progression-free survival was 5.4 months (95% CI, 2.1 to 9.4) (data not shown). In addition, among patients with high-risk cytogenetic abnormalities (defined as 17p deletion, [t(4;14)] translocation, [t(14;16)] translocation, or 1q21 amplification [≥4 copies]), the overall response was 32% (95% CI, 18 to 50), the median duration of response was 10.0 months (95% CI, 1.9 to could not be estimated), and the median progression-free survival was 2.8 months (95% CI, 1.9 to 4.7) (data not shown).

Pharmacodynamics

In a patient population in which 96% of the patients had disease that was refractory to pomalidomide, robust increases in proliferating (Ki-67+) T cells and an immunophenotypic shift toward an activated or effector memory phenotype were observed with mezigdomide at the 1.0-mg dose on the 21-day schedule, including in patients who had received pomalidomide as their most recent therapy. These findings suggest that mezigdomide remains immune-stimulatory after treatment with pomalidomide (Fig. S8).

DISCUSSION

We used a parallel-group study design to determine the dose and schedule of the novel agent

Table 2. Adverse Events That Occurred in More Than 20% of the Patients and Adverse Events of Interest.*

Adverse Event	Dose-Escalation Cohort (N=77)			Dose-Expansion Cohort (N=101)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Hematologic						
Neutropenia	62 (81)	18 (23)	37 (48)	78 (77)	22 (22)	54 (54)
Anemia	47 (61)	29 (38)	0	53 (52)	35 (35)	1 (1)
Thrombocytopenia	39 (51)	9 (12)	9 (12)	43 (43)	14 (14)	14 (14)
Febrile neutropenia	7 (9)	4 (5)	3 (4)	15 (15)	13 (13)	2 (2)
Nonhematologic						
Infections and infestations	57 (74)	28 (36)	3 (4)	66 (65)	29 (29)	6 (6)
Pneumonia†	19 (25)	16 (21)	0	22 (22)	13 (13)	3 (3)
Covid-19	1 (1)	1 (1)	0	17 (17)	7 (7)	0
Fatigue	31 (40)	8 (10)	0	36 (36)	5 (5)	0
Nausea	21 (27)	1 (1)	0	21 (21)	1 (1)	0
Decreased appetite	20 (26)	1 (1)	0	21 (21)	1 (1)	1 (1)
Diarrhea	20 (26)	2 (3)	0	31 (31)	3 (3)	0
Pyrexia	20 (26)	2 (3)	0	15 (15)	3 (3)	0
Peripheral edema	17 (22)	1 (1)	0	8 (8)	0	0
Arthralgia	12 (16)	2 (3)	0	21 (21)	2 (2)	0
Insomnia	12 (16)	0	0	20 (20)	1 (1)	0
Constipation	11 (14)	0	0	24 (24)	0	0
Dyspnea	11 (14)	3 (4)	0	22 (22)	5 (5)	0
Peripheral neuropathy‡	7 (9)	0	0	7 (7)	1 (1)	0
Deep-vein thrombosis	1 (1)	0	0	3 (3)	1 (1)	0

* Adverse events were assessed with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Covid-19 denotes coronavirus 2019.

† For the dose-escalation cohort, pneumonia includes the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0, preferred terms pneumonia, pneumonia respiratory syncytial viral, *Pneumocystis jirovecii* pneumonia, viral pneumonia, bacterial pneumonia, and staphylococcal pneumonia. For the dose-expansion cohort, pneumonia includes preferred terms pneumonia, *P. jirovecii* pneumonia, Covid-19 pneumonia, viral pneumonia, bacterial pneumonia, *Haemophilus influenzae* pneumonia, and *Pseudomonas aeruginosa* pneumonia.

‡ Peripheral neuropathy includes the MedDRA, version 22.0, preferred terms peripheral sensory neuropathy, neuralgia, and peripheral sensorimotor neuropathy.

mezigdomide, when administered with dexamethasone, on the basis of pharmacokinetic, pharmacodynamic, safety, and efficacy data. This study confirmed that the potent substrate degradation observed in preclinical studies of mezigdomide[15,16,21,22] translated into clinical efficacy among patients with relapsed and refractory myeloma, even in patients with disease that was refractory to lenalidomide and pomalidomide.

Mezigdomide plus dexamethasone was associated with myelosuppression and infections in these patients with heavily pretreated disease. Most cases of neutropenia resolved without sequelae with the use of dose interruptions, dose reductions, and supportive care. In the dose-expansion cohort, treatment-related adverse events led to dose reductions of mezigdomide in 29% of patients and discontinuation in 6% of patients. Disease-related adverse events were the most common cause of death during the study in this heavily pretreated population, with only a small number of adverse events considered to be related to the study drug. Given the safety profile of the 1.0-mg dose, dosing options for mezigdomide plus dexamethasone in combination with other agents will continue to be explored.

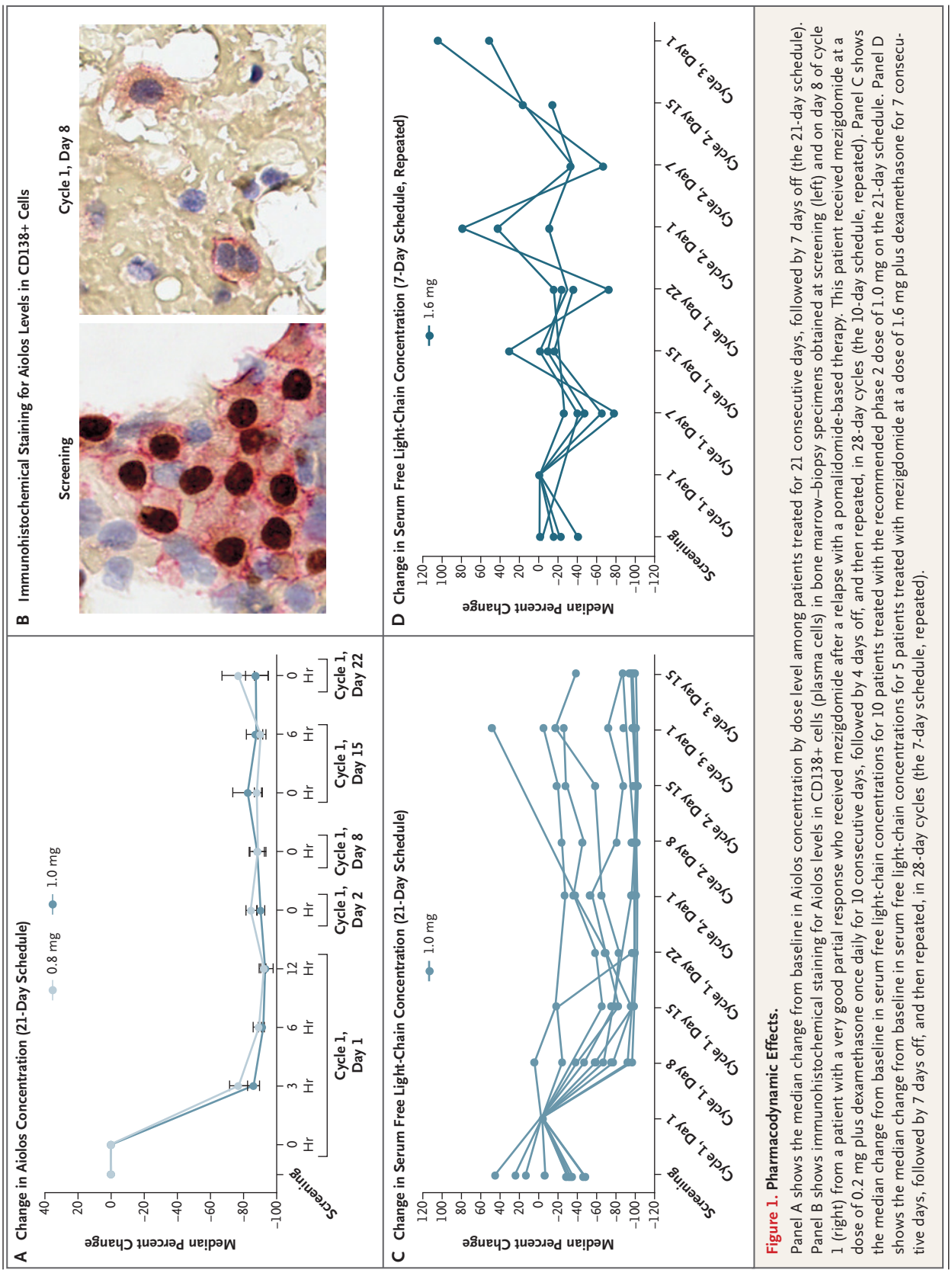


Figure 1. Pharmacodynamic Effects.

Panel A shows the median change from baseline in Aiolos concentration by dose level among patients treated for 21 consecutive days, followed by 7 days off (the 21-day schedule). Panel B shows immunohistochemical staining for Aiolos levels in CD138+ cells (plasma cells) in bone marrow–biopsy specimens obtained at screening (left) and on day 8 of cycle 1 (right) from a patient with a very good partial response who received mezigdomide after a relapse with a pomalidomide-based therapy. This patient received mezigdomide at a dose of 0.2 mg plus dexamethasone once daily for 10 consecutive days, followed by 4 days off, and then repeated, in 28-day cycles (the 10-day schedule, repeated). Panel C shows the median change from baseline in serum free light-chain concentrations for 10 patients treated with the recommended phase 2 dose of 1.0 mg on the 21-day schedule. Panel D shows the median change from baseline in serum free light-chain concentrations for 5 patients treated with mezigdomide at a dose of 1.6 mg plus dexamethasone for 7 consecutive days, followed by 7 days off, and then repeated, in 28-day cycles (the 7-day schedule, repeated).

Table 3. Summary of Best Overall Response.*

Variable	Dose-Escalation Cohort			Dose-Expansion Cohort		
	All Patients (N=77)	10-Day Schedule, Repeated† (N=10)	21-Day Schedule‡ (N=11)	All Patients (N=101)	Patients with Plasmacytomas§ (N=40)	Patients with Previous Anti-BCMA Therapy (N=30)
	number of patients (percent)					
Overall response¶	19 (25)	4 (40)	6 (55)	41 (41)	12 (30)	15 (50)‖
Stringent complete response	0	0	0	2 (2)	0	0
Complete response	1 (1)	0	1 (9)	3 (3)	2 (5)	1 (3)
Very good partial response	9 (12)	2 (20)	3 (27)	20 (20)	7 (18)	9 (30)
Partial response	9 (12)	2 (20)	2 (18)	16 (16)	3 (8)	5 (17)
Minimal response	4 (5)	1 (10)	1 (9)	6 (6)	0	1 (3)
Stable disease	34 (44)	4 (40)	4 (36)	39 (39)	21 (52)	11 (37)
Progressive disease	17 (22)	1 (10)	0	10 (10)	4 (10)	3 (10)
Response could not be evaluated**	3 (4)	0	0	5 (5)	3 (8)	0

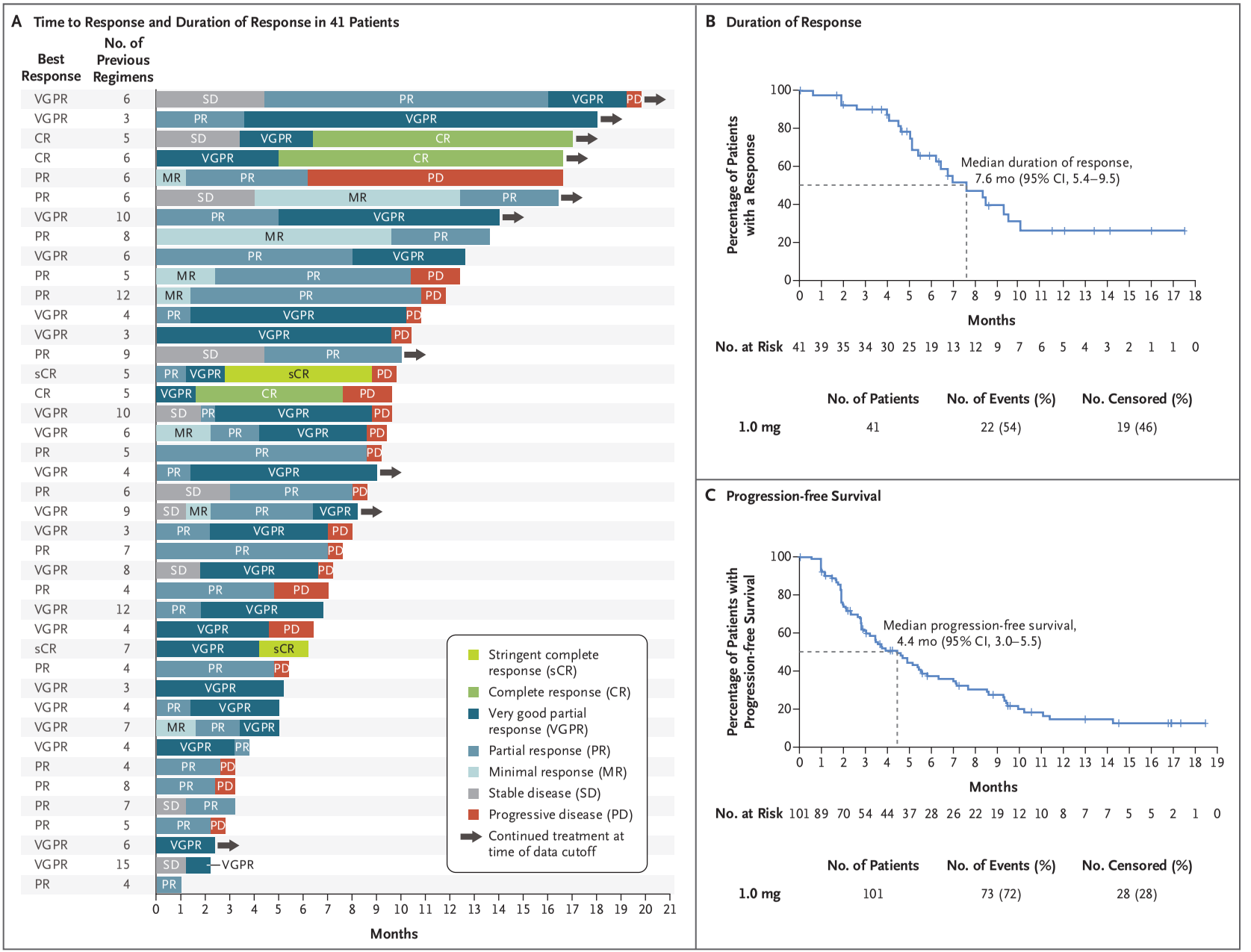
* Response was assessed according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. Percentages may not total 100 because of rounding.
† The 10-day schedule, repeated, was 10 days of consecutive treatment, followed by 4 days off, and then repeated, in 28-day cycles. Mezigdomide was administered at a maximum tolerated dose of 1.0 mg plus dexamethasone.
‡ The 21-day schedule was 21 days of consecutive treatment, followed by 7 days off, in 28-day cycles. Mezigdomide was administered at the recommended phase 2 dose of 1.0 mg once daily plus dexamethasone.
§ Plasmacytomas included extramedullary soft-tissue only and bone-based plasmacytomas with a measurable soft-tissue component.
¶ An overall response was defined as partial response or better. A stringent complete response was defined as a complete response with a normal serum free light-chain ratio and an absence of clonal plasma cells according to the IMWG response criteria.
‖ Of the 15 patients who had a response and had received previous anti-BCMA therapy, 12 had received antibody–drug conjugates, 2 had received T-cell engagers, and 1 had received CAR T-cell therapy.
** Included are patients whose assessment could not be evaluated for response or who did not have response-assessment data.

In the dose-expansion cohort, the overall response was 41%, with a median progression-free survival of 4.4 months, findings that confirm the activity of mezigdomide plus dexamethasone in these patients, all of whom had triple-class–refractory disease and had received previous treatment with lenalidomide and pomalidomide. Among the 30 patients with previous anti-BCMA therapy, the overall response was 50%, with a median progression-free survival of 5.4 months, findings that suggest that mezigdomide plus dexamethasone has an effect after treatment with anti-BCMA therapy has failed.

The prognostic factors that were associated with shorter survival included extramedullary disease and cytogenetic abnormalities (e.g., t[4;14] and del[17p]), and novel treatments are needed for these subgroups of patients in particular.[28-32] We observed an overall response of 30% in patients with plasmacytomas and 32% in patients with known high-risk cytogenetic abnormalities; thus, mezigdomide activity in these patient subgroups warrants further investigation.

Novel and effective therapies that can improve response and survival among patients with myeloma in later lines of treatment are also needed.[33] The expected median overall survival is 3 to 9 months among patients with disease that is refractory to at least three previous drug classes[6,34]; thus, the results achieved with mezigdomide are promising. A study of iberdomide plus dexa-

Figure 2 (facing page). Response Dynamics and Progression-free Survival in the Dose-Expansion Cohort.
Panel A shows the time to response and duration of response in each of the 41 patients in the dose-expansion cohort who had a response (partial response or better) with mezigdomide at a dose of 1.0 mg plus dexamethasone on the 21-day schedule. Kaplan–Meier estimates of duration of response and progression-free survival are shown in Panels B and C, respectively. CI denotes confidence interval.


A Time to Response and Duration of Response in 41 Patients
Best Response
No. of Previous Regimens
VGPR 6 SD PR VGPR PD
VGPR 3 PR VGPR
CR 5 SD VGPR CR
CR 6 VGPR CR
PR 6 MR PR PD
PR 6 SD MR PR
VGPR 10 PR VGPR
PR 8 MR PR
VGPR 6 PR VGPR
PR 5 MR PR PD
PR 12 MR PR PD
VGPR 4 PR VGPR PD
VGPR 3 VGPR PD
PR 9 SD PR
sCR 5 PR VGPR sCR PD
CR 5 VGPR CR PD
VGPR 10 SD PR VGPR PD
VGPR 6 MR PR VGPR PD
PR 5 PR PD
VGPR 4 PR VGPR
PR 6 SD PR PD
VGPR 9 SD MR PR VGPR
VGPR 3 PR VGPR PD
PR 7 PR PD
VGPR 8 SD VGPR PD
PR 4 PR PD
VGPR 12 PR VGPR
VGPR 4 VGPR PD
sCR 7 VGPR sCR
PR 4 PR PD
VGPR 3 VGPR
VGPR 4 PR VGPR
VGPR 7 MR PR VGPR
VGPR 4 VGPR PR
PR 4 PR PD
PR 8 PR PD
PR 7 SD PR
PR 5 PR PD
VGPR 6 VGPR
VGPR 15 SD VGPR
PR 4 PR
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Months
Stringent complete response (sCR)
Complete response (CR)
Very good partial response (VGPR)
Partial response (PR)
Minimal response (MR)
Stable disease (SD)
Progressive disease (PD)
Continued treatment at time of data cutoff
B Duration of Response
Percentage of Patients with a Response
100 80 60 40 20 0
Median duration of response, 7.6 mo (95% CI, 5.4–9.5)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Months
No. at Risk 41 39 35 34 30 25 19 13 12 9 7 6 5 4 3 2 1 1 0
No. of Patients No. of Events (%) No. Censored (%)
1.0 mg 41 22 (54) 19 (46)
C Progression-free Survival
Percentage of Patients with Progression-free Survival
100 80 60 40 20 0
Median progression-free survival, 4.4 mo (95% CI, 3.0–5.5)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Months
No. at Risk 101 89 70 54 44 37 28 26 22 19 12 10 8 7 7 5 5 2 1 0
No. of Patients No. of Events (%) No. Censored (%)
1.0 mg 101 73 (72) 28 (28)

methasone showed a 26% response in patients with triple-class–refractory disease, which indicates that cereblon remains a valid therapeutic target in later lines of treatment.[18] In addition, responses of 26% with selinexor plus dexamethasone[35] and 31 to 34% with belantamab mafodotin[36] have been reported in patients with triple-class–refractory disease. Greater efficacy may be possible with CAR T-cell therapy in patients with at least three previous therapies, given the 73% response with idecabtagene vicleucel and 97% with ciltacabtagene autoleucel.[7-9] Bispecific antibodies targeting BCMA are also promising (e.g., teclistamab led to a 63% response in this context).[10] However, these therapies may not be available or appropriate for all patients, and the risk of severe toxic effects such as cytokine release syndrome, neurotoxicity, and serious life-threatening infections may outweigh the potential benefit in some patient populations.[11] Oral regimens such as mezigdomide and dexamethasone can readily translate a potential clinical benefit into real-world practice, especially among patients with limited access to specialized hospitals, since patients do not have to be hospitalized to receive these treatments.[37,38] Despite high rates of neutropenia observed with the use of mezigdomide, the incidence of grade 3 or 4 infections was lower than that observed with other treatments (e.g., teclistamab was associated with a greater incidence of serious infections, including opportunistic infections).[10] In addition, given the immune-stimulatory properties of mezigdomide, its combination with T-cell–directing therapies may prove to be an excellent treatment option, which provides a rationale for investigating these combinations in the future. Mezigdomide combined with other standard therapies in relapsed or refractory myeloma has yielded promising results thus far in a phase 1–2 study (ClinicalTrials.gov number, NCT03989414),[39] and phase 3 trials of mezigdomide in combination with dexamethasone and bortezomib (SUCCESSOR-1; NCT05519085) or carfilzomib (SUCCESSOR-2; NCT05552976) are under way.

This study represents the culmination of discoveries made over the past decade related to the mechanism of action of immunomodulatory agents in multiple myeloma. Lenalidomide and pomalidomide were developed empirically on the basis of clinical observations. The understanding that they act as molecular glues to co-opt cereblon to target Ikaros and Aiolos for ubiquitination and proteasomal degradation came after their approval.[12,13] This finding also led to novel insights into mechanisms of resistance, including cereblon dysregulation.[40] Mezigdomide was designed on the basis of these insights to achieve deep and sustained Ikaros and Aiolos degradation and overcome cereblon down-regulation and mutations observed in some patients. This study aimed to determine the therapeutic window and achieve rapid, prolonged, and maximal substrate degradation for rapid disease response while mitigating hematologic toxic effects. Mezigdomide plus dexamethasone showed promising preliminary efficacy in this heavily pretreated population, with myelosuppression and infection as the main toxic effects.

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APPENDIX

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