ORIGINAL ARTICLE

Talquetamab plus Teclistamab in Relapsed or Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

Talquetamab (anti–G protein–coupled receptor family C group 5 member D) and teclistamab (anti–B-cell maturation antigen) are bispecific antibodies that activate T cells by targeting CD3 and that have been approved for the treatment of triple-class–exposed relapsed or refractory multiple myeloma.

METHODS

We conducted a phase 1b–2 study of talquetamab plus teclistamab in patients with relapsed or refractory multiple myeloma. In phase 1, we investigated five dose levels in a dose-escalation study. Talquetamab at a dose of 0.8 mg per kilogram of body weight plus teclistamab at a dose of 3.0 mg per kilogram every other week was selected as the recommended phase 2 regimen. The primary objective was to evaluate adverse events and dose-limiting toxic effects.

RESULTS

A total of 94 patients received treatment, with the recommended phase 2 regimen used in 44. The median follow-up was 20.3 months. Three patients had dose-limiting toxic effects (including grade 4 thrombocytopenia in 1 patient with the recommended phase 2 regimen). Across all dose levels, the most common adverse events were cytokine release syndrome, neutropenia, taste changes, and nonrash skin events. Grade 3 or 4 adverse events, most commonly hematologic events, occurred in 96% of the patients. Grade 3 or 4 infections occurred in 64% of the patients. With the recommended phase 2 regimen, a response occurred in 80% of the patients (including in 61% of those with extramedullary disease); across all dose levels, a response occurred in 78%. The likelihood of patients continuing in response at 18 months was 86% with the recommended phase 2 regimen (82% among those with extramedullary disease) and 77% across all dose levels.

CONCLUSIONS

The incidence of grade 3 or 4 infections with talquetamab plus teclistamab was higher than has been observed with either therapy alone. A response was observed in a high percentage of patients across all dose levels, with durable responses with the recommended phase 2 regimen. (Funded by Janssen Research and Development; RedirecTT-1 ClinicalTrials.gov number, NCT04586426.)

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*A list of the investigators in the RedirecTT-1 study is provided in the Supplementary Appendix, available at NEJM.org.

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Patients with relapsed or refractory multiple myeloma who have had exposure to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 therapies (i.e., triple-class exposure) have a poor prognosis with standard treatments.[1-4] Despite the approval of chimeric antigen receptor (CAR) T-cell and bispecific antibody therapies,[5-16] multiple myeloma remains incurable.[17-19] Outcomes are worse in patients with high-risk features, such as extramedullary disease.[12,13,17-20]

Teclistamab is a T-cell–redirecting bispecific antibody that targets B-cell maturation antigen (BCMA).[11,12] In the MajesTEC-1 study, 63% of the patients had a response and 57% remained in response at 18 months with the approved subcutaneous teclistamab dose (1.5 mg per kilogram of body weight weekly, with a reduction in frequency to every other week in patients in whom a deep response was maintained).[21] Cytokine release syndrome, hematologic adverse events, and infections were common; however, the percentage of patients who discontinued owing to adverse events was low.[21]

Talquetamab is a T-cell–redirecting bispecific antibody targeting G protein–coupled receptor class C group 5 member D (GPRC5D).[13-15] In the MonumenTAL-1 study, more than 71% of the patients had a response with the approved subcutaneous doses of talquetamab of 0.4 mg per kilogram weekly and 0.8 mg per kilogram every other week, and the likelihood of remaining in response at 18 months was 37% and 49% with the two doses, respectively.[14,15] Common adverse events included cytokine release syndrome and taste-, skin-, and nail-related events, which were not treatment-limiting.[14] The limited expression of GPRC5D on normal hematopoietic cells, such as B cells and bone marrow progenitors,[22,23] and the relatively low incidence of high-grade infections and neutropenia support combining talquetamab with other antimyeloma therapies, including BCMA-directed therapies.[14,24]

Dual antigen targeting with talquetamab plus teclistamab may further enhance treatment potency, maximize tumor eradication in heterogeneous cell populations, prevent resistance due to tumor antigen escape, and increase durability of response. Here, we report the early safety and efficacy results from the phase 1 dose-escalation portion of the phase 1b–2 RedirecTT-1 study of talquetamab plus teclistamab in patients with relapsed or refractory multiple myeloma.

Methods

Study Design and Patients

We conducted an ongoing, multicenter, nonrandomized, open-label, phase 1b–2 study of talquetamab plus teclistamab. We conducted the phase 1 dose-escalation study with the use of a Bayesian optimal interval design[25] to help identify the recommended phase 2 regimen while minimizing the chance of exposing patients to subtherapeutic or overly toxic dose levels (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Further details about the design variables and decision rules for dose escalation are provided in Table S1. The safety data at each dose-escalation step were reviewed by the study evaluation team.

Eligible patients from Canada, Israel, South Korea, and Spain had measurable myeloma according to International Myeloma Working Group criteria[26] and had disease that had relapsed or was refractory to established therapies or had had an unacceptable level of adverse events with established therapies, including the last line of therapy. Patients had to have previous exposure to a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody (i.e., at least triple-class exposure) and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale from 0 to 5, with higher numbers indicating greater disability). Patients with extramedullary disease with at least one nonradiated, bone-independent lesion (≥2 cm in the greatest dimension) were enrolled. Patients with nonsecretory or oligosecretory extramedullary disease were permitted. Full eligibility criteria are provided in the protocol, available at NEJM.org.

Study Oversight

Janssen Research and Development sponsored the study and designed the study in collaboration with the academic authors. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation guidelines for

Good Clinical Practice. The study protocol and amendments were approved by the institutional review board at each study site. All the patients provided written informed consent. The authors vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol. The manuscript was developed with medical writing assistance (funded by Janssen Global Services) under the direction of the authors, who reviewed, revised, and approved the final manuscript for submission for publication.

TREATMENT

Patients in the various cohorts received escalating doses of subcutaneous talquetamab plus teclistamab in 28-day cycles. Five dose levels of talquetamab plus teclistamab were investigated: talquetamab at 0.2 mg per kilogram plus teclistamab at 0.75 mg per kilogram weekly (dose level 1), talquetamab at 0.2 mg per kilogram plus teclistamab at 1.5 mg per kilogram weekly (dose level 2), talquetamab at 0.4 mg per kilogram plus teclistamab at 1.5 mg per kilogram weekly (dose level 3), talquetamab at 0.8 mg per kilogram plus teclistamab at 1.5 mg per kilogram every 2 weeks (dose level 4), and talquetamab at 0.8 mg per kilogram plus teclistamab at 3.0 mg per kilogram every 2 weeks (dose level 5). Dose level 5 was selected as the recommended phase 2 regimen. Step-up doses were adapted from schedules used with each monotherapy to mitigate severe cytokine release syndrome and were administered 2 to 4 days apart and before full treatment doses. Both bispecific antibodies were administered on the same day, approximately 30 minutes apart, for all step-up and full treatment doses. The administration schedule for the recommended phase 2 regimen, including information on prophylactic measures, is shown in Table S2.[11-15]

Patients could transition from weekly administration to administration every other week and subsequently to monthly administration of talquetamab and teclistamab after the occurrence of a partial response or better after cycle 4. Patients received study treatment until the occurrence of an unacceptable level of toxic events, consent withdrawal, confirmed disease progression, death, investigator or sponsor decision to discontinue treatment, or the end of the study.

END POINTS AND ASSESSMENTS

The primary end point of phase 1 was dose-limiting toxic effects. Secondary end points included overall response (partial response or better), duration of response, time to response, pharmacokinetics, pharmacodynamics, and immunogenicity. Progression-free survival was assessed. Investigator-assessed response was reported every 4 weeks and up to 16 weeks after the end of treatment. Confirmed response required at least two consecutive identical assessments of response by the investigators. Overall response across clinically relevant subgroups was also assessed.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 5.0, and were recorded up to 30 days after the last receipt of study treatment. Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded according to American Society for Transplantation and Cellular Therapy guidelines.[27] Blood and serum samples were obtained for pharmacokinetic, pharmacodynamic, and immunogenicity analyses.

STATISTICAL ANALYSIS

Safety, response-related end points, pharmacokinetics, pharmacodynamics, and immunogenicity were assessed in patients who received at least one dose of study treatment. The percentage of patients with a response was estimated according to the best confirmed response of a partial response or better, divided by the number of treated patients. Exact 95% confidence intervals are reported. The Kaplan–Meier method was used to estimate time to response, duration of response, and progression-free survival. No formal statistical hypothesis was tested. All the data were analyzed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

Between December 9, 2020, and April 26, 2023, a total of 116 patients underwent screening (Fig. 1). As of March 15, 2024, a total of 94 patients had received talquetamab plus teclistamab, including 44 who had received doses according to the recommended phase 2 regimen.

The median follow-up was 20.3 months (range, 0.5 to 37.1) overall and 18.2 months (range, 0.7 to 27.0) with the recommended phase 2 regimen. Across all dose levels, 49 patients (52%) were continuing with dual therapy, and 1 patient (1%) had discontinued talquetamab only and continued to receive teclistamab monotherapy.

Across all dose levels, the median age of the patients was 64.5 years, and patients had received a median of four previous lines of therapy over a median duration of 6.1 years since diagnosis (Table 1). All the patients had triple-class exposure, and most patients (65%) had penta-drug exposure. Seven patients had received bispecific antibodies previously, and 4 had received CAR T-cell therapy previously. A total of 87 patients (93%) had disease that was refractory to their last line of therapy, and 81 (86%) had disease that was triple-class refractory. A total of 34 patients (36%) had extramedullary disease, and 21 of 51 patients (41%) had a high-risk cytogenetic profile.

SAFETY

Three patients had dose-limiting toxic effects: one patient each treated with talquetamab at a dose of 0.2 mg per kilogram plus teclistamab at a dose of 0.75 mg per kilogram weekly (grade 3 oral herpes), with talquetamab at a dose of 0.4 mg per kilogram plus teclistamab at

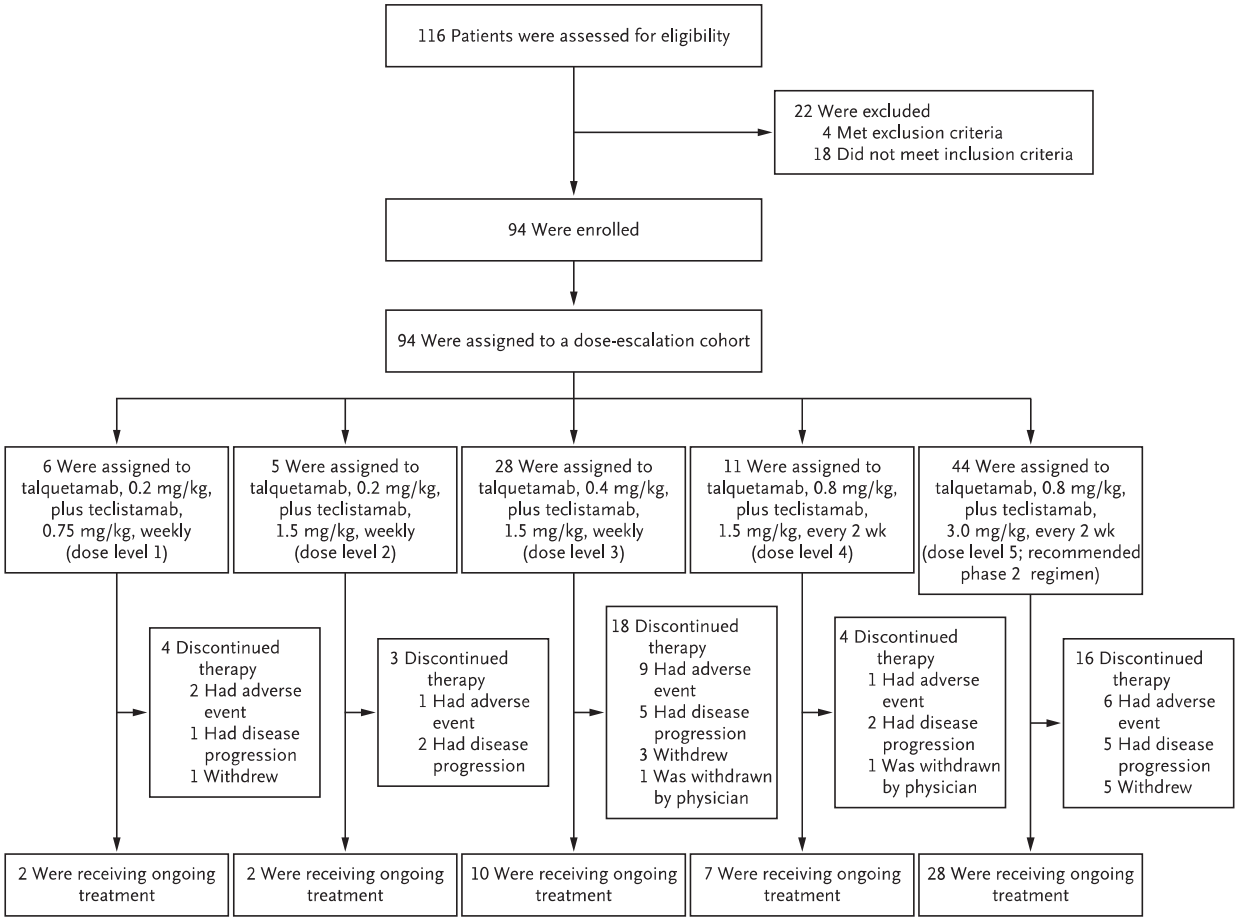


Figure 1. Dose-Cohort Assignment and Follow-up.

One patient in the cohort that was assigned to the recommended phase 2 regimen (i.e., talquetamab at a dose of 0.8 mg per kilogram of body weight plus teclistamab at a dose of 3.0 mg per kilogram every other week) discontinued talquetamab because of having more than one adverse event but continued receiving teclistamab as permitted by the study protocol.

Table 1. Baseline Characteristics of Patients Who Received Talquetamab plus Teclistamab.*

Characteristic	All Dose Levels (N=94)	Recommended Phase 2 Regimen (N=44)
Median age (range) — yr	64.5 (39–81)	63 (41–80)
Male sex — no. (%)	49 (52)	23 (52)
Race — no. (%)†		
White	75 (80)	32 (73)
Asian	17 (18)	12 (27)
Black	1 (1)	0
Unknown	1 (1)	0
Bone marrow plasma cells ≥60% — no./total no. (%)‡	19/89 (21)	9/40 (22)
≥1 Extramedullary plasmacytoma — no. (%)§	34 (36)	18 (41)
High-risk cytogenetic profile — no./total no. (%)¶	21/51 (41)	8/19 (42)
International Staging System class — no./total no. (%)‖		
I	38/85 (45)	19/41 (46)
II	26/85 (31)	14/41 (34)
III	21/85 (25)	8/41 (20)
ECOG performance-status score — no. (%)**		
0	34 (36)	15 (34)
1	60 (64)	29 (66)
Median time since diagnosis (range) — yr	6.1 (0.3–14.6)	5.5 (0.3–12.9)
Median no. of previous lines of therapy (range)	4 (1–11)	4 (2–10)
Stem-cell transplantation — no. (%)	74 (79)	33 (75)
Exposure status — no. (%)		
Triple-class exposure	94 (100)	44 (100)
Penta-drug exposure	61 (65)	28 (64)
Belantamab mafodotin	18 (19)	5 (11)
Bispecific antibody††	7 (7)	2 (5)
CAR T-cell therapy	4 (4)	2 (5)
Refractory status — no. (%)		
Proteasome inhibitor	85 (90)	41 (93)
Carfilzomib	62 (66)	27 (61)
Bortezomib	58 (62)	30 (68)
Ixazomib	10 (11)	6 (14)
Immunomodulatory drug	91 (97)	41 (93)
Lenalidomide	83 (88)	36 (82)
Pomalidomide	62 (66)	28 (64)
Thalidomide	18 (19)	8 (18)
Anti-CD38 monoclonal antibody	93 (99)	43 (98)
Daratumumab	91 (97)	42 (95)
Isatuximab	5 (5)	4 (9)
Last line of therapy	87 (93)	39 (89)
Triple-class–refractory disease‡‡	81 (86)	37 (84)

Table 1. (Continued.)

Characteristic	All Dose Levels (N=94)	Recommended Phase 2 Regimen (N=44)
Penta-refractory disease§§	31 (33)	13 (30)

* The phase 1, dose-escalation portion of this study evaluated five dose levels of talquetamab and teclistamab. Talquetamab at a dose of 0.8 mg per kilogram of body weight plus teclistamab at a dose of 3.0 mg per kilogram, administered every other week (dose level 5), was selected as the recommended phase 2 regimen. Percentages may not total 100 because of rounding. CAR denotes chimeric antigen receptor.
† Race was reported by the patient, and the data were entered by the investigators or research staff.
‡ The percentage of bone marrow plasma cells was assessed with the use of bone marrow biopsies or aspirates in patients with available data.
§ The presence of at least one extramedullary plasmacytoma was defined as at least one bone-independent lesion (≥2 cm in the greatest dimension) that had not been previously exposed to radiation therapy.
¶ A high-risk cytogenetic profile was defined as a del(17p), t(4;14), or t(14;16) abnormality, as assessed by means of fluorescence in situ hybridization or karyotype testing.
‖ The International Staging System class was assessed on the basis of the combination of serum β_2-microglobulin and albumin in patients with available data.
** Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale from 0 to 5, with higher scores indicating greater disability.
†† Patients had received previous therapy with a B-cell maturation antigen–directed bispecific antibody (alnuctamab in four patients, WVT078 in two, and teclistamab in one). Of the four patients across all dose levels who had received alnuctamab, two were in the group with the recommended phase 2 regimen.
‡‡ Triple-class–refractory disease was defined as disease refractory to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 therapy.
§§ Penta-refractory disease was defined as disease refractory to two or more immunomodulatory drugs, two or more proteasome inhibitors, and one or more anti-CD38 therapies.

a dose of 1.5 mg per kilogram weekly (grade 3 elevated alanine aminotransferase and aspartate aminotransferase levels), and at the recommended phase 2 regimen (grade 4 thrombocytopenia). Across all dose levels, 90 patients (96%) had a grade 3 or 4 adverse event (Table 2). The most common adverse events were cytokine release syndrome, neutropenia, taste changes, and nonrash skin events. The most common adverse events of grade 3 or 4 were hematologic events (in 80% of the patients).

A total of 87 patients (93%) had cycle delays or dose modifications that were due to adverse events, primarily infections (in 64 of 94 patients [68%]). Adverse events led to the discontinuation of one or both agents in 15 patients (16%) (Table S3), of which seven discontinuations (in 7% of the patients) were considered by the investigator to be related to a study drug (with five discontinuations [in 5% of the patients] due to infections).

Overall, 14 patients (15%) died because of adverse events, including pneumonia in 2 patients and adenovirus infection, coronavirus disease 2019 (Covid-19), Covid-19–associated pneumonia, JC virus infection, aspiration pneumonia, cytomegalovirus-associated pneumonia, respiratory tract infection, sepsis, septic shock, cardiac arrest, leptomeningeal myelomatosis, and respiratory failure in 1 patient each (Table S4). A total of 11 grade 5 adverse events (in 12% of patients) were infections. Six grade 5 events were considered by the investigator to be related to a study drug, but insufficient detail exists to rule out attribution to treatment for the other events. Four patients (4%) died from disease progression.

Infection of any grade occurred in 84 patients (89%), with grade 3 or 4 infection in 60 patients (64%) (Table S5). Across all dose levels, the incidence of first onset of infection of grade 3 or above was higher in the first 6 months of study treatment and plateaued thereafter (Table S6). Antiviral prophylaxis was given to 77 of 94 patients (82%), and 46 patients (49%) received prophylaxis against *Pneumocystis jirovecii* pneumonia. A total of 59 patients (63%) received a Covid-19 vaccine. Among the 38 patients (40%) who had Covid-19, a total of 17 (18%) had grade 3 or 4 events and 2 (2%) died. Opportunistic infections occurred in 10 patients (11%). Most pyrexia events occurred within the first 6 months of study treatment, which coincided with the occurrence of most infections, events of cytokine release syndrome, and injection-site reactions (Table S7).

Table 2. Hematologic and Nonhematologic Adverse Events, According to Grade, in 94 Patients Who Received Talquetamab plus Teclistamab at Any Dose Level.*

Event	Any Grade	Grade 3 or 4
	number of patients (percent)	
Any adverse event	94 (100)	90 (96)
Hematologic event		
Neutropenia	69 (73)	64 (68)
Anemia	53 (56)	36 (38)
Thrombocytopenia	40 (43)	28 (30)
Nonhematologic event		
Cytokine release syndrome	74 (79)	2 (2)
Taste changes†	61 (65)	NA
Nonrash skin adverse event‡	57 (61)	0
Nail-related adverse event§	49 (52)	0
Pyrexia¶	48 (51)	2 (2)
Diarrhea	45 (48)	3 (3)
Cough	42 (45)	1 (1)
Dry mouth	40 (43)	0
Covid-19	38 (40)	17 (18)
Rash adverse event‖	37 (39)	1 (1)
Pneumonia	34 (36)	19 (20)
Weight decrease	32 (34)	5 (5)
Fatigue	26 (28)	8 (9)

* The adverse events listed here are those that occurred in more than 25% of the total study population. Adverse events were reported up to 30 days after the patient received the last dose of study treatment. Patients could have had multiple adverse events. Covid-19 denotes coronavirus disease 2019, and NA not applicable.
† Taste changes included dysgeusia, ageusia, hypogeusia, and taste disorder. According to the Common Terminology Criteria for Adverse Events, version 5.0, the maximum grade for taste changes is 2.
‡ Nonrash skin adverse events included skin exfoliation, dry skin, pruritus, and palmar–plantar erythrodysesthesia syndrome.
§ Nail-related adverse events included nail discoloration, nail disorder, onycholysis, onychomadesis, onychoclasis, nail dystrophy, nail toxic effects, and nail ridging.
¶ Two patients had grade 3 pyrexia that was not considered by the investigators to be serious. Neither event occurred concurrently with an infection of grade 3 or higher.
‖ Rash adverse events included rash, maculopapular rash, erythematous rash, and erythema.

At baseline, 53 of 94 patients (56%) had non-IgG myeloma. Overall, 37 of these 53 patients with non-IgG myeloma (70%) had hypogammaglobulinemia (defined as an IgG value <400 mg per deciliter) at baseline, and 30 (57%) had post-treatment hypogammaglobulinemia. Assessments excluded patients with IgG myeloma and those who received intravenous immune globulin replacement. A total of 30 patients (57%) with non-IgG myeloma received intravenous immune globulin.

Cytokine release syndrome occurred in 74 patients (79%). Most events were of grade 1 or 2 and occurred during the step-up and early cycles of treatment administration; grade 3 cytokine release syndrome occurred in 2 patients (2%). Cytokine release syndrome led to cycle delays or dose modifications in 14 patients (15%). The median time to onset and the duration of cytokine release syndrome were 2 days each. A total of 61 patients (65%) received supportive measures, including 24 (26%) who received tocilizumab. Overall, recovery occurred in 98% of the events observed in the patients, recovery with sequelae in 1%, and incomplete recovery in 1%. ICANS occurred in 3 patients (3%), with one grade 3 event reported; 1 patient had two events. All these events occurred during the step-up phase and had a median time to onset of 2.5 days and a median duration of 3 days; recovery occurred in all events observed in the patients. Two of the four ICANS events occurred concurrently with cytokine release syndrome. One patient (1%) had a grade 3 tumor flare reaction.

Taste changes (i.e., taste disorder, dysgeusia, hypogeusia, or ageusia) occurred in 61 patients (65%) and led to cycle delays or dose modifications in 5 patients (5%) (Table S8) and to the discontinuation of talquetamab in 1 patient (1%). Adverse events of rash occurred in 37 patients (39%), and nonrash skin adverse events occurred in 57 (61%); all these events were of grade 1 or 2, except for one grade 3 event of rash at the recommended phase 2 regimen. Rashes led to cycle delays or dose modifications in 2 patients (2%), although none led to discontinuation. Nail-related adverse events were of grade 1 or 2 and occurred in 49 patients (52%); none of these events led to cycle delays, dose modifications, or discontinuations.

EFFICACY

With the recommended phase 2 regimen, a response occurred in 35 of 44 patients (80%) (Fig. 2A), and the median time to first response was 1.4 months (range, 0.3 to 5.1). A total of 34 patients (77%) had a very good partial response or better, and 23 (52%) had a complete response or better. A high percentage of patients had a response with the recommended phase 2 regimen across clinically relevant subgroups, including in patients with International Staging System III myeloma (7 of 8 patients [88%]), in those

who had received three or more lines of therapy previously (29 of 38 patients [76%]), in those with a high-risk cytogenetic profile (6 of 8 patients [75%]), and in those with extramedullary disease (11 of 18 patients [61%]) (Fig. S2A).

Across all dose levels, a response occurred in 73 of 94 patients (78%) (Fig. 2A), and the median time to first response was 1.8 months (range, 0.3 to 7.7). A total of 70 patients (74%) had a very good partial response or better, and 45 (48%) had a complete response or better. Responses were consistent across clinically relevant subgroups (Fig. S2B). Although a numerically higher percentage of patients without extramedullary disease had a response (53 of 60 patients [88%]), a response was observed in the majority of patients with extramedullary disease (20 of 34 patients [59%]).

The likelihood of continuing to have a response at 12 months and 18 months was 91% (95% confidence interval [CI], 75 to 97) and 86% (95% CI, 66 to 95), respectively, with the recommended phase 2 regimen and 86% (95% CI, 75 to 92) and 77% (95% CI, 64 to 85), respectively, across all dose levels (Fig. 2B). Among patients with extramedullary disease, the likelihood of continuing to have a response at 12 months and 18 months was 82% (95% CI, 45 to 95) at both time points with the recommended phase 2 regimen and 70% (95% CI, 45 to 85) at 12 months and 52% (95% CI, 25 to 74) at 18 months across all dose levels. Responses were maintained or deepened in all 28 patients who transitioned from administration every other week to monthly administration with the recommended phase 2 regimen (Fig. S3).

With the recommended phase 2 regimen, the estimated progression-free survival was 74% (95% CI, 57 to 84) at 12 months and 70% (95% CI, 52 to 82) at 18 months (Fig. 3). Among patients with extramedullary disease, progression-free survival was 53% (95% CI, 28 to 73) at both time points. Across all dose levels, the estimated progression-free survival was 71% (95% CI, 60 to 79) at 12 months and 62% (95% CI, 51 to 72) at 18 months.

PHARMACOKINETICS, PHARMACODYNAMICS, AND IMMUNOGENICITY

At the recommended phase 2 regimen, talquetamab and teclistamab exposures were similar to those observed with each agent as monotherapy

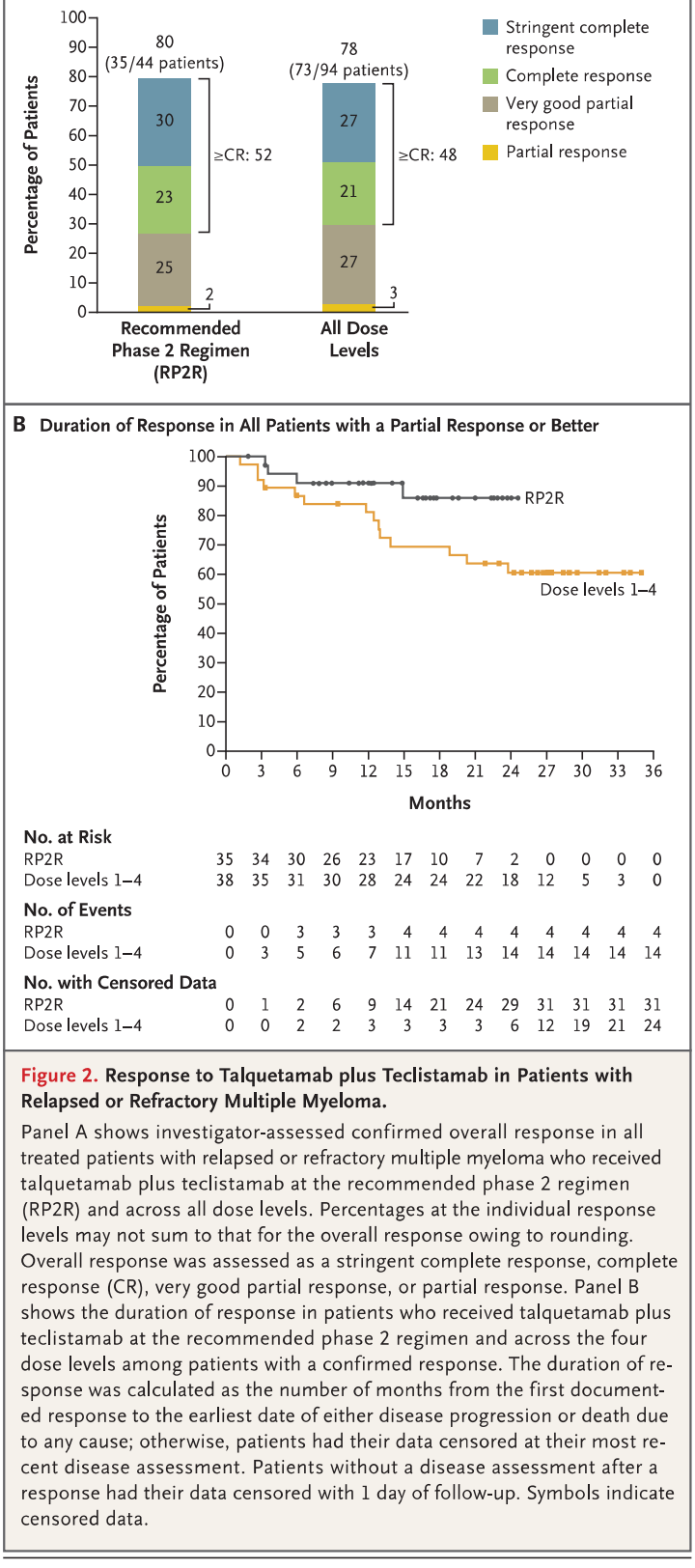
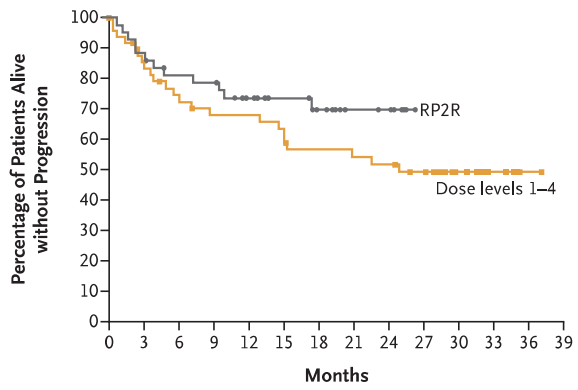


Figure 2. Response to Talquetamab plus Teclistamab in Patients with Relapsed or Refractory Multiple Myeloma.

Panel A shows investigator-assessed confirmed overall response in all treated patients with relapsed or refractory multiple myeloma who received talquetamab plus teclistamab at the recommended phase 2 regimen (RP2R) and across all dose levels. Percentages at the individual response levels may not sum to that for the overall response owing to rounding. Overall response was assessed as a stringent complete response, complete response (CR), very good partial response, or partial response. Panel B shows the duration of response in patients who received talquetamab plus teclistamab at the recommended phase 2 regimen and across the four dose levels among patients with a confirmed response. The duration of response was calculated as the number of months from the first documented response to the earliest date of either disease progression or death due to any cause; otherwise, patients had their data censored at their most recent disease assessment. Patients without a disease assessment after a response had their data censored with 1 day of follow-up. Symbols indicate censored data.



No. at Risk														
RP2R	44	38	33	32	26	20	16	8	7	0	0	0	0	0
Dose levels 1–4	50	39	34	30	30	28	24	23	22	19	10	4	1	0
No. of Events														
RP2R	0	5	8	9	11	11	12	12	12	12	12	12	12	12
Dose levels 1–4	0	8	12	15	15	17	20	21	22	23	23	23	23	23
No. with Censored Data														
RP2R	0	1	3	3	7	13	16	24	25	32	32	32	32	32
Dose levels 1–4	0	3	4	5	5	5	6	6	6	8	17	23	26	27

Figure 3. Kaplan–Meier Analysis of Progression-free Survival.

Progression-free survival, as assessed from the start of treatment, is shown among all treated patients who received talquetamab plus teclistamab at the recommended phase 2 regimen and across the four dose levels. Events were defined as the earliest date of either disease progression or death due to any cause; otherwise, patients had their data censored at their most recent disease assessment. Patients without disease assessments had their data censored with 1 day of follow-up. Symbols indicate censored data.

(Fig. S4). T-cell activation was highly variable but consistent across all dose levels (Figs. S5 and S6). Further pharmacodynamic and immunogenicity results are described in the Supplementary Appendix.

DISCUSSION

Combination therapy with teclistamab plus talquetamab showed encouraging antitumor activity in a majority of patients with relapsed or refractory multiple myeloma. The most common adverse events were cytokine release syndrome, neutropenia, taste changes, and nonrash skin adverse events — findings that are consistent with the treatment profiles of the monotherapies.[12,13] Cytokine release syndrome was common and mostly of low grade (no grade 4 or 5 events), which is consistent with T-cell–redirection therapies, including talquetamab and teclistamab monotherapies.[14,21] ICANS was rare, typically of low grade, and reversible with standard mitigation measures. GPRC5D-associated adverse events were common, were of low grade, and were managed according to protocol recommendations. In particular, oral adverse events, including dysgeusia, were managed with salt water or glucocorticoid rinses, nutrition consultation, pain management, short courses of oral glucocorticoids, or dose modifications. Although efficacy was maintained in patients who switched to less-frequent administration, the effect on the safety profile was not evaluated owing to confounding factors, such as small patient numbers and the fact that dose changes roughly coincided with plateaus in the cumulative incidence of adverse events of interest. Finally, the incidence of treatment-related adverse events leading to death or discontinuation was low, and these adverse events were mostly due to infections. As compared with the initial results from this study that were reported in 2023,[28] four additional grade 5 adverse events were observed, none of which were considered by the investigator to be related to a study drug.

At a median follow-up of 20.3 months (range, 0.5 to 37.1), serious infections were common and the incidence of grade 3 or 4 infections (64% across all dose levels) was higher than was seen in studies of each agent as monotherapy: 20% (at a dose of 0.4 mg per kilogram weekly) and 14% (at a dose of 0.8 mg per kilogram every other week) with talquetamab (median follow-up, 18.8 months [range, 0.5 to 32.9] and 12.7 months [range, 0.2 to 26.1], respectively) and 55% with teclistamab (median follow-up, 22.8 months [range, 0.3 to 33.6]).[14,21] Prophylactic infection measures were recommended and administered according to institutional guidelines, but the proportion of patients receiving infection prophylaxis may have differed among the dose cohorts given that enrollment commenced at different time points and infection-management guidelines evolved during the conduct of the study. The protocol recommended immune globulin replacement therapy in patients with a serum IgG level below 400 mg per deciliter, which is consistent with current treatment guidelines.[29] Overall, these results reinforce the importance of infection screening, prophylaxis, management, and surveillance of hypogammaglobulinemia and neutropenia.[29,30]

Previously, we reported response in the RedirecTT-1 study among patients who could be

evaluated for response (Table S9).[28] Here, we report response in all patients who had their best response confirmed by at least two consecutive assessments. A response occurred in 80% of the patients with the recommended phase 2 regimen and in 78% of the patients across all dose levels.

Cross-study comparisons must be interpreted with caution. However, a response was observed in 74% of patients treated with talquetamab at a dose of 0.4 mg per kilogram weekly and in 72% of those treated with talquetamab at a dose of 0.8 mg per kilogram every other week,[14] in 63% of those treated with teclistamab,[21] in 61% of those treated with elranatamab,[16] in 83% of those treated with ciltacabtagene autoleucel (among patients who had undergone apheresis),[5] and in 67% of those treated with idecabtagene vicleucel (among patients who had undergone apheresis).[9] Deep responses were observed with talquetamab plus teclistamab, with 52% of the patients having a complete response or better with the recommended phase 2 regimen and with 48% of patients having a complete response or better across all dose levels. In a previous study of talquetamab monotherapy, a complete response or better was observed in 34% of patients who received 0.4 mg per kilogram weekly and in 39% of those who received 0.8 mg per kilogram every other week[14]; in a previous study of teclistamab monotherapy, 45% of the patients treated with a dose of 1.5 mg per kilogram weekly had a complete response or better.[21] With a median follow-up of 18.2 months with the recommended phase 2 regimen, responses were highly durable, with an 86% likelihood of patients continuing to have a response at 18 months. The likelihood of continuing to have a response at 18 months was 37% with talquetamab monotherapy at a dose of 0.4 mg per kilogram weekly and 49% with a dose of 0.8 mg per kilogram every other week and was 57% with teclistamab monotherapy at a dose of 1.5 mg per kilogram weekly.[15,21] Although heterogeneous target antigen expression can decrease the potency of T-cell–redirection therapies,[31,32] these findings suggest that dual targeting of two distinct myeloma antigens may enhance efficacy in heterogeneous cell populations, improve durability as compared with single targeting monotherapies, and reduce the risk of relapse.

Among patients with extramedullary disease who were treated with standard regimens, the proportion of patients who have a response is lower and progression-free survival is shorter than among patients without extramedullary disease.[10] BCMA-targeting CAR T-cell therapies have shown high percentages of patients with a response among those with extramedullary disease, although patient populations included those with paramedullary lesions,[6,10] who have a better prognosis than patients with extramedullary disease.[33,34] However, the durability of response and progression-free survival with CAR T-cell therapies were shorter among patients with extramedullary disease than in the overall study populations.[6,10]

Among patients with extramedullary disease, a response to talquetamab monotherapy occurred in 16 of 33 patients (48%) at a dose of 0.4 mg per kilogram weekly and in 17 of 41 patients (41%) at a dose of 0.8 mg per kilogram every other week, and the median duration of response was 8.1 months (among patients treated at either dose) (data on file, Janssen Biotech). Among patients with extramedullary disease who received teclistamab monotherapy at a dose of 1.5 mg per kilogram weekly, a response occurred in 10 of 28 patients (36%), and the median duration of response was 14.0 months.[12]

In the RedirecTT-1 study, 61% of patients with extramedullary disease had a response with the recommended phase 2 regimen, and the likelihood of continuing to have a response at 18 months was 82% — a finding that approximated the durability of response at 18 months that was seen among all the patients with the recommended phase 2 regimen (86%). Limitations of our study include the relatively short follow-up, a small overall sample size, the low representation of Black patients (1 patient) (Table S10), a lack of formal hypothesis testing, the use of investigator-assessed responses, and the open-label, nonrandomized nature of the study.

In this study, talquetamab plus teclistamab had a similar safety profile to each agent as monotherapy, although the observed incidence of grade 3 or 4 infections was higher with the combination than with talquetamab or teclistamab as monotherapies. Responses were observed across dose levels and were particularly deep and durable with the recommended phase 2 regimen. On the basis of these results, this dual-targeting, off-the-shelf combination therapy

warrants further investigation in patients with relapsed or refractory multiple myeloma.

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APPENDIX

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REFERENCES

1. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. Leukemia 2017;31:2443-8.
2. Wang PF, Yee CW, Gorsh B, et al. Treatment patterns and overall survival of patients with double-class and triple-class refractory multiple myeloma: a US electronic health record database study. Leuk Lymphoma 2023;64:398-406.
3. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266-75.
4. Mateos M-V, Weisel K, De Stefano V, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 2022;36:1371-6.
5. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398:314-24.
6. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol 2023;41:1265-74.
7. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med 2023;389:335-47.
8. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. N Engl J Med 2019;380:1726-37.
9. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med 2021;384:705-16.
10. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med 2023;388:1002-14.
11. Usmani SZ, Garfall AL, van de Donk NWCJ, et al. Teclistamab, a B-cell maturation antigen × CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet 2021;398:665-74.
12. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 2022;387:495-505.
13. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med 2022;387:2232-44.
14. Schinke C, Touzeau C, Minnema M, et al. Pivotal phase 2 MonumenTAL-1 results of talquetamab, a GPRC5D×CD3 bispecific antibody, for relapsed/refractory multiple myeloma. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 2–6, 2023. poster.
15. Touzeau C, Schinke C, Minnema M, et al. Pivotal phase 2 MonumenTAL-1 results of talquetamab, a GPRC5D×CD3 bispecific antibody, for relapsed/refractory multiple myeloma. Presented at the European Hematology Association Annual Meeting, Frankfurt, Germany, June 8–11, 2023.
16. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 2023;29:2259-67.
17. Gagelmann N, Ayuk FA, Klyuchnikov E, Wolschke C, Berger SC, Kröger N. Impact of high-risk disease on the efficacy of chimeric antigen receptor T-cell therapy for multiple myeloma: a meta-analysis of 723 patients. Haematologica 2023;108:2799-802.
18. Swan D, Murphy P, Glavey S, Quinn J. Bispecific antibodies in multiple myeloma: opportunities to enhance efficacy and improve safety. Cancers (Basel) 2023;15:1819.
19. Rosiñol L, Beksac M, Zamagni E, et al. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. Br J Haematol 2021;194:496-507.
20. Moreau P, Mateos M-V, Goldschmidt H, et al. Outcomes of patients with extramedullary disease in triple-class exposed relapsed/refractory multiple myeloma from the LocoMMotion + MoMMent Studies. Blood 2023;142:Suppl:4698. abstract.

21. van de Donk NWCJ, Moreau P, Garfall AL, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a BCMA×CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 2–6, 2023. poster.
22. Verkleij CPM, Broekmans MEC, van Duin M, et al. Preclinical activity and determinants of response of the GPRC5DxCD3 bispecific antibody talquetamab in multiple myeloma. Blood Adv 2021;5:2196-215.
23. Kodama T, Kochi Y, Nakai W, et al. Anti-GPRC5D/CD3 bispecific T-cell-redirecting antibody for the treatment of multiple myeloma. Mol Cancer Ther 2019;18:1555-64.
24. Rodríguez-Otero P, Schinke CD, Chari A, et al. Analysis of infection and parameters of humoral immunity in patients (pts) with relapsed/refractory multiple myeloma (RRMM) treated with talquetamab (tal) monotherapy in MonumenTAL-1. J Clin Oncol 2023;41:Suppl:8020. abstract.
25. Yuan Y, Hess KR, Hilsenbeck SG, Gilbert MR. Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. Clin Cancer Res 2016;22:4291-301.
26. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.
27. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.
28. Cohen YC, Morillo M, Gatt ME, et al. First results from the RedirecTT-1 study with teclistamab + talquetamab simultaneously targeting BCMA and GPRC5D in patients with relapsed/refractory multiple myeloma. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 2–6, 2023.
29. Raje N, Anderson K, Einsele H, et al. Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. Blood Cancer J 2023;13:116.
30. Ludwig H, Terpos E, van de Donk N, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol 2023;24(6):e255-e269.
31. Pillarisetti K, Edavettal S, Mendonça M, et al. A T-cell-redirecting bispecific G-protein-coupled receptor class 5 member D x CD3 antibody to treat multiple myeloma. Blood 2020;135:1232-43.
32. Fernandez de Larrea C, Staehr M, Lopez A, et al. Optimal dual-targeted CAR construct simultaneously targeting Bcma and GPRC5D prevents Bcma-escape driven relapse in multiple myeloma. Blood 2019;134:Suppl:136. abstract.
33. Pour L, Sevcikova S, Greslikova H, et al. Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. Haematologica 2014;99:360-4.
34. Beksac M, Seval GC, Kanellias N, et al. A real world multicenter retrospective study on extramedullary disease from Balkan Myeloma Study Group and Barcelona University: analysis of parameters that improve outcome. Haematologica 2020;105:201-8.