ORIGINAL ARTICLE

Teclistamab plus Daratumumab in Relapsed or Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

In a phase 1–2 trial, teclistamab, a bispecific antibody targeting CD3 on T-cell surfaces and B-cell maturation antigen on myeloma cells, showed durable responses in heavily pretreated patients with relapsed or refractory multiple myeloma. Daratumumab, a monoclonal antibody targeting CD38 protein, has shown survival benefit in patients with multiple myeloma.

METHODS

In this phase 3 trial, we randomly assigned patients with one to three previous lines of therapy to receive combination therapy with teclistamab–daratumumab or daratumumab combined with dexamethasone plus the investigator's choice of pomalidomide (DPd) or bortezomib (DVd) — the DPd or DVd group. The primary end point was progression-free survival, as assessed by an independent review committee.

RESULTS

A total of 587 patients underwent randomization (291 to receive teclistamab-daratumumab and 296 to receive DPd or DVd). At a median of 34.5 months, progression-free survival was significantly longer with teclistamab-daratumumab than with DPd or DVd. The estimated 36-month progression-free survival was 83.4% in the teclistamab–daratumumab group and 29.7% in the DPd or DVd group (hazard ratio, 0.17; 95% confidence interval, 0.12 to 0.23; P<0.001). More patients in the teclistamab-daratumumab group than in the DPd or DVd group had a complete response or better (81.8% vs. 32.1%), an overall response (89.0% vs. 75.3%), and minimal residual disease negativity (10^{-5}; 58.4% vs. 17.1%) (P<0.001 for all comparisons). Serious adverse events occurred in 70.7% of the patients in the teclistamab–daratumumab group and in 62.4% of those in the DPd or DVd group; death from adverse events occurred in 7.1% and 5.9%, respectively.

CONCLUSIONS

In patients with multiple myeloma who had received one to three previous lines of therapy, those in the teclistamab–daratumumab group had significantly longer progression-free survival than those in the DPd or DVd group. (Funded by Johnson & Johnson; ClinicalTrials.gov number, NCT05083169.)

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*A complete list of the investigators in the MajesTEC-3 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Multiple myeloma is characterized by progressive immune dysfunction and multiple relapses. The treatment of relapsed or refractory multiple myeloma is increasingly challenging[1,2] because the evolving frontline landscape complicates second-line treatment selection. Challenges are compounded by limited effective salvage treatment options[3] and high attrition.[4] Emerging anti–B-cell maturation antigen (BCMA) treatments, including chimeric antigen receptor T-cell (CAR-T) therapy and antibody drug conjugates, offer promise, with ciltacabtagene autoleucel therapy resulting in a high incidence of minimal residual disease negativity and durable progression-free survival.[5] However, off-the-shelf and highly effective regimens are needed to fully address the needs of individual patients.

In the phase 1–2 MajesTEC-1 trial, teclistamab, a bispecific antibody targeting CD3 on T-cell surfaces and B-cell maturation antigen on myeloma cells and B cells,[6] showed deep and durable responses in heavily pretreated patients with relapsed or refractory multiple myeloma.[7,8] Daratumumab, an anti-CD38–targeting monoclonal antibody, is a cornerstone of standard treatment regimens for multiple myeloma, with a survival benefit across all lines of therapy.[9-14] In addition to direct on-tumor effects, daratumumab sensitizes the immune microenvironment by depleting immunosuppressive T cells and enhancing CD8+ T-cell cytotoxicity, which creates synergistic effects with teclistamab-mediated eradication of myeloma cells.[15] This off-the-shelf immunotherapy combination of teclistamab and daratumumab is a potential therapeutic strategy to improve outcomes in second- or subsequent-line relapsed or refractory multiple myeloma.

We designed the MajesTEC-3 trial to evaluate the combination of teclistamab and daratumumab as compared with the investigator's choice of a daratumumab-based regimen in patients with relapsed or refractory multiple myeloma who had received one to three previous lines of therapy. Here, we report results from the primary analysis of efficacy and safety, performed at the planned first interim analysis.

Methods

Design and Oversight

In this phase 3, multicenter, open-label trial, patients underwent randomization at 150 sites across 20 countries between October 22, 2021, and September 29, 2023. The local independent ethics committee or institutional review board at each trial site approved the protocol and amendments. The trial was conducted in accordance with the provisions of the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and country-specific regulations. An independent data and safety monitoring committee regularly reviewed all the safety data, with efficacy included during the primary analysis review. All the patients provided written informed consent.

Johnson & Johnson funded the trial and provided medical writing assistance. Representatives of the company designed the trial in consultation with key investigators and compiled, maintained, and analyzed the data. All the authors had access to and can vouch for the integrity of the data and for the adherence of the trial to the approved protocol, available with the full text of this article at NEJM.org. All the drafts of the manuscript were critically reviewed, revised, and approved by all the authors.

Patients

Eligible patients had received one to three lines of antimyeloma therapy, including a proteasome inhibitor and lenalidomide, with documented disease progression on or after the last therapy line. Patients who had received only one previous line of therapy were required to have lenalidomide-refractory myeloma, according to the criteria of the International Myeloma Working Group.[16-18]

Key exclusion criteria were previous BCMA-directed therapy or refractoriness to anti-CD38 monoclonal antibodies. Patients with pomalidomide-refractory and bortezomib-refractory myeloma were not allowed to receive daratumumab with pomalidomide and dexamethasone (DPd) and daratumumab with bortezomib and dexamethasone (DVd), respectively. Full eligibility criteria are provided in the protocol.

Treatments

Patients were randomly assigned in a 1:1 ratio to receive teclistamab–daratumumab or the investigator's choice of standard-care regimens of DPd or DVd — the DPd or DVd group.[19] Patients were stratified according to the investigator's choice of DPd or DVd, the International Staging System disease stage (I, II, or III), previous exposure to

monoclonal antibodies against CD38, and the number of previous lines of therapy (one, two, or three).

The teclistamab–daratumumab group received teclistamab in 28-day cycles, with a dose of 1.5 mg per kilogram of body weight weekly in cycle 1 following two step-up doses of 0.06 and 0.3 mg per kilogram; 1.5 mg per kilogram weekly in cycle 2; 3 mg per kilogram every 2 weeks in cycles 3 to 6; and 3 mg per kilogram every 4 weeks from cycle 7 onward. A dose of 3 mg per kilogram every 4 weeks provides pharmacokinetic exposure that is similar to that of the approved dose of 1.5 mg per kilogram every 2 weeks. Subcutaneous daratumumab was administered according to the approved dosing schedule (Table S1 in the Supplementary Appendix, available at NEJM.org).[20] The teclistamab administration schedule aligned with the approved daratumumab schedule to increase dosing convenience. Dose reductions from 3 mg per kilogram to 1.5 mg per kilogram or a decrease in the dosing frequency for teclistamab were permitted with sponsor approval. Patients who discontinued at least one component of the assigned treatment could continue to receive other components, as assigned. Premedication with dexamethasone, acetaminophen, and diphenhydramine was required for the first 2 weeks; subsequent dexamethasone was not required.

The DPd or DVd group received treatment according to established schedules (Table S2).[21] Treatment in the two trial groups continued until confirmed progressive disease, death, unacceptable side effects, or withdrawal of consent.

Infection prophylaxis, including immune globulin supplementation, antibiotics, and prophylaxis for *Pneumocystis jirovecii* pneumonia and herpes zoster reactivation, was administered according to institutional guidelines. Immune globulin therapy and infection-prophylaxis guidance were reinforced according to a protocol amendment that was adopted in February 2023, which affirmed the importance of medical monitoring of IgG levels and adherence to protocol-specified supplementation guidance. Tocilizumab was permitted for the treatment of grade 1 cytokine release syndrome and was recommended for higher grades of this syndrome.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, as assessed by an independent review committee and defined according to a time-to-event analysis. Key secondary end points were a complete response or better (a complete or stringent complete response), an overall response (a partial response or better), minimal residual disease negativity (10^{-5} threshold), overall survival, and worsening of symptoms. A stringent complete response was defined as fulfilling the criteria for a standard complete response plus a normal serum free light chain ratio and the absence of clonal plasma cells in the bone marrow. Worsening of symptoms was evaluated in a time-to-event analysis according to the total score on the Multiple Myeloma Symptom and Impact Questionnaire symptom scale, with single-item scores ranging from 0 to 4. Additional secondary end points included safety, pharmacokinetics, and immunogenicity. Additional analyses of minimal residual disease and end-point definitions are provided in the Supplementary Appendix.

Response and disease progression were assessed by a blinded institutional review committee according to the criteria of the International Myeloma Working Group.[16-18] Disease evaluations were performed centrally; imaging and bone marrow analysis for response were performed locally. Minimal residual disease was assessed in bone marrow aspirates by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in accordance with International Myeloma Working Group guidelines.[18] Minimal residual disease was assessed in patients with a suspected complete response or better and at 6, 12, 18, and 24 months after day 1 in cycle 1 for patients with a confirmed complete response. Serum was collected to assess the pharmacokinetics and immunogenicity of teclistamab and daratumumab. Assessment timing is summarized in the Supplementary Appendix.

Adverse events were monitored continuously and graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 5.0)[22]; details are provided in the Supplementary Appendix. Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome were graded according to the guidelines of the American Society for Transplantation and Cellular Therapy.[23]

STATISTICAL ANALYSIS

We estimated that a sample size of 560 patients and the occurrence of 335 events of disease progression or death would provide the trial with 90%

power to detect a 30% lower risk of disease progression or death with teclistamab–daratumumab than with DPd or DVd at an overall two-sided alpha level of 0.05. A group sequential design with one interim analysis was planned for progression-free survival when approximately 251 progression events or deaths had occurred. The significance level that was required to establish superiority with respect to progression-free survival at the interim analysis was determined on the basis of the number of events that had been observed, according to O'Brien–Fleming boundaries and implemented by the Lan–DeMets alpha spending method. The use of group sequential design and a hierarchical testing procedure for the key secondary end points ensured control for multiple testing (see the Supplementary Appendix).

The primary and efficacy end points (with the exclusion of minimal residual disease negativity) were analyzed in the intention-to-treat population, which included all the patients who had undergone randomization. Minimal residual disease negativity was assessed by next-generation sequencing in all patients who had undergone randomization, except for those recruited in China, for whom only next-generation flow cytometry was available. Adverse events were evaluated in the safety population, which included all the patients in the primary population who had received any trial treatment.

We used a two-sided stratified log-rank test to compare time-to-event end points between groups. Hazard ratios and 95% confidence intervals were estimated by means of a stratified Cox regression model, with treatment as the sole explanatory variable. When the proportional-hazards assumption did not hold, the interpretation of the hazard ratio would represent an average effect over time and a prespecified analysis of restricted mean survival time was performed. The Kaplan–Meier method was used to estimate distributions, including findings at landmark times (e.g., 36 months). Additional details regarding methods for the handling of intercurrent events and censoring rules for analyses of progression-free and overall survival are provided in the Supplementary Appendix.

Binary outcomes were compared between groups with stratified Cochran–Mantel–Haenszel estimates of odds ratio with calculation of two-sided 95% confidence intervals and P values. Given that odds ratios may inflate the apparent magnitude of the effect, stratified estimates of risk ratios are also provided. For all stratified analyses, stratification was based on the International Staging System (stage I vs. stage II or stage III) and the number of previous lines of therapy (one line vs. two or three lines). Of note, the widths of all confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Post hoc analyses were also performed, and these results should be interpreted with caution.

RESULTS

PATIENTS

A total of 587 patients underwent randomization: 291 to receive teclistamab–daratumumab and 296 to receive DPd or DVd (Fig. S1). Of these patients, 573 received the assigned treatment: 283 in the teclistamab–daratumumab group and 290 in the DPd or DVd group. In the DPd or DVd group, 263 patients (90.7%) received DPd, and 27 (9.3%) received DVd. The demographic and disease characteristics of the patients at baseline were similar in the two groups (Table 1 and Table S3). The real-world representativeness is summarized in Table S4.

As of the clinical cutoff date (August 1, 2025), discontinuation of treatment had been reported in 29.0% of the patients in the teclistamab–daratumumab group and in 71.7% of those in the DPd or DVd group. Discontinuation occurred primarily because of progressive disease, which was reported in 7.4% of the patients in the teclistamab–daratumumab group and in 57.9% of those in the DPd or DVd group. At the time of this report, treatment was continuing in 71.0% of the patients in the teclistamab–daratumumab group and in 28.3% of those in the DPd or DVd group. The median duration of treatment was twice as long with teclistamab–daratumumab as with DPd or DVd (32.4 months vs. 16.1 months, respectively). The median relative dose intensity was 97.1% with teclistamab and ranged from 90.0 to 97.8% with daratumumab across groups (Table S5). Reductions in the dose of teclistamab were reported in 28.5% of the patients who received at least one dose of teclistamab; most of these reductions occurred in cycle 7 or later (Table S6). The median follow-up was 34.5 months (range, 0.03 to 45.3).

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Teclistamab–Daratumumab (N=291)	DPd or DVd (N=296)	All Patients (N=587)
Median age (range) — yr	64 (36–88)	63 (25–84)	64 (25–88)
Male sex — no. (%)	156 (53.6)	169 (57.1)	325 (55.4)
Race or ethnic group — no. (%)†			
White	190 (65.3)	194 (65.5)	384 (65.4)
Asian	68 (23.4)	63 (21.3)	131 (22.3)
Black	13 (4.5)	20 (6.8)	33 (5.6)
Other ethnic group	20 (6.9)	19 (6.4)	39 (6.6)
ECOG performance-status score — no. (%)‡			
0	167 (57.4)	160 (54.1)	327 (55.7)
1	108 (37.1)	127 (42.9)	235 (40.0)
2	16 (5.5)	9 (3.0)	25 (4.3)
Stage on International Staging System — no. (%)§			
I	182 (62.5)	185 (62.5)	367 (62.5)
II	85 (29.2)	88 (29.7)	173 (29.5)
III	24 (8.2)	23 (7.8)	47 (8.0)
Previous therapy exposure			
Median number of previous lines of therapy (range)	2 (1–3)	2 (1–3)	2 (1–3)
Medications — no. (%)			
Proteasome inhibitor	290 (99.7)	296 (100)	586 (99.8)
Immunomodulatory drug	291 (100)	296 (100)	587 (100)
Anti-CD38 antibody	15 (5.2)	16 (5.4)	31 (5.3)
Refractory status — no. (%)			
Any proteasome inhibitor	117 (40.2)	104 (35.1)	221 (37.6)
Any immunomodulatory drug	247 (84.9)	253 (85.5)	500 (85.2)
Median time from diagnosis of multiple myeloma to randomization — yr (range)	3.7 (0.4–20.3)	3.9 (0.2–22.3)	3.8 (0.2–22.3)
Cytogenetic risk — no./total no. (%)¶			
Standard	126/285 (44.2)	145/294 (49.3)	271/579 (46.8)
High	104/285 (36.5)	104/294 (35.4)	208/579 (35.9)
Undetermined	55/285 (19.3)	45/294 (15.3)	100/579 (17.3)

* DPd denotes daratumumab in combination with dexamethasone and pomalidomide, and DVd denotes daratumumab in combination with dexamethasone and bortezomib, which were administered according to the investigator's choice.
† Race or ethnic group was reported by the patients. Other ethnic groups included Native Hawaiian or Pacific Islander, American Indian or Alaska Native, and unknown.
‡ Scores regarding Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with higher scores indicating greater disability.
§ The International Staging System categorizes the stage of myeloma according to serum levels of beta-2-microglobulin and albumin.
¶ Cytogenetic risk abnormalities are based on central testing with fluorescence in situ hybridization (FISH) testing or on local FISH or karyotype testing if central FISH testing was not available. High cytogenetic risk was defined as the presence of at least one of the following abnormalities: del(17p), t(4;14), or t(14;16).

EFFICACY

Patients in the teclistamab–daratumumab group had a significantly lower risk of disease progression or death than those in the DPd or DVd group (P<0.001); the P value crossed the prespecified stopping boundary for superiority at the first interim analysis (P=0.0139). The estimated 36-month progression-free survival was 83.4% (95% confidence interval [CI], 78.2 to 87.4) in the teclistamab–daratumumab group and 29.7% (95% CI, 23.6 to 36.0) in the DPd or DVd group (hazard ratio, 0.17; 95% CI, 0.12 to 0.23) (Fig. 1A). In subgroup analyses, progression-free survival favored teclistamab–daratumumab across all prespecified and clinically relevant subgroups (Fig. 1B).

The percentage of patients who had a complete response or better was significantly higher in the teclistamab–daratumumab group than in the DPd or DVd group (81.8% vs. 32.1%); in a post hoc calculation, the risk ratio was 2.55 (95% CI, 2.14 to 3.03) (Table 2). A significant between-group difference was also seen among the patients who had an overall response (89.0% and 75.3%, respectively), with a risk ratio of 1.18 (95% CI, 1.09 to 1.27). Odds ratios are reported in Table S7. Among the patients who had a response in the two trial groups, the median time was 1.2 months until the first response and 6.9 months until the occurrence of a complete response or better. The estimated percentage of patients who continued to have a response at 36 months was 88.5% (95% CI, 83.7 to 92.0) in the teclistamab–daratumumab group and 36.4% (95% CI, 28.9 to 43.9) in the DPd or DVd group (Fig. S2).

In the primary analysis set for next-generation sequencing, the percentage of patients with minimal residual disease negativity (10^{-5}) was higher with teclistamab–daratumumab than with DPd or DVd (58.4% vs. 17.1%), with a risk ratio of 3.43 (95% CI, 2.58 to 4.55) (Table 2). Odds ratios are reported in Table S7. Additional analyses of minimal residual disease are provided in Table S8 and Figure S3.

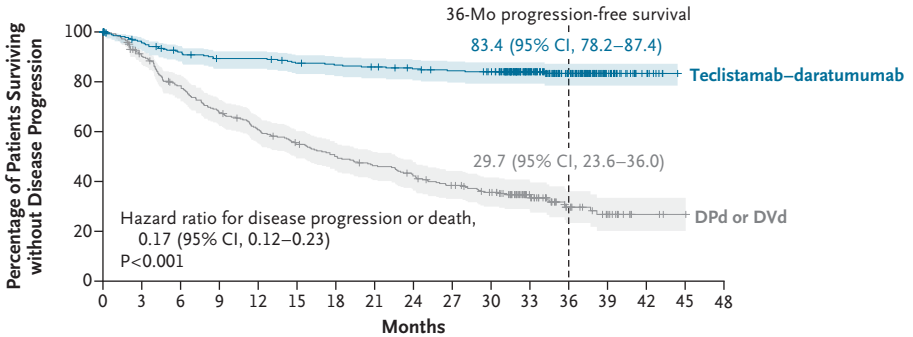
Patients in the teclistamab–daratumumab group had a significantly lower risk of death than those in the DPd or DVd group (P<0.0001 by stratified log-rank test). The estimated 36-month overall survival was 83.3% (95% CI, 78.3 to 87.2) with teclistamab–daratumumab and 65.0% (95% CI, 58.8 to 70.5) with DPd or DVd (Fig. 2 and Table S9). The overall survival curves crossed at approximately 10 months of follow-up, primarily owing to early deaths from infection in the teclistamab–daratumumab group. Analysis of the restricted mean survival time showed an overall survival benefit for teclistamab–daratumumab as compared with DPd or DVd (difference, 2.15 months; 95% CI, 0.54 to 3.77) (Table S9). In the teclistamab–daratumumab group, 92.2% of the patients were alive at 6 months and 84.3% at 30 months post-treatment, findings that suggest a survival plateau starting around 6 months; the corresponding percentages were 94.5% and 69.6% with DPd or DVd.

No worsening of symptoms at 36 months was reported in an estimated 75.6% of patients (95% CI, 68.1 to 81.6) in the teclistamab–daratumumab group and in 63.3% (95% CI, 54.7 to 70.6) in the DPd or DVd group (hazard ratio, 0.50; 95% CI, 0.34 to 0.72; P<0.001), according to the Multiple Myeloma Symptom and Impact Questionnaire total symptom score (Table S10).

Figure 1 (facing page). Progression-free Survival.

Panel A shows Kaplan–Meier estimates of progression-free survival at 36 months among patients who were randomly assigned to receive teclistamab in combination with daratumumab (teclistamab–daratumumab) or daratumumab in combination with dexamethasone and the investigator's choice of either pomalidomide or bortezomib (DPd or DVd); shading indicates 95% confidence intervals, and tick marks indicate censored data. At a median follow-up of 34.5 months, the median progression-free survival was not reached in the teclistamab–daratumumab group and was 18.1 months in the DPd or DVd group, therefore favoring teclistamab–daratumumab treatment. Panel B shows the results of a prespecified subgroup analysis of the risk of disease progression or death in the intention-to-treat population. A hazard ratio of less than 1.0 indicates an advantage for teclistamab–daratumumab as compared with DPd or DVd. The International Staging System (ISS) consists of three stages (with a higher stage indicating more severe disease) and is based on levels of serum beta-2-microglobulin and albumin. High cytogenetic risk is defined by fluorescence in situ hybridization or karyotype testing of patients having one or more of the following abnormalities: t(4;14), t(14;16), and del(17p). The performance-status score on Eastern Cooperative Oncology Group (ECOG) scale ranges from 0 to 5, with higher scores indicating greater disability. Baseline soft-tissue plasmacytomas include both extramedullary and paraskeletal plasmacytomas. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Several subgroup analyses — geographic region, previous exposure to anti-CD38 therapy, and refractory status to lenalidomide — were performed post hoc.

A Progression-free Survival



No. at Risk

Teclistamab–daratumumab	291	262	249	240	240	233	230	227	222	218	214	142	89	34	9	0	0
DPd or DVd	296	254	218	188	167	149	135	124	112	99	87	52	26	14	3	1	0

B Subgroup Analysis

Subgroup	Teclistamab–Daratumumab	DPd or DVd	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
Age			
<65 yr	18/147	103/160	0.13 (0.08–0.22)
65 to <75 yr	19/113	71/111	0.17 (0.10–0.29)
≥75 yr	7/31	13/25	0.35 (0.14–0.89)
Sex			
Male	27/156	106/169	0.20 (0.13–0.30)
Female	17/135	81/127	0.13 (0.08–0.23)
Race			
White	33/190	124/194	0.18 (0.12–0.27)
Asian	8/68	43/63	0.11 (0.05–0.24)
Black	1/13	9/20	0.19 (0.02–1.49)
Other	2/20	11/19	0.14 (0.03–0.62)
Geographic region			
North America	4/35	21/46	0.18 (0.06–0.54)
Europe	28/176	101/158	0.18 (0.11–0.27)
Other	12/80	65/92	0.15 (0.08–0.27)
Previous anti-CD38 therapy			
Yes	3/15	12/16	0.19 (0.05–0.67)
No	41/276	175/280	0.17 (0.12–0.23)
Refractory to lenalidomide			
Yes	38/240	162/251	0.17 (0.12–0.24)
No	6/51	25/45	0.17 (0.07–0.41)
Renal function at baseline			
≤60 ml/min	14/56	36/55	0.31 (0.16–0.57)
>60 ml/min	30/235	150/240	0.14 (0.09–0.20)
Baseline ECOG performance-status score			
0	23/167	98/160	0.16 (0.10–0.25)
≥1	21/124	89/136	0.18 (0.11–0.29)
Investigator's choice of DPd or DVd			
DPd	42/267	166/269	0.18 (0.13–0.26)
DVd	2/24	21/27	0.05 (0.01–0.24)
No. of lines of previous therapy			
1	13/108	71/114	0.14 (0.08–0.25)
2 or 3	31/183	116/182	0.18 (0.12–0.27)
ISS disease stage at baseline			
I	19/182	110/185	0.12 (0.07–0.20)
II	19/85	59/88	0.23 (0.13–0.38)
III	6/24	18/23	0.31 (0.12–0.79)
Soft-tissue plasmacytomas at baseline			
No	30/250	158/255	0.13 (0.09–0.20)
Yes	14/41	29/41	0.33 (0.17–0.63)
Cytogenetic risk group			
High-risk	20/104	78/104	0.15 (0.09–0.25)
Standard-risk	15/126	84/145	0.16 (0.09–0.27)
Percent plasma cells in bone marrow			
≤30	31/216	140/234	0.17 (0.11–0.25)
>30 to <60	7/42	24/35	0.17 (0.07–0.39)
≥60	6/28	21/24	0.17 (0.07–0.43)

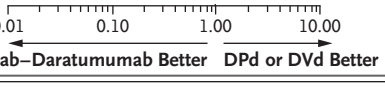


Table 2. Treatment Response and Minimal Residual Disease Negativity (Intention-to-Treat Population).

Variable	Teclistamab–Daratumumab (N=291)	DPd or DVd (N=296)	Risk Ratio (95% CI)*
Overall response — no. (%)†	259 (89.0)	223 (75.3)	1.18 (1.09–1.27)
Response — no. (%)‡			
Stringent complete response§	225 (77.3)	69 (23.3)	—
Complete response	13 (4.5)	26 (8.8)	—
Very good partial response	14 (4.8)	74 (25.0)	—
Partial response	7 (2.4)	54 (18.2)	—
Minimal response	1 (0.3)	13 (4.4)	—
Stable disease	13 (4.5)	46 (15.5)	—
Progressive disease	3 (1.0)	5 (1.7)	—
Not evaluable	15 (5.2)	9 (3.0)	—
Complete response or better	238 (81.8)	95 (32.1)	2.55 (2.14–3.03)
Very good partial response or better	252 (86.6)	169 (57.1)	1.52 (1.36–1.69)
Measure of response			
Median duration — mo (95% CI)	NE (NE–NE)	23.5 (19.8–29.9)	—
Median time until first response — mo (range)	1.2 (0.9–25.0)	1.2 (0.7–6.3)	—
Median time until complete response or better — mo (range)	6.9 (1.0–34.5)	6.9 (1.5–18.8)	—
Minimal residual disease¶			
Patients in sequencing analysis set — no.‖	262	269	—
Patients with negativity of 10^{-5} — no. (%)	153 (58.4)	46 (17.1)	3.43 (2.58–4.55)

* Listed are the stratified estimates of risk ratios. A risk ratio of more than 1 indicates an advantage for teclistamab–daratumumab. The widths of confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. NE denotes not evaluable.
† Overall response is defined as a partial response or better.
‡ Response and disease progression were assessed by an independent review committee in accordance with the response criteria of the International Myeloma Working Group.
§ A stringent complete response was defined as fulfilling the criteria for a standard complete response plus a normal serum free light chain ratio and the absence of clonal plasma cells in the bone marrow.
¶ Minimal residual disease was assessed in bone marrow aspirates by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in accordance with the guidelines of the International Myeloma Working Group.
‖ Minimal residual disease negativity was evaluated in the sequencing primary analysis set, which was defined as all the randomly assigned patients, except for those recruited in China. Chinese patients were assessed according to flow cytometry.

SAFETY

The most common adverse events of any grade during treatment are reported in Table 3. The most common grade 3 or 4 adverse event was neutropenia, which was reported in 75.6% of the patients in the teclistamab–daratumumab group and in 78.6% of those in the DPd or DVd group. Serious adverse events occurred in 70.7% of the patients in the teclistamab–daratumumab group and in 62.4% of those in the DPd or DVd group; the most common of these events was pneumonia, which was reported in 16.6% and 13.1% of the patients, respectively (Table S11). Adverse events leading to treatment discontinuation oc-

curred in 4.6% and 5.5% of the patients, respectively.

Deaths were reported in 45 patients (15.9%) in the teclistamab–daratumumab group and in 96 patients (33.1%) in the DPd or DVd group, mainly due to adverse events and disease progression, respectively (Table S12). The number of deaths from adverse events during treatment was 20 (7.1%) in the teclistamab–daratumumab group and 17 (5.9%) in the DPd or DVd group. Of these deaths, the investigator determined that the event was related to a trial treatment in 12 patients (4.2%) in the teclistamab–daratumumab group and in 5 patients (1.7%) in the DPd or DVd group (Table S13).

Cytokine release syndrome occurred in 60.1% of the patients in the teclistamab–daratumumab group, all of which were grade 1 (44.2%) or grade 2 (15.9%) events (Table S14). These events were transient, with a median duration of 2 days (range, 1 to 22). All the events resolved, and none led to treatment discontinuation. Most events occurred during the step-up dosing schedule; no grade 2 events occurred after cycle 1 (Table S15). Supportive measures are summarized in Table S14. Immune effector cell–associated neurotoxicity syndrome occurred in 3 patients (1.1%) with teclistamab–daratumumab (2 patients with grade 1 and 1 patient with grade 4), with resolution of all events. The grade 4 event led to the discontinuation of teclistamab in this patient, who continued to receive daratumumab (Table S16).

The frequency of grade 3 or 4 neutropenia, anemia, or thrombocytopenia was similar in the two groups (Table 3). The frequency of new-onset cytopenias of grade 3 or higher was highest in the first 6 months of therapy and decreased thereafter (Table S17).

Infections of any grade were common in both groups and were reported in 96.5% of the patients in the teclistamab–daratumumab group and in 84.1% of those in the DPd or DVd group (Table S18); grade 3 or 4 infections were reported in 54.1% and 43.4% of the patients, respectively. New-onset infections of grade 3 or higher decreased after 6 months of treatment (Table S19), coinciding with transition to monthly drug administration. The incidence of coronavirus disease 2019 (Covid-19) was higher with teclistamab–daratumumab than with DPd or DVd (any grade, 43.8% vs. 33.4%; grade 3 or 4, 6.0% vs. 2.1%; and serious infection, 6.7% vs. 2.1%), as was pneumo-

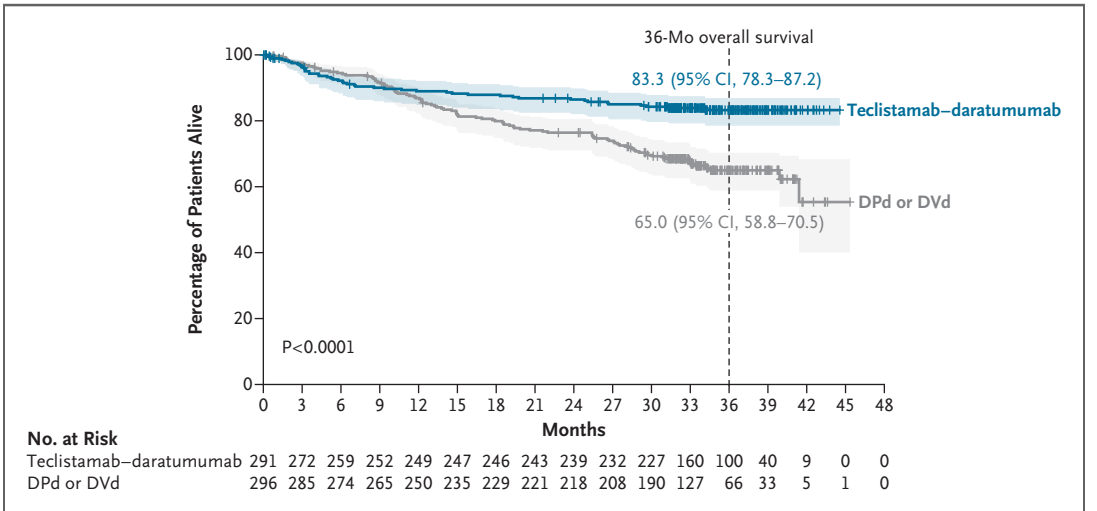


Figure 2. Overall Survival.

Shown is the Kaplan–Meier estimate of overall survival at 36 months among the patients in the teclistamab–daratumumab group and the DPd or DVd group; shading indicates 95% confidence intervals, and tick marks indicate censored data. At a median follow-up of 34.5 months, the treatment effect on overall survival significantly favored teclistamab–daratumumab as compared with DPd or DVd. The P value was calculated by the log-rank test, stratified according to the International Staging System (stage I vs. stage II or III) and the number of lines of previous therapy (one vs. two or three). The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Table 3. Most Common Adverse Events (Safety Population).*

Adverse Event	Teclistamab–Daratumumab (N=283)		DPd or DVd (N=290)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	283 (100)	269 (95.1)	290 (100)	280 (96.6)
Hematologic				
Neutropenia	222 (78.4)	214 (75.6)	240 (82.8)	228 (78.6)
Anemia	111 (39.2)	58 (20.5)	103 (35.5)	50 (17.2)
Thrombocytopenia	103 (36.4)	55 (19.4)	126 (43.4)	68 (23.4)
Lymphopenia	63 (22.3)	59 (20.8)	50 (17.2)	32 (11.0)
Leukopenia	51 (18.0)	30 (10.6)	61 (21.0)	46 (15.9)
Nonhematologic				
Hypogammaglobulinemia	194 (68.6)	16 (5.7)	104 (35.9)	4 (1.4)
Cytokine release syndrome	170 (60.1)	0	0	0
Diarrhea	147 (51.9)	10 (3.5)	89 (30.7)	7 (2.4)
Cough	136 (48.1)	1 (0.4)	66 (22.8)	0
Covid-19	124 (43.8)	17 (6.0)	97 (33.4)	6 (2.1)
Upper respiratory tract infection	115 (40.6)	12 (4.2)	88 (30.3)	7 (2.4)
Pyrexia	104 (36.7)	4 (1.4)	55 (19.0)	1 (0.3)
Pneumonia	65 (23.0)	47 (16.6)	53 (18.3)	43 (14.8)
Covid-19 pneumonia	34 (12.0)	32 (11.3)	12 (4.1)	7 (2.4)

* The safety population included all the patients who had received at least one dose of a trial treatment. In either trial group, the most common adverse events of any grade occurred in at least 30% of the patients, and the most common grade 3 or 4 adverse events occurred in at least 10% of the patients. Covid-19 denotes coronavirus disease 2019.

nia caused by Covid-19 (any grade, 12.0% vs. 4.1%; grade 3 or 4, 11.3% vs. 2.4%; and serious infection, 11.3% vs. 2.8%).

Fatal infections occurred in 13 patients (4.6%) in the teclistamab–daratumumab group (3 from Covid-19) and in 4 patients (1.4%) in the DPd or DVd group. In the teclistamab–daratumumab group, 12 of 13 infection-related deaths occurred within 6 months after the initiation of treatment before the implementation of reinforced protocol-specified immune globulin treatment (Fig. S4); thus, 9 of the 12 patients did not receive this treatment. Hypogammaglobulinemia occurred in 239 patients (84.5%) in the teclistamab–daratumumab group and in 175 (60.3%) in the DPd or DVd group. At least one dose of immune globulin was administered to 247 patients (87.3%) in the teclistamab–daratumumab group and to 130 patients (44.8%) in the DPd or DVd group.

Second primary cancer was observed in 35 patients (12.4%) in the teclistamab–daratumumab group and in 25 patients (8.6%) in the DPd or DVd group; most of these cases were cutaneous or noninvasive (8.1% and 4.5%, respectively) (Table S20). After the exclusion of cutaneous or noninvasive cases, the incidence of second cancers was well balanced between the two groups.

PHARMACOKINETICS AND IMMUNOGENICITY

The trough serum concentration of teclistamab increased with the weekly dose of 1.5 mg per kilogram, remained steady with the dose of 3 mg per kilogram every 2 weeks, and then declined with the monthly dose of 3 mg per kilogram, findings that were consistent with the predicted pharmacokinetics profile for the administered dosing regimen (Fig. S5). The trough serum concentration of daratumumab in the teclistamab–daratumumab group was similar to the levels observed in the DPd or DVd group (Fig. S6). An-

tibodies against teclistamab or daratumumab developed in less than 1% of the patients.

DISCUSSION

After a median follow-up of almost 3 years, patients with relapsed or refractory multiple myeloma who received teclistamab–daratumumab had significantly longer progression-free survival than those who received DPd or DVd, with an 83% reduction in the risk of disease progression or death. Progression-free survival benefits favored teclistamab–daratumumab across all prespecified subgroups. Furthermore, the patients who received teclistamab–daratumumab had significantly better results for a complete response or better and an overall response (including response durability), minimal residual disease negativity (10^{-5}), overall survival, and time until the worsening of symptoms than those who received DPd or DVd.

The treatment of relapsed or refractory multiple myeloma is increasingly challenging, with progressive immune dysfunction, multiple relapses, and often poor survival outcomes.[24] Emerging treatment options include novel BCMA-targeting therapies, which have reshaped the therapeutic landscape. Ciltacabtagene autoleucel, a BCMA autologous CAR-T therapy, has significantly improved progression-free and overall survival as compared with DPd or PVd, with an improving adverse event profile from late to earlier lines of treatment.[5,25] Belantamab mafodotin, a BCMA-directed antibody-drug conjugate, has also shown improved progression-free and overall survival in patients with early-line relapsed or refractory multiple myeloma.[26,27] Although infections of grade 3 or higher have been reported in up to half the patients receiving belantamab mafodotin, along with high incidences of ocular toxicity, management decisions in such cases can be informed by regular ophthalmic monitoring, dose modifications, and supportive care.[26,28] Investigators are evaluating other bispecific antibodies with activity in advanced myeloma and targeting BCMA — including elranatamab[29] and linvoseltamab,[30] as well as talquetamab targeting GPRC5D-expressing myeloma cells[31] — in patients with earlier-line relapsed or refractory multiple myeloma.

Teclistamab–daratumumab is a synergistic immunotherapy combination that is administered subcutaneously in step-up dosing, along with the well-established daratumumab dosing schedule. With the significant progression-free and overall survival benefit, and a low incidence of grade 2 cytokine release syndrome, teclistamab–daratumumab may address the need for a highly effective regimen with community accessibility. Guidelines on the use of prophylactic tocilizumab and well-established infection protocols will further inform community adoption; however, treatment choice will be guided by individual risk–benefit considerations, access, and patient choice. With the advent of ciltacabtagene autoleucel and teclistamab–daratumumab offering immunotherapy-based options with plateauing survival curves, we may be entering a new era of resetting survival expectations in a cancer that has been historically described as incurable.

As shown, teclistamab–daratumumab conferred a significant progression-free survival benefit as compared with DPd or DVd.[5,13,26,28,32] In our trial, the progression-free survival benefit with teclistamab–daratumumab was observed even though DPd or DVd outperformed expectation (median progression-free survival, 18.1 months), as compared with the results of the APOLLO trial (DPd, 12.4 months), the CASTOR trial (DVd, 16.7 months), and the CARTITUDE-4 trial (DPd–PVd, 11.8 months).[5,12,33] Although only a few patients in our trial had received previous anti-CD38 therapy, a progression-free survival benefit was reported with teclistamab–daratumumab in this subgroup. The percentages of patients who were older than 75 years of age or had an Eastern Cooperative Oncology Group performance-status score of 2 were small but consistent with results reported in studies involving similar populations[5,26,28,33]; a progression-free survival benefit was still observed with teclistamab–daratumumab in these subgroups. Ongoing studies and real-world evidence will build on the body of evidence in these groups. Finally, in the teclistamab–daratumumab group, more than 90% of the patients who were alive at 6 months remained alive at 30 months, which suggests a plateau in the survival curve.

The safety profile of teclistamab–daratumumab therapy was well characterized. No new adverse events were noted as compared with the safety profile of each individual agent. The incidence of cytokine release syndrome with teclistamab–daratumumab in our trial was lower than that observed with teclistamab monotherapy in the MajesTEC-1 trial (60.1% and 72.1%, respectively),[8]

with most events being grade 1 and occurring during the step-up dosing schedule. Of note, prophylactic tocilizumab, which was not permitted in our trial, is now recommended in guidelines and reduces the incidence and severity of cytokine release syndrome.[34,35] Nearly all the patients in the teclistamab–daratumumab group had a grade 3 or higher adverse event, with 7.1% dying from adverse events during treatment, most of which were cytopenias and infections. These events can be controlled with established immune globulin therapy and infection prevention and treatment protocols. The trial enrollment began during the Covid-19 pandemic, before the adoption of guidelines regarding infection-prevention strategies for patients receiving BCMA-directed therapy. After reinforced recommendations for immune globulin treatment and adherence to infection management, one fatal infection was noted with teclistamab–daratumumab and new-onset grade 3 or higher infections decreased after 6 months, which coincided with a monthly dosing schedule. Results further emphasize the importance of early infection prevention in patients receiving bispecific antibodies, including the use of immune globulin treatment according to International Myeloma Working Group guidelines to reduce high-grade infections.[36-40] Teclistamab–daratumumab was administered according to the approved schedule for the administration of daratumumab, with monthly administration of teclistamab starting with cycle 7, which could potentially ease treatment burden and provide a regimen that is familiar to health care providers. Results support the potential administration of this off-the-shelf combination in a community-based setting, as shown in the real world with teclistamab monotherapy.[41]

In the MajesTEC-3 trial, we found a significant benefit with teclistamab–daratumumab regarding progression-free and overall survival. The use of this combination was associated with a risk of adverse events that can be ameliorated with the use of established protocols.

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