

Teclistamab versus lenalidomide-dexamethasone in high-risk smoldering multiple myeloma: a randomized phase 2 trial

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Teclistamab, a B cell maturation antigen-targeting bispecific antibody, has demonstrated substantial activity in relapsed multiple myeloma (MM), particularly in earlier lines of therapy, and may have higher efficacy in high-risk smoldering MM (HR-SMM) with a more functional immune system. In the randomized phase 2 ImmunoPRISM trial, we compared fixed-duration teclistamab with lenalidomide–dexamethasone (Rd) in HR-SMM. After a six-patient safety run-in, patients were randomized 2:1 to teclistamab or Rd. The primary endpoint was complete response (CR) rate. As of 26 May 2026, 59 patients were treated—45 received teclistamab and 14 received Rd. Teclistamab treatment induced a CR in 77.8% patients versus 0% with Rd, and minimal residual disease negativity at 10^{-5} in 82.2% patients. At a median follow-up of 24.5 months, 2-year progression-free survival was 92% with teclistamab versus 49% with Rd. Overall, response rates, duration of response and time to progression (TTP) were significantly improved in teclistamab compared to Rd. Toxicities in the teclistamab arm included grades 1–2 cytokine release syndrome, no neurotoxicity and no increase in grade 3 infections compared to Rd (20% versus 21%). No deaths occurred in either arm. Teclistamab represents a highly active immune-interception strategy for HR-SMM. ClinicalTrials.gov registration: [NCT05469893](https://clinicaltrials.gov/ct2/show/study/NCT05469893).

Teclistamab is an anti-B cell maturation antigen (BCMA) bispecific T-cell engager that is approved for the treatment of patients with relapsed or refractory multiple myeloma (RRMM). In heavily pre-treated patients, single-agent teclistamab has demonstrated clinically meaningful activity, although the durability of disease control remains limited in this advanced-disease setting^{1–4}. In MajesTEC-1, median progression-free survival (PFS) was 11.8 months, a complete response (CR) or better was achieved in 39.4% patients and minimal residual disease (MRD) negativity was observed in 26.7% patients. More recently, teclistamab was approved in combination with daratumumab in RRMM patients after one to three prior lines of therapy, demonstrating higher MRD-negativity rates and improved PFS of 83% at 3 years compared with standard therapies⁵. Single-agent teclistamab also has recently demonstrated substantial improvement in outcomes

compared to conventional regimens in RRMM after one to three prior lines of therapy, further supporting higher efficacy of earlier use of bispecific antibodies⁶.

High-risk smoldering multiple myeloma (HR-SMM) is an asymptomatic plasma-cell neoplasm that shares recurrent genomic features with multiple myeloma (MM)^{7–9} and carries a high-risk of progression to overt MM based on established clinical and genomic criteria^{10–15}. Compared with advanced myeloma, SMM is generally characterized by lower tumor burden, less complex genomic architecture and relatively intact immune function^{7,16–19}. Historically, patients were placed on observation with treatment only initiated at the time of symptomatic disease progression. Daratumumab was the first agent approved for the treatment of patients with HR-SMM in 2025 based on positive results from the AQUILA trial compared to active monitoring²⁰. Previous

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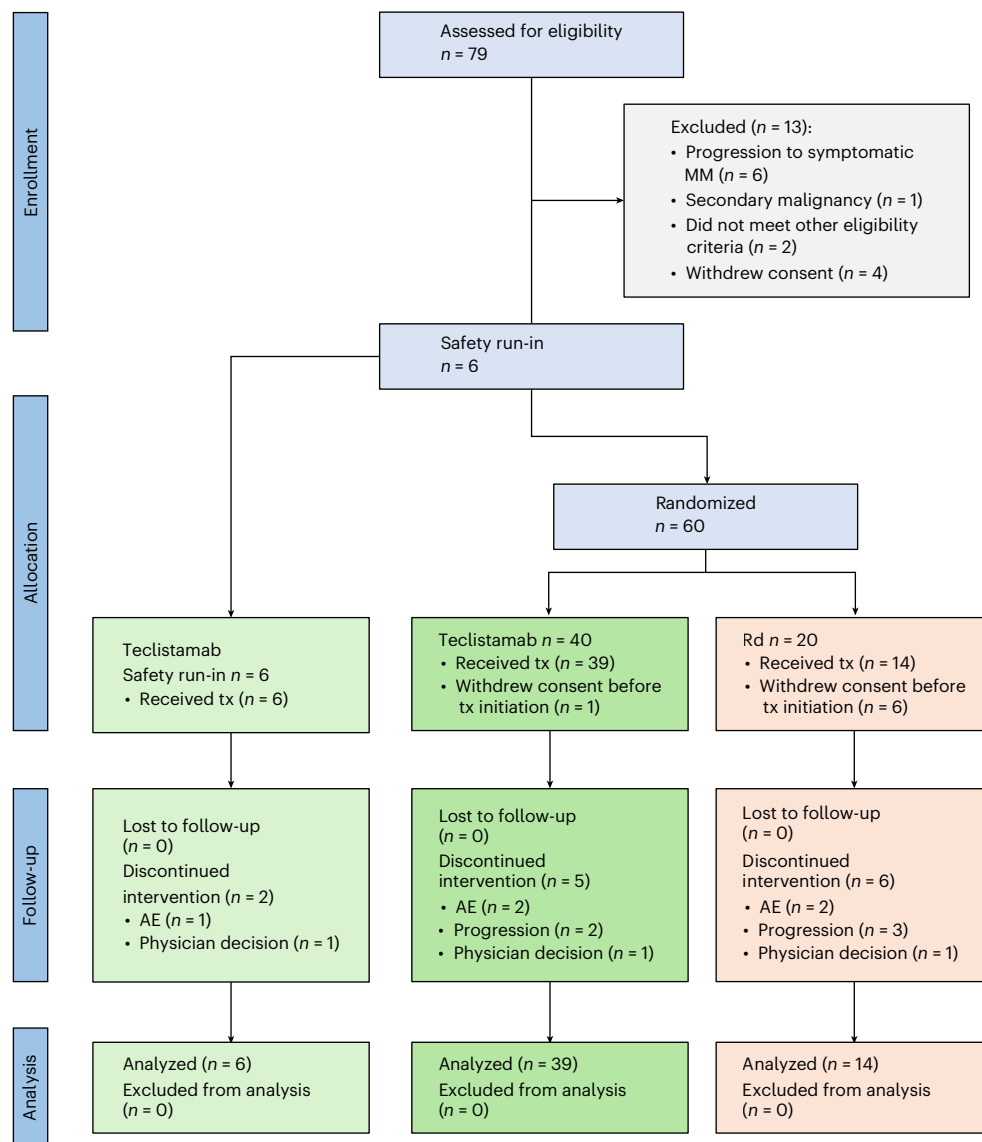


Fig. 1 | CONSORT diagram for the ImmunoPRISM study. CONSORT flow diagram. Numbers of participants screened, enrolled, treated and included in analyses are shown, with reasons for exclusion and allocation to each protocol phase. CONSORT, Consolidated Standards of Reporting Trials. tx, treatment.

phase 3 studies of lenalidomide with or without dexamethasone have also shown benefit in this population compared to observation^{21,22}. However, despite this observed benefit, patients still develop disease progression, likely due to a lack of deep responses seen with these less intensive therapies. While additional studies using more potent combination regimens have improved depth of response in HR-SMM, these therapies have also not yielded curative potential^{23,24}. We hypothesized that the use of immunotherapy with teclistamab would lead to deep remissions in HR-SMM by leveraging the lower tumor burden and more immunocompetent host in these patients as compared to later lines of therapy. Hence, we conducted a phase 2 trial of teclistamab and compared it to the previous standard of care of lenalidomide–dexamethasone (Rd) in HR-SMM.

Results

Patient disposition and baseline demographics

Between 15 April 2023 and 3 July 2025, 64 patients with HR-SMM were enrolled in this randomized phase 2 trial of teclistamab versus Rd. The initial teclistamab dosing schema included a safety run-in of six patients, in which patients received a lower cycle 1 dose of 720 $\mu\text{g kg}^{-1}$ weekly, followed by 1.5 mg kg^{-1} weekly for 2 cycles, 3 mg kg^{-1} every 2

weeks for 4 cycles and then 3 mg kg^{-1} monthly to complete 24 cycles (Extended Data Fig. 1). After an observed efficacy signal and to reduce cumulative treatment exposure in this precursor-disease population, the protocol was amended to limit teclistamab therapy to a maximum of 12 cycles or a total of 15 months of treatment. Patients assigned to Rd received lenalidomide 25 mg orally on days 1–21 of each 28-day cycle for cycles 1–12, together with dexamethasone 40 mg orally on days 1, 8 and 15. For cycles 13–24, patients continued lenalidomide alone at 15 mg orally on days 1–21 of each 28-day cycle. Dexamethasone dose modification or discontinuation was allowed for intolerance, with continuation of lenalidomide monotherapy allowed per protocol.

At the data cutoff for this analysis, on 26 May 2026, 59 patients had completed at least one cycle of assigned treatment and were included in the primary analysis population (Fig. 1). Of these, 45 patients received teclistamab, including those treated during the safety run-in, and 14 received Rd. In the teclistamab group, 20 patients were treated before and 25 after the protocol amendment limiting treatment duration. At data cutoff, 8 teclistamab-treated patients remained on treatment, 30 had completed the planned number of cycles according to their assigned protocol version and 7 had discontinued teclistamab early because of progressive disease ($n = 2$), adverse events (AEs; $n = 3$)

Table 1 | Patient demographics based on the treatment group

Characteristics	All, n=59	Teclistamab SRI, n=6	Teclistamab, n=39	Rd, n=14
Demographic features				
Age—years (range)	65 (34–79)	59 (34–71)	65 (48–79)	69 (45–75)
Sex, female—n (%)	23 (39)	2 (33)	13 (33)	8 (57)
Site				
DFCI	46 (78)	6 (100)	29 (74)	11 (79)
CBCI	8 (14)	0 (0)	6 (15)	2 (14)
OHSU	5 (8)	0 (0)	4 (10)	1 (7)
Ethnicity—n (%)				
White, non-Hispanic	51 (86)	6 (100)	33 (85)	12 (86)
Hispanic or Latino	2 (3)	0 (0)	1 (3)	1 (7)
Other or not known	6 (10)	0 (0)	5 (13)	1 (7)
ECOG PS—n (%)				
0	54 (92)	6 (100)	35 (90)	13 (93)
1	3 (5)	0 (0)	2 (5)	1 (7)
Disease features				
Myeloma type—n (%)				
IgG (κ/λ)	40 (68)	4 (67)	26 (67)	10 (72)
IgA (κ/λ)	11 (19)	2 (33)	6 (15)	3 (21)
Kappa FLC	7 (12)	0 (0)	7 (18)	0 (0)
IgM λ	1 (2)	0 (0)	0 (0)	1 (7)
Laboratory values—median (IQR)				
M-spike at screening (g dl ⁻¹)	2.2 (1.5–2.6)	1.2 (0.8–1.9)	2.3 (1.6–2.6)	2.16 (1.7–2.6)
Involved/uninvolved LC ratio	24.3 (11.1–50.8)	11.1 (9.5–65.1)	24.3 (13.4–43.6)	32.38 (8.5–59.0)
BMPC infiltration	25 (20–40)	35 (25–40)	25 (20–40)	30 (20–30)
LDH at screening (U l ⁻¹)	181 (148–198)	193 (165–200)	186 (154–200)	170 (138–185)
Cytogenetics ^a —n (%)				
High-risk cytogenetics	26/59 (44)	3/6 (50)	16/39 (41)	7/14 (50)
del17p	5/51 (10)	0/5 (0)	3/33 (9)	2/13 (15)
del13q	0/49 (0)	0/5 (0)	0/31 (0)	0/13 (0)
t(4;14)	6/49 (12)	1/5 (20)	3/31 (10)	2/13 (15)
t(14;16)	3/49 (6)	1/5 (20)	1/31 (3)	1/13 (8)
t(14;20)	1/49 (2)	0/5 (0)	1/31 (3)	0/13 (0)
gain1q/amp1q	18/52 (35)	3/5 (60)	11/34 (32)	4/13 (31)
t(11;14)	13/53 (25)	2/5 (40)	7/34 (21)	4/14 (29)
Treatment-related features—n (%)				
Prior SMM treatment ^b	11 (19)	2 (33)	6 (15)	3 (21)
Risk stratification—n (%)				
IMWG 20-2-20				
Low risk ^c	4 (7)	1 (17)	2 (5)	1 (7)
Intermediate risk ^c	17 (29)	1 (17)	12 (31)	4 (29)
High risk	38 (64)	4 (67)	25 (64)	9 (64)
PANGEA-SMM				
Low risk	15 (25)	1 (17)	10 (26)	4 (29)
Intermediate risk	27 (46)	5 (83)	16 (41)	6 (43)
High risk	17 (29)	0 (0)	13 (33)	4 (29)

^aBM samples obtained before screening were included. Percentages were calculated using evaluable results for each marker; denominators vary due to unavailable BM samples or probes not tested. ^bAmong the 11 patients with prior SMM-directed therapy, prior regimens included ixazomib/lenalidomide/dexamethasone, n=6; nivolumab/lenalidomide/dexamethasone, n=2; elotuzumab/lenalidomide/dexamethasone, n=1; isatuximab/lenalidomide/dexamethasone, n=1; and lenalidomide monotherapy, n=1. No patient had progressed on prior lenalidomide-containing therapy. In the Rd arm, two patients previously treated with ixazomib/lenalidomide/dexamethasone had achieved partial responses and completed protocol-defined therapy; one patient had received daratumumab monotherapy in a clinical trial, followed by lenalidomide. The median time to next therapy among previously treated patients in the teclistamab arm was 40 months (range=13–72) and in the Rd arm was 34 months (range=6–34). ^cAll 20-2-20 low-risk patients had high-risk cytogenetics; three also had immunoparesis and one met evolving criteria. All intermediate-risk patients had ≥1 additional high-risk feature—high-risk cytogenetics, n=7; evolving criteria, n=6; and immunoparesis, n=8. ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LDH, lactate dehydrogenase; M-spike, monoclonal protein ('M-protein') spike; FLC, free light chain; del, deletion.

or physician or patient decision ($n = 2$). Both patients who discontinued for physician or patient decision had achieved MRD-negative CRs; one discontinued because of an unrelated medical condition requiring prioritized management, and one elected to stop after 9 cycles before the planned 12 cycles. In the Rd group, four patients remained on treatment, four had completed protocol-defined treatment and six had discontinued treatment because of CRAB progression ($n = 3$), AEs ($n = 2$) and one following a joint patient-physician decision to stop therapy after 21 cycles while in adequate response. Moreover, in the Rd arm, four patients required lenalidomide dose reductions beyond the planned protocol-specified reduction from 25 mg to 15 mg beginning at cycle 13, with documented reasons including fatigue/brain fog, gastrointestinal symptoms, rash and recurrent neutropenia.

The median age of treated patients was 65 years (range = 34–79), and 23 patients (39%) were female (Table 1). Median bone marrow plasma-cell (BMPC) involvement was 25% (interquartile range = 20–40). Cytogenetic data were available for 55 patients, of whom 26 (44.1%) had high-risk abnormalities, including del(17p), $t(4;14)$, $t(14;16)$, $t(14;20)$ or gain or amplification of chromosome 1q. According to the 20-2-20 risk model, 38 patients (64%) were classified as high risk (Supplementary Table 1). Baseline imaging to exclude myeloma-defining bone disease, using PET/CT or whole-body magnetic resonance imaging (MRI) in accordance with International Myeloma Working Group (IMWG) guidelines, was performed in all patients according to the protocol criteria, with PET/CT performed in 53 patients and MRI performed as the primary or additional imaging modality in 6 patients. The baseline characteristics were balanced in both treatment arms.

Primary outcome: CR rate

The primary endpoint of this study was CR rate in the randomized population, defined as the proportion of patients achieving CR or better. At a median follow-up of 24.5 months, 29 of 39 patients (74%) randomized to receive teclistamab achieved CR or better compared with none among patients treated with Rd (Fig. 2a,b).

Because the safety run-in cohort had comparable baseline characteristics and outcomes to the randomized teclistamab cohort, we also performed additional analysis including all teclistamab-treated patients. In this expanded teclistamab-treated population, 35 of 45 patients achieved a CR or better, corresponding to a CR rate of 77.8%.

Secondary efficacy outcomes

Secondary efficacy endpoints included overall response rate, MRD negativity, PFS, duration of response, TTP and overall survival. Additional planned secondary endpoints not reported in this manuscript are PFS after initiation of active myeloma therapy (PFS2), measures of teclistamab pharmacokinetics and immunogenicity. Secondary efficacy outcomes are reported descriptively for all teclistamab-treated patients, including those treated in the safety run-in, and compared with the Rd control arm, unless otherwise indicated.

The distribution of best overall responses differed between treatment groups (Fig. 2b). In the teclistamab group, 39 patients (86.7%) achieved a very good partial response (VGPR) or better, while 3 patients with a partial response (PR) remained on treatment and had nine cycles

or less, and 3 patients were nonresponders, achieving best response of stable disease. Among Rd-treated patients, 2 patients achieved a VGPR (14.3%) and 12 patients (85.7%) achieved a PR. In prespecified subgroup analyses, best response did not differ by age group or cytogenetic risk status (Extended Data Fig. 2).

MRD negativity at a sensitivity threshold of 10^{-5} by next-generation sequencing (NGS) differed among treatment groups—37 of 45 (82.2%) teclistamab-treated patients and none of the Rd-treated patients achieved MRD negativity during treatment (Fig. 2c). The MRD-negativity rate at a sensitivity threshold of 10^{-6} in the teclistamab arm was 77.8% (35/45). Overall, 33 of 45 patients achieved both a CR or stringent CR (sCR) and MRD negativity, corresponding to a combined sCR/CR with MRD-negative rate of 73.3%. Among the 35 patients who achieved sCR/CR, 33 (94.3%) were MRD-negative. The median time to MRD negativity was 6.2 months. Among 28 patients with serial MRD assessments who were MRD-negative at the first assessment, MRD negativity was sustained in 100% patients through the latest available assessment.

At the time of data cutoff, nine patients had progressed by either SLiM-CRAB and/or biochemical progression, including three teclistamab-treated and six Rd-treated patients. Five patients developed a myeloma-defining event, two in the teclistamab arm and three in the Rd arm. All progressions involved myeloma-related bone disease measured by MRI ($n = 2$) or PET-CT ($n = 3$); two patients also had an involved/uninvolved free light-chain (LC) ratio of >100 .

Median PFS was not reached in the teclistamab arm compared with 20.3 months in the Rd arm, with significantly improved PFS observed for teclistamab versus Rd (log-rank $P = 0.002$; Fig. 2d). In a Cox proportional hazards model, treatment with teclistamab was associated with a lower risk of progression or death compared with Rd (hazard ratio = 0.15; 95% confidence interval (CI) = 0.04–0.59; $P = 0.007$). The Kaplan–Meier-estimated 2-year PFS rate was 92% (95% CI = 84–100) with teclistamab and 49% (95% CI = 26–91) with Rd. There were no differences in PFS when stratified for age group or cytogenetic status (Extended Data Fig. 3). Duration of response was significantly improved in the teclistamab versus Rd arms; among responders, the estimated 24-month probability of maintaining response was 100% with teclistamab and 49% with Rd ($P < 0.001$; Extended Data Fig. 4). Results were consistent when analysis was restricted to the randomized population (Extended Data Fig. 5). No deaths occurred in either arm (Extended Data Fig. 6).

In post hoc exploratory subgroup analyses, response rates and PFS were consistent across clinically relevant subgroups, including prior therapy exposure, duration of therapy with teclistamab preprotocol and postprotocol amendment, and baseline 20-2-20 risk category. No significant differences in response distribution or PFS were observed across these subgroups (Extended Data Figs. 7–9).

Secondary safety outcomes

AEs were reported in all treated patients (Table 2 and Supplementary Table 2). No patient in the safety run-in cohort met protocol-defined dose-limiting toxicity criteria.

Hematologic AEs were common and were primarily driven by neutropenia. Any-grade neutropenia occurred in 28 teclistamab-treated

Fig. 2 | Teclistamab induces deep remissions and prolongs PFS in HR-SMM.

a, Swimmer plots showing longitudinal IMWG response categories for each treated participant from treatment initiation to last follow-up, stratified by treatment arm. Bars indicate response category over time, and diamonds indicate MRD status at a sensitivity threshold of 10^{-5} . Black crosses indicate first documented progressive disease. Teclistamab-treated patients include participants treated in the safety run-in and randomized teclistamab cohorts; the control arm includes patients treated with Rd. **b**, Best overall response by treatment arm, shown as the proportion of patients achieving sCR/CR, VGPR, PR or stable disease (SD). The teclistamab group includes all treated patients,

including those enrolled in the safety run-in. **c**, MRD-negativity rates among MRD-evaluable teclistamab-treated patients over time at sensitivity thresholds of 10^{-5} and 10^{-6} . Bars show the proportion of evaluable patients who were MRD-negative or MRD-positive at each prespecified time point; fractions indicate the number of MRD-negative patients among evaluable patients. The median month of MRD assessment from randomization is shown below each time point. **d**, Kaplan–Meier estimates of PFS among all teclistamab-treated patients and patients treated with Rd. Tick marks indicate censored observations. The two-sided log-rank P value is shown. MR, minimal response; PD, progressive disease.

patients (62%) and 11 Rd-treated patients (79%). Grade 3 or 4 neutropenia occurred in 16 teclistamab-treated patients (35.6%, grade 3 = 8, grade 4 = 8), and in 4 Rd-treated patients (29%, all grade 3). Severe thrombocytopenia was uncommon, with grade 3 or 4 thrombocytopenia occurring in two patients in each arm (teclistamab 4%, Rd 14%). No grade 3 or 4 anemia was observed.

Most infections were grade 1 or 2 with any-grade infections in 54 of 59 patients (91.5%) and similar frequencies across treatment arms. Grade 3 infections occurred in nine teclistamab-treated patients (20%) and three Rd-treated patients (21%). Among teclistamab-treated patients, grade 3 infections included respiratory infections, including COVID-19, influenza A, upper respiratory infections

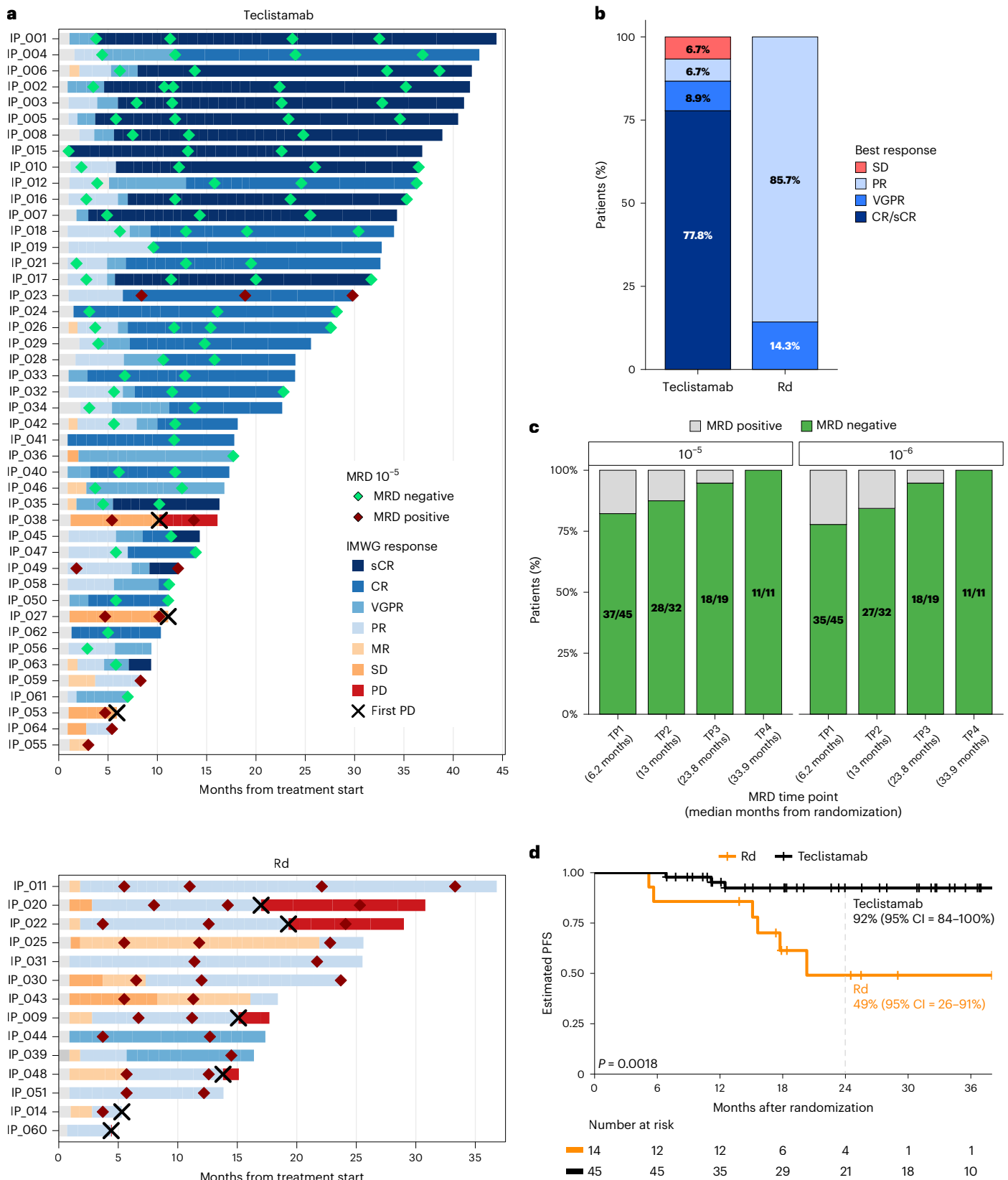


Table 2 | Adverse events based on treatment group

AE, n (%)	All, n=59		Teclistamab, n=45		Rd, n=14	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Hematologic events						
Neutrophil count decreased	39 (66.1)	20 (33.9)	28 (62.2)	16 (35.6)	11 (78.6)	4 (28.6)
White blood cell decreased	37 (62.7)	9 (15.3)	26 (57.8)	8 (17.8)	11 (78.6)	1 (7.1)
Platelet count decreased	26 (44.1)	4 (6.8)	21 (46.7)	2 (4.4)	5 (35.7)	2 (14.3)
Lymphocyte count decreased	6 (10.2)	4 (6.8)	5 (11.1)	4 (8.9)	1 (7.1)	0
Anemia	34 (57.6)	0	26 (57.8)	0	8 (57.1)	0
Infections						
Any infection	54 (91.5)	12 (20.3)	42 (93.3)	9 (20)	12 (85.7)	3 (21.4)
Lung infection	–	5 (8.5)	–	4 (6.7)	–	1 (7.1)
Upper respiratory infection	–	2 (3.4)	–	2 (4.4)	–	0
Sinusitis	–	1 (1.7)	–	1 (2.2)	–	0
Abdominal infection	–	4 (6.8)	–	2 (4.4)	–	2 (14.3)
Gastrointestinal disorders						
Diarrhea	29 (49.2)	1 (1.7)	19 (42.2)	1 (2.2)	10 (71.4)	0
Colitis	2 (3.4)	1 (1.7)	1 (2.2)	0	1 (7.1)	1 (7.1)
Nausea	10 (16.9)	0	5 (11.1)	0	5 (35.7)	0
Constipation	6 (10.2)	0	1 (2.2)	0	5 (35.7)	0
Vomiting	3 (5.1)	0	0	0	3 (21.4)	0
Immune-related AEs						
CRS	32 (54.2)	0	32 (71.1)	0	0	0
ICANS	0	0	0	0	0	0
Others						
Alanine aminotransferase increased	37 (62.7)	4 (6.8)	31 (68.9)	4 (8.9)	6 (42.9)	0
Aspartate aminotransferase increased	38 (64.4)	2 (3.4)	30 (66.7)	2 (4.4)	8 (57.1)	0
Maculopapular rash	19 (32.2)	1 (1.7)	14 (31.1)	1 (2.2)	5 (35.7)	0
Insomnia	8 (13.6)	1 (1.7)	0	0	8 (57.1)	1 (7.1)
Hypokalemia	5 (8.5)	1 (1.7)	1 (2.2)	0	4 (28.6)	1 (7.1)
Hypoxia	1 (1.7)	1 (1.7)	1 (2.2)	1 (2.2)	0	0
Alkaline phosphatase increased	22 (37.3)	0	18 (40.0)	0	4 (28.6)	0
Hypocalcemia	17 (28.8)	0	11 (24.4)	0	6 (42.9)	0
Hyperhidrosis	16 (27.1)	0	14 (31.1)	0	2 (14.3)	0
Headache	12 (20.3)	0	7 (15.6)	0	5 (35.7)	0
Nasal congestion	10 (16.9)	0	10 (22.2)	0	0	0
Hyperglycemia	8 (13.6)	0	3 (6.7)	0	5 (35.7)	0
Paresthesia	8 (13.6)	0	4 (8.9)	0	4 (28.6)	0
Hypophosphatemia	7 (11.9)	0	4 (8.9)	0	3 (21.4)	0
Flushing	4 (6.8)	0	0	0	4 (28.6)	0
Palpitations	3 (5.1)	0	0	0	3 (21.4)	0
Hypomagnesemia	3 (5.1)	0	0	0	3 (21.4)	0
Muscle cramp	3 (5.1)	0	0	0	3 (21.4)	0
Tremor	3 (5.1)	0	0	0	3 (21.4)	0

AEs that occurred in at least 20% patients in either arm or AEs of special interest are listed and were considered by the investigator to be related to the trial treatment or occurred after the initiation of treatment. Grade 3 infections are further categorized by infection type.

and pneumonia, as well as gastrointestinal infections, including *Salmonella*-associated and astrovirus-associated diarrhea. In the Rd arm, grade 3 infections included an acute infection of unknown origin, infectious enterocolitis and one febrile gastrointestinal infectious episode. All grade 3 infections resolved, and no grade 4

infections were observed. Per protocol, immunoglobulin replacement was recommended for hypogammaglobulinemia, generally defined as IgG <400–500 mg dl⁻¹, with initiation at the discretion of the treating physician. In the teclistamab arm, every patient received at least one dose of intravenous immunoglobulin. Grade 3 infections

Table 3 | Characteristics of teclistamab-treated, MRD-positive patients

Patient ID	Sex	Age at infusion	Previous anti-MM treatment	Cycles received	Doses omitted	BMPC at baseline	High-risk cytogenetic alterations FISH	High-risk cytogenetic alterations WGS	SNV WGS	Neg of detected NGS MRD clones	Flow cytometry detection of clones	sBCMA (pgml ⁻¹)
Primary resistant												
IP 027	Male	71	Anti-CD38/Len	11	0	50%	gain(1q)	gain(1q), del(13q), del(17p)	RB1 p.R556*	0/2	NA	128
IP 038	Female	49	tx naive	12	1	20%	–	del(13q)	TENT5C p.I155S	0/5	NA	71.9
IP 053	Male	69	tx naive	6	0	50%	–	None	TENT5C p.R174*, SP140 p.R673*	0/2	NA	194
Ongoing treatment												
IP 055	Male	63	Len	4, tx ongoing	0	40%	–	NA	NA	0/4	NA	133
IP 059	Male	74	tx naive	9, tx ongoing	0	50%	gain(1q)	NA	NA	4	NA	154
IP 064	Female	74	tx naive	6, tx ongoing	0	20%	–	NA	NA	2	NA	NA
Mixed clonal response												
IP 023	Male	76	PD-1/Len/Dex	7	2	25%	–	NA	NA	3/6	Negative	NA
IP 049	Male	56	tx naive	12	2	50%	t(4;14)	NA	NA	3/4	Negative	NA

Asterisks indicate nonsense mutations. Dex, dexamethasone; FISH, fluorescence in situ hybridization; Len, lenalidomide; NA, not available; Neg, negative; SNV, single-nucleotide variant; tx, treatment.

were not temporally associated with initiation of intravenous immunoglobulin replacement.

Teclistamab-associated immune effector cell-related toxicities were predominantly low grade. Cytokine release syndrome (CRS) occurred in 32 teclistamab-treated patients (71.1%), including 29 grade 1 events (64.4%) and 3 grade 2 events (6.7%); no grade 3 or higher CRS was observed. No patients received prophylactic tocilizumab. Tocilizumab was administered after CRS onset in five patients (11.1%), two of whom also received dexamethasone (4.4%). No immune effector cell-associated neurotoxicity syndrome or other treatment-emergent neurotoxicity was reported.

In the teclistamab arm, nonhematologic laboratory abnormalities included grade 3 alanine or aspartate aminotransferase elevations in five patients in the context of CRS. One patient developed grade 3 pancreatitis with concurrent lipase elevation that was attributed to trimethoprim–sulfamethoxazole. One patient had a grade 3 maculopapular rash that was deemed unrelated to teclistamab. All of these toxicities were completely resolved.

Serious AEs considered unrelated to study treatment in the teclistamab arm included three skin-localized malignancies, comprising two basal cell carcinomas and one squamous cell carcinoma, as well as one umbilical hernia and one episode of atrial flutter with rapid ventricular response. Separately, in the Rd arm, one patient developed a transient ischemic attack despite thromboprophylaxis.

Stem-cell mobilization and collection were allowed while patients remained on study and could be performed after four cycles, at best response, or at the investigator's discretion as part of standard-of-care planning. Among treated patients, 24 underwent stem-cell mobilization and all successfully completed collection, with a median collected CD34-positive cell yield of $8.8 \times 10^6 \text{ kg}^{-1}$ (interquartile range = 6.2–10.9). Mobilization was performed with filgrastim alone, filgrastim plus plerixafor or plerixafor alone in 6, 4 and 13 patients, respectively. Treatment was resumed after collection and recovery according to protocol-defined timelines.

Step-up dosing was initially conducted in the inpatient setting and later transitioned to outpatient administration for eligible patients. All six patients in the safety run-in and 21 randomized patients in teclistamab arm completed step-up dosing inpatient. Among randomized teclistamab patients treated at the DFCl, ten initiated step-up dosing outpatient and six completed step-up dosing outpatient without CRS-related hospitalization, whereas four required subsequent admission for CRS.

Correlative analyses of residual disease and teclistamab resistance

We first examined the subset of patients who remained MRD-positive after teclistamab (Table 3). These patients comprised biologically and clinically distinct groups. Three patients were primary nonresponders, refractory to treatment initiation, and not achieving an objective response. An additional three patients had received fewer than nine cycles of teclistamab at the time of analysis and remained on active treatment, leaving open the possibility of further response deepening with continued therapy. The remaining two patients achieved CR but had persistent molecular disease by NGS. In one patient, three of six baseline B cell receptor clonotypes became undetectable, whereas the remaining three decreased but remained measurable (Fig. 3a). In the second patient, three of four baseline clonotypes became undetectable, whereas the remaining clonotype decreased but remained measurable (Fig. 3b). To determine whether persistent molecular MRD was accompanied by a detectable residual plasma-cell population, we performed exploratory multiparameter flow cytometry on CD138-enriched, cryopreserved BM samples. No residual viable phenotypically identifiable plasma-cell population was detected in either patient at the corresponding MRD-assessment time point (Supplementary Fig. 1), indicating that these cells may not represent residual malignant plasma cells. In summary, persistent MRD positivity reflected heterogeneous clinical states, including primary refractoriness, ongoing response maturation and residual subclones by NGS.

To explore potential determinants of primary nonresponse and persistent MRD positivity, we performed correlative analyses of baseline tumor burden, genomic features, soluble BCMA (sBCMA) concentrations and circulating tumor cells (CTCs). The three teclistamab-treated primary nonresponders did not differ from the remainder of the teclistamab cohort in conventional disease-burden markers, including M-protein concentration and involved/uninvolved free LC ratio. Baseline whole-genome sequencing (WGS) did not identify BCMA mutations, structural alterations or BCMA loss in any of the three nonresponders, excluding an obvious tumor-intrinsic mechanism of antigen escape as a mediator of primary resistance (Table 3). Of note, one nonresponder had received prior therapy for SMM and harbored high-risk genomic alterations, including gain (1q) and deletion (17p). Other recurrent genomic alterations in this patient and the remaining nonresponders were consistent with known driver lesions and did not reveal a shared resistance-associated genomic pattern⁷⁹. As part of postprotocol treatment, two primary nonresponders achieved deep responses to conventional myeloma induction regimens, including daratumumab, lenalidomide, bortezomib and dexamethasone and autologous stem-cell transplantation. These postprotocol outcomes suggest that primary nonresponse to teclistamab did not preclude subsequent disease control with alternative antimyeloma strategies.

Given prior evidence that elevated sBCMA may attenuate the activity of BCMA-directed antibodies, we then assessed baseline and longitudinal sBCMA concentrations^{25,26}. Baseline sBCMA was available for 25 patients. Patients who achieved sCR/CR had lower baseline sBCMA levels than those with a best response of VGPR or less ($P < 0.001$; Fig. 3c). Similarly, patients who achieved MRD negativity had lower baseline sBCMA concentrations than those who remained MRD-positive ($P = 0.012$; Fig. 3d). Longitudinal profiling showed that sBCMA levels generally remained stable or increased during teclistamab treatment in nonresponders (Fig. 3e–g). In patient 38, sBCMA levels initially increased, followed by a decline between cycles 4 and 7. At cycle 11, plasmapheresis was additionally performed as a rescue strategy to reduce circulating sBCMA and potentially mitigate soluble antigen-mediated neutralization of teclistamab activity²⁷. However, sBCMA levels increased again after cycle 12, without evidence of clinical benefit from the intervention.

We also evaluated CTCs as a complementary marker of disseminated disease and a proliferative tumor biology²⁸. Baseline CTC burden did not differ significantly between teclistamab responders and nonresponders (Supplementary Fig. 2a). However, during treatment, CTC burden declined more substantially with teclistamab than with Rd (Fig. 3h), consistent with systemic tumor clearance. Among teclistamab-treated patients, lower on-treatment CTC levels were observed in patients achieving CR or better compared with those with PR or less (Fig. 3i). In contrast, longitudinal CTC trajectories did not clearly distinguish patients who achieved MRD negativity from those who remained MRD-positive (Supplementary Fig. 2b).

Discussion

In this phase 2 trial in HR-SMM, teclistamab was superior to Rd, with higher rates of CR, MRD negativity and PFS. The safety profile of teclistamab was as expected, with no new safety signals and no high-grade

CRS events. Patients experienced lower rates of high-grade infections than RRMM patients, and, notably, there was no difference in the incidence of grade 3 infections between teclistamab and Rd. The responses are durable, and patients who achieved MRD negativity have sustained it at the time of the data cutoff with a median follow-up of 24.5 months.

These data compare favorably to previous studies in HR-SMM. In our study, the overall response rate was 93.3%, with 77.8% teclistamab-treated patients achieving CR or better and 82.2% patients achieving MRD negativity. Triplet and quadruplet regimens in HR-SMM have demonstrated lower rates of CR and MRD negativity compared with single-agent teclistamab in this study, further highlighting the benefit of early immune interception^{18,23,24,29}. In the GEM-CESAR trial of carfilzomib, lenalidomide and dexamethasone induction followed by autologous stem-cell transplantation in HR-SMM, the MRD-negativity rate was approximately 60%, but was sustained in only 31% at 4 years²⁴. Similarly, preliminary data from the quadruplet studies in HR-SMM demonstrate lower MRD-negativity rates of approximately 60% despite these combination regimens administered for up to 2 years^{30,31}. In the CAR-PRISM trial, ciltacabtagene autoleucel was administered to 20 patients with HR-SMM, all of whom demonstrated universal MRD negativity³². While the MRD-negativity rate with teclistamab appears lower in our study, the toxicity profile and management approach are vastly different, with no observed cases of neurological toxicities. The choice between CAR T-cell therapy and bispecific antibodies remains an area of ongoing investigation in MM, as these approaches differ substantially in their efficacy, toxicity profile and logistics of administration, leading to individualized decision-making.

Teclistamab also produced substantially deeper responses in this HR-SMM population than has been reported in later-line RRMM cohorts. In the MajesTEC-1 trial, 39.4% patients achieved CR or better with teclistamab monotherapy⁴. The difference was even more pronounced compared with real-world teclistamab cohorts CR/ $\geq$ CR rates of 20–29% have been reported, although these comparisons are limited by the more heavily pretreated and clinically heterogeneous nature of real-world RRMM populations and by incomplete marrow-based response confirmation in routine practice^{2–4}. In contrast, the response depth in our study was closer to that reported with earlier-line teclistamab-based therapies in MajesTEC-9 and MajesTEC-3 trials, where teclistamab alone or in combination with daratumumab achieved a CR-or-better rate of 65.9% and 81.8%, respectively^{5,6}. However, MajesTEC-3 evaluated a two-antibody combination, whereas our study used single-agent teclistamab in HR-SMM, highlighting the depth of response achieved with a lower treatment burden in a precursor-disease setting. MRD negativity at 10^{-5} was achieved in 82.2% teclistamab-treated patients in our study, exceeding the 26.7% rate reported in the overall MajesTEC-1 population and the 58.4% rate reported with teclistamab as well as daratumumab in MajesTEC-3. Thus, despite the higher CR-or-better rate reported with the combination regimen in MajesTEC-3, single-agent teclistamab in HR-SMM produced a high frequency of molecular disease clearance, supporting the concept that earlier intervention with T-cell-redirecting therapy may enable particularly deep responses before the emergence of advanced treatment resistance. It will be important to determine how these findings compare with ongoing studies evaluating teclistamab-based

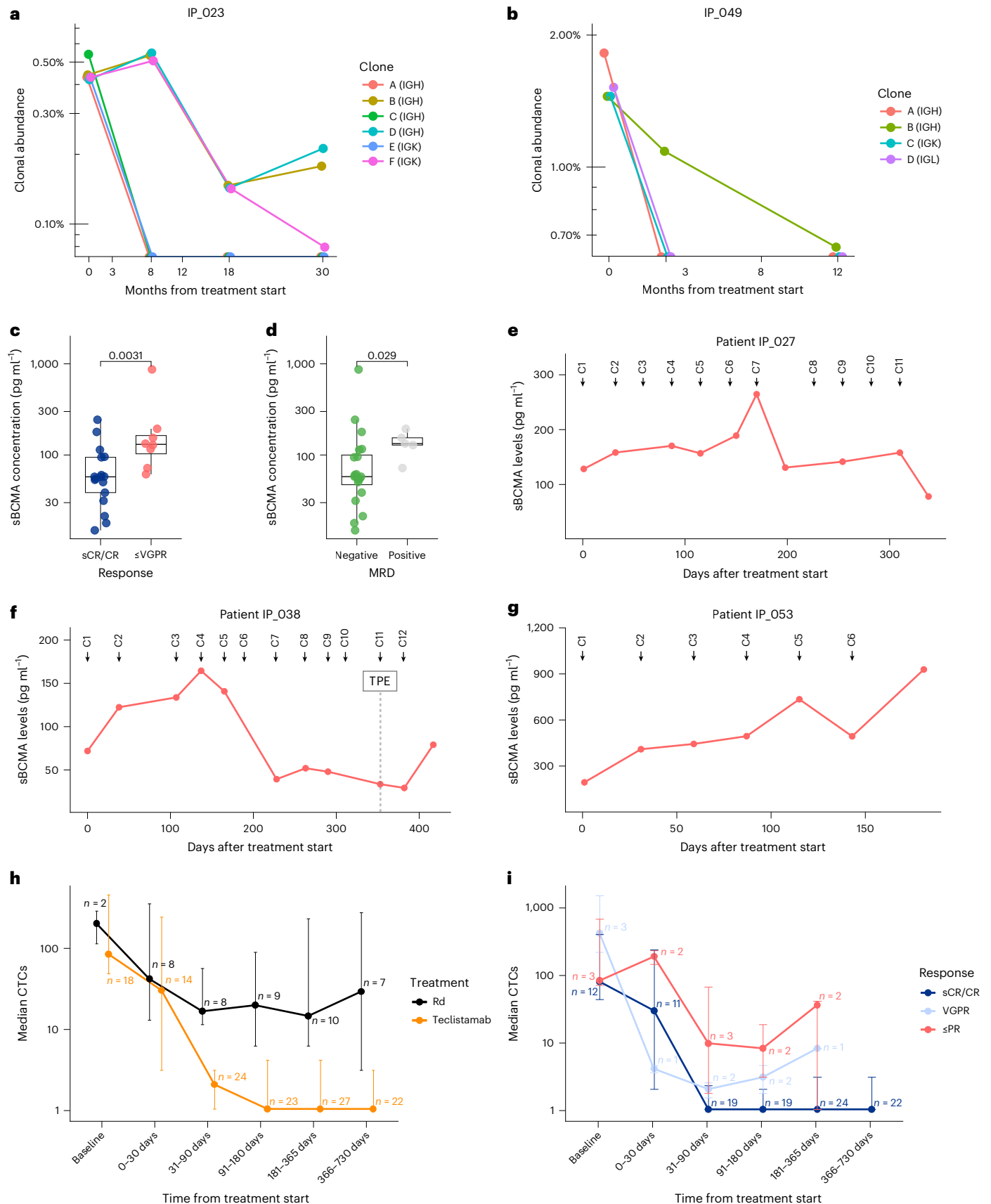
Fig. 3 | Biomarkers associated with response and resistance to teclistamab.

a,b, Longitudinal clonal abundance of baseline B-cell receptor clonotypes measured by NGS in the teclistamab-treated patients IP 023 (**a**) and IP 049 (**b**) with persistent MRD positivity and mixed clonal responses. Individual clonotypes are shown as separate lines and annotated by immunoglobulin locus. **c,d**, Baseline sBCMA concentrations according to depth of response. sBCMA concentrations are shown for patients achieving sCR/CR versus VGPR or less (**c**) and for patients achieving MRD negativity versus those remaining MRD-positive (**d**). Boxes indicate the median and IQR, whiskers indicate $1.5 \times$ IQR and points represent individual patients. P values were calculated using two-sided Wilcoxon

rank-sum tests. Baseline sBCMA was available for 25 patients. **e–g**, Longitudinal sBCMA concentrations in the three teclistamab-treated primary nonresponders IP 027 (**e**), IP 038 (**f**) and IP 053 (**g**). Treatment cycles are indicated by arrows above each plot. In patient IP 038 (**f**), the boxed annotation indicates the timing of TPE. **h,i**, Longitudinal CTC levels during treatment. Data are presented as median values, with error bars indicating the IQR (25th–75th percentiles), by treatment arm (**h**) and by best IMWG response category among teclistamab-treated patients, stratified as sCR/CR, VGPR or $\leq$ PR (**i**). Samples were grouped into the indicated treatment windows. Numbers adjacent to each time point indicate the number of patients included in the analysis. TPE, therapeutic plasma exchange.

combinations in SMM, as well as with frontline newly diagnosed multiple myeloma studies incorporating teclistamab into induction therapy^{33,34}, where deeper responses may be achieved at the cost of greater treatment intensity.

The occurrence of primary nonresponse in three patients with SMM was unexpected, as canonical mechanisms of resistance to BCMA-directed therapy in RRMM, including prior BCMA exposure, antigen loss or BCMA structural alteration, were absent in these patients^{35,36}.



Baseline WGS did not identify BCMA mutations or structural variants affecting the BCMA locus. Elevated sBCMA has been implicated as a potential mediator of resistance to BCMA-targeting T-cell engagers, possibly by acting as a soluble antigen sink^{1,25–27}; however, the sBCMA concentrations observed in our primary nonresponders were below previously proposed resistance-associated thresholds, and absolute values are difficult to compare across studies because of differences in assay platforms and units. Thus, although higher baseline sBCMA was associated with inferior response depth and persistent MRD positivity in our cohort, soluble antigen burden alone is unlikely to fully explain primary nonresponse. Prior SMM-directed therapy introduced some heterogeneity across arms, although sensitivity analyses did not suggest a meaningful effect on outcomes. Other tumor-extrinsic factors, including baseline T-cell fitness, effector-to-target ratio and immune microenvironmental suppression, may contribute but were not comprehensively assessed in the present analysis^{25,37}. These findings highlight the need for integrated biomarker studies in earlier disease settings to distinguish antigen-dependent resistance from immune-contexture-dependent failure of T-cell redirection.

Overall, single-agent teclistamab was associated with a manageable safety profile in this HR-SMM population. In later-line RRMM teclistamab monotherapy studies, grade ≥ 3 infections were reported in 41.6–44.8% patients in the primary MajesTEC-1 and MajesTEC-9 analyses and in approximately 22–26% patients in real-world cohorts, with infection-related mortality reported across several datasets^{1–4,6,38}. By contrast, grade 3 infections in our study were at the lower end of the RRMM range, and no fatal infections occurred. Notably, no ICANS was observed, compared with ICANS rates of 7.3–14% in real-world RRMM cohorts and 4.1% in MajesTEC-9, including occasional grade ≥ 3 events.

In this randomized phase 2 study, teclistamab produced frequent deep responses, including high rates of MRD negativity, in patients with HR-SMM. These results suggest that early BCMA-directed T-cell redirection can achieve substantial molecular disease clearance in a precursor-disease state, with a manageable safety profile and without the added treatment burden of combination therapy. Longer follow-up will be required to determine whether these deep responses and the observed improvement in PFS translate into durable prevention of progression to symptomatic myeloma, and no conclusions regarding overall survival benefit or disease eradication can be drawn from the current follow-up period. Additional studies will also be needed to define how bispecific antibody therapy should be integrated into risk-adapted treatment strategies for HR-SMM.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04642-w>.

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Methods

Trial design and patient selection

ImmunoPRISM is a multicenter phase 2 study evaluating the efficacy and safety of teclistamab versus Rd in patients with HR-SMM (see Supplementary Information—ImmunoPRISM Study Protocol). Planned dosing included an initial safety run-in (six patients) to evaluate a lower dose of teclistamab ($720 \mu\text{g kg}^{-1}$) in cycle 1 (Fig. 1). Due to the emerging efficacy data and the goal to limit long-term toxicities, the protocol was amended and patients received teclistamab for a maximum of 12 cycles (15 months) instead of 24 cycles as originally planned. Rd was administered for 2 years. Patients were recruited at the Dana–Farber Cancer Institute, the Oregon Blood Cancer Institute and the Knight Cancer Institute.

Eligible participants were adults with HR-SMM defined according to established clinical risk models, including the 20-2-20 criteria or an equivalent validated scoring system, and could also be established in patients with at least 10% BMPCs as well as additional high-risk features such as evolving disease, adverse plasma-cell immunophenotype with immunoparesis, high-risk cytogenetic abnormalities ($t(4;14)$, $t(14;16)$, $t(14;20)$, $\text{del}(17p)$, TP53 mutation, 1q21 gain or $\text{del}(13q)$) or marked urinary LC excretion^{10,11}. Patients were required to have no evidence of symptomatic MM or myeloma-defining events, an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate hematologic, hepatic and renal function, and to provide written informed consent. Participants of reproductive potential were required to have a negative pregnancy test and use effective contraception. Participants also had to be willing to comply with protocol-specific monitoring requirements.

Key exclusion criteria included prior SMM-directed therapy within 6 months, any history of symptomatic MM or prior therapy for active myeloma, prior anti-BCMA therapy, recent anticancer therapy or vaccination within protocol-defined washout periods, active central nervous system involvement, myelodysplastic syndrome, uncontrolled infection or other uncontrolled intercurrent illness, substantial cardiac disease, recent stroke or seizure, recent major surgery, pregnancy or breastfeeding, and serious medical, neurologic or psychiatric conditions that could interfere with study participation or safety. Patients with another active malignancy were excluded unless the malignancy was considered cured or at very low risk of recurrence. Active viral infection with human immunodeficiency virus, hepatitis B virus, hepatitis C virus or SARS-CoV-2 was generally exclusionary, although patients with controlled or resolved infection meeting protocol-specified virologic criteria could be enrolled. Patients who received prior lenalidomide-based therapy should have had at least a minimal response to be included in this study.

Participant characteristics and sex/gender reporting

A total of 59 treated participants were included in this study. Participant age and sex are summarized in Table 1. Sex was recorded from the clinical record as part of standard study enrollment procedures. Sex identity was not collected. Sex and gender were considered in study reporting in accordance with journal guidance. Given the small sample size and the limited number of outcome events, the study was not designed or powered to detect sex-based or gender-based differences in efficacy, toxicity or correlative biomarkers; therefore, no formal sex-based or gender-stratified analyses were performed. Participants were not financially compensated for participation in this investigator-initiated clinical study beyond protocol-specified clinical care and study procedures.

Ethical approval and study oversight

The study was designed by the authors in collaboration with the sponsor. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The Institutional Review Board of the Dana–Farber Cancer Institute approved the study (protocol 22-154; ClinicalTrials.gov registration: [NCT05469893](https://clinicaltrials.gov/ct2/show/study/NCT05469893)); the study protocol

is available in the Supplementary Information. All patients provided written informed consent before enrollment. The authors collected the data, performed the analyses and interpreted the results. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

Primary endpoint

The primary endpoint was the proportion of participants with HR-SMM who achieved a CR or better after initiation of treatment with teclistamab, as defined by International Myeloma Working Group response criteria³⁹.

Secondary endpoints

Secondary endpoints included MRD negativity at 6 months, 1 year and 2 years; PFS until progression to overt MM; PFS after initiation of active myeloma therapy (PFS2); TTP; duration of response; overall survival; safety; feasibility of stem-cell collection after teclistamab; and measures of teclistamab pharmacokinetics, immunogenicity and pharmacodynamic antimyeloma and immune activity. MRD was evaluated in BM aspirates using an NGS-based assay performed by Adaptive Biotechnologies. Safety was assessed by investigator-reported AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0). CRS and immune effector cell-associated neurotoxicity syndrome were graded according to established consensus criteria⁴⁰.

Assays for correlative studies

Soluble BCMA measurements. Plasma specimens collected from patients enrolled in the ImmunoPRISM trial were stored at -80°C until further processing. After thawing, samples were serially diluted at least thrice, with dilution factors ranging from 1:5 to 1:400. Soluble BCMA concentrations were quantified by enzyme-linked immunosorbent assay using the Human BCMA/TNFRSF17 DuoSet ELISA kit (R&D Systems, DY193), following the manufacturer's instructions and consistent with previously reported protocols^{41–43}. Absorbance was measured at 450 nm on a SpectraMax M3 Multi-Mode Microplate Reader (Molecular Devices), and data were acquired and analyzed using SoftMax Pro Data Acquisition and Analysis Software (v7.1). For each sample, sBCMA values were calculated as the mean of duplicate measurements across three sequential dilutions and are reported in ng mL^{-1} .

DNA isolation and library construction for WGS. BM samples from the three patients who did not respond to teclistamab were selected for WGS, as previously described³⁰. Genomic DNA was extracted from tumor plasma cells and matched normal peripheral blood mononuclear cells using the Monarch Genomic DNA Purification Kit (NEB). DNA yield was determined using a Qubit 3.0 fluorometer (Thermo Fisher Scientific). A total input of 50–100 ng genomic DNA was used for sequencing library preparation with the NEBNext Ultra II FS DNA Library Prep Kit (NEB). Unique dual-index adaptors from the NEBNext Multiplex Oligos set were incorporated according to the manufacturer's protocol. Final library size distributions were assessed on a Bioanalyzer 2100 system (Agilent Technologies), and library concentrations were quantified using both Qubit fluorometry and qPCR with the KAPA Library Quantification Kit.

WGS and genomic data analysis. WGS data were generated for the three teclistamab nonresponders and processed using previously established analytical workflows^{30,44}. Prepared libraries were normalized, pooled and sequenced at the Broad Institute of MIT and Harvard Genomics Platform using Illumina NovaSeq 6000 S4 flow cells with 300-cycle, 2×150 bp paired-end sequencing.

Genomic analyses, including copy number and structural variant detection, were performed using an in-house cloud-based high-performance computing environment. Sequencing reads were aligned

to the GRCh38 reference genome using BWA-MEM (v0.7.7; ref. 45). Duplicate reads were marked with Picard MarkDuplicates (v1.457), followed by local indel realignment using GATK 3.4 IndelRealigner and base-quality score recalibration with GATK BQSR.

Downstream analysis was conducted using the Cancer Genome Analysis workflow developed by the Cancer Program at the Broad Institute. Small insertions and deletions were identified with Strelka2 and subsequently filtered against a panel of normals; potential oxidative artifacts and multiple-alignment artifacts were identified by BLAT⁴⁶. Copy-number profiles were normalized using AllelicCapSeg, and ABSOLUTE solutions were manually curated to infer tumor purity, ploidy and cancer cell fraction estimates⁴⁷. Structural variants were called and filtered according to previously published methods⁴⁸.

Enrichment and enumeration of CTCs. Peripheral blood samples were collected into CellRescue Preservation Tubes (Menarini Silicon Biosystems) and analyzed using the CellSearch platform, consisting of the CELLTRACKS AUTOPREP System and CELLTRACKS ANALYZER II. CTCs were enriched and enumerated with the CELLSEARCH Circulating Multiple Myeloma Cell Assay (Menarini Silicon Biosystems). The analytical sensitivity and linearity of this assay for circulating myeloma cell detection have been described previously⁴⁹.

Briefly, 4 ml of peripheral blood was processed on the CELLTRACKS AUTOPREP System according to the manufacturer's recommendations. Myeloma cells were enriched by immunomagnetic capture using anti-CD138 antibody-conjugated ferrofluid. Captured cells were then stained with anti-CD38 antibody conjugated to phycoerythrin and an anti-CD19/CD45 antibody cocktail conjugated to allophycocyanin to distinguish circulating myeloma cells from leukocytes. Nuclei were counterstained with DAPI, and cells were fixed with paraformaldehyde.

After enrichment, cartridges were loaded onto the CELLTRACKS ANALYZER II for semi-automated fluorescence imaging. Image files were exported and analyzed using GateWorks software, which segmented candidate objects, extracted object-level features and applied gating to identify events consistent with circulating myeloma cells for manual review. Circulating myeloma cells were defined phenotypically as CD138-positive, CD38-positive, DAPI-positive, CD19-negative and CD45-negative. Background leukocytes, characterized as CD138-negative, CD38-negative, DAPI-positive, CD19-positive and CD45-positive, were excluded from enumeration. After analysis, samples were removed from the cartridges and stored in glycerol stocks at -20°C for downstream molecular characterization.

Flow cytometry. Flow cytometry was performed to assess residual tumor cells in two patients with mixed clonal responses by NGS. BM mononuclear cells were enriched for CD138-positive cells using magnetic-activated cell sorting beads before cryopreservation. Cryopreserved CD138-enriched BM samples were rapidly thawed in a 37°C water bath for 1–3 min, washed in PBS containing 2% FBS, and centrifuged at $330g$ for 7 min. Cell pellets were resuspended in $100\text{-}\mu\text{l}$ sorting buffer composed of PBS with 2% FBS.

Cells were stained with fluorophore-conjugated antibodies against CD38-APC, CD319/SLAMF7-PE, CD56-PE-Cy7, CD138-BV421, CD19-BV510, CD45-BV711 and CD269/BCMA-PE-Dazzle-594 (BioLegend). Viability staining was performed using LIVE/DEAD Fixable Near-IR Dead Cell Stain and Calcein AM (Life Technologies).

The plasma-cell population assessed at the MRD time point was defined using a patient-adapted gating strategy—CD38-positive, or CD38-dim in patients previously exposed to anti-CD38 therapy; CD138-positive or dim, accounting for antigen changes after cryopreservation; CD269/BCMA-positive, or CD269-dim in patients previously exposed to anti-BCMA therapy; CD19-negative; CD45-negative; CD56-positive or negative according to the patient's prior diagnostic flow phenotype; CD319-positive; LIVE/DEAD-negative; and Calcein-positive (Supplementary Fig. 1a).

Statistical analysis

Sample size justification. The planned sample size was based on comparing the proportion of participants achieving CR or better within 2 years of randomization between the experimental and control arms. Per protocol, 30 participants were planned for each experimental arm and 15 concurrently randomized participants for the control arm. This design provided 73% power to detect a CR rate of 45% in the experimental arm versus 10% in the control arm, and 82% power to detect a CR rate of 50% versus 10%, using a one-sided Fisher's exact test with α of 0.05. After early release of randomized data for abstract reporting, the protocol was amended to enroll six additional participants to the teclistamab arm and three additional participants to the control arm. The primary efficacy analysis included randomized participants who received at least one dose of study treatment and excluded the non-randomized safety run-in cohort, which was included only in secondary and descriptive analyses of teclistamab-treated patients. Missing disease assessments, death or loss to follow-up before the primary analysis were handled as nonresponse in the primary analysis.

Analysis of patient data and outcomes. All treated participants were included in the safety and efficacy analyses. Safety outcomes, including AEs, were summarized descriptively. Response outcomes were summarized as proportions with exact binomial CIs. Continuous variables were summarized as medians with ranges, and categorical variables as counts and percentages. Associations between categorical and continuous variables were assessed using the Wilcoxon rank-sum test or Kruskal–Wallis test, as appropriate, and associations across categorical variables were assessed using Fisher's exact test. Time-to-event outcomes were estimated using the Kaplan–Meier method, with CIs calculated using Greenwood's formula; patients without an event were censored at the date of last follow-up. Median follow-up was estimated using the reverse Kaplan–Meier method. All statistical tests were two sided unless otherwise specified, and P values <0.05 were considered nominally significant. No formal adjustment for multiple testing was applied. Missing data were not imputed. Statistical analyses were performed in R software (v4.4.2), using the packages stats, survival, survminer, dplyr and tidyr.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data supporting the findings of this study are derived from an ongoing clinical trial and are not publicly available. Qualified researchers may submit requests for de-identified participant data to the corresponding author, together with a description of the specific data requested, the proposed analyses and the dissemination plan. Requests will be reviewed by the study lead and the trial sponsor, and data may be shared upon publication following review and execution of a data-sharing agreement, subject to participant confidentiality and applicable regulatory requirements. Responses to data requests are typically provided within 3 months. The study protocol including the statistical analysis plan is available in the Supplementary Information.

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Author contributions

O.N., L.T. and I.M.G. conceptualized the study. O.N., J.M., E.M. and I.M.G. performed the investigation. O.N., D.M.C.d.S., R.A.R., L.T. and I.M.G. performed formal analysis and visualization. All authors performed the methodology. O.N., D.M.C.d.S. and I.M.G. contributed to writing the original draft of the paper. All authors contributed to writing, reviewing and editing. All authors read and approved the final paper.

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Competing interests

O.N. receives research funding from BMS and JNJ, and serves on advisory boards for BMS, JNJ, Sanofi, GPCR Therapeutics, Kite Pharma and AstraZeneca. D.M.C.d.S. receives research funding from Regeneron. E.M. receives research funding from JNJ, AbbVie and AstraZeneca, and is a consultant at Prothena. E.O. serves as a consultant for Exact Sciences, Natera, GRAIL and Sanofi, and receives research funding from Regeneron. Y.L. has participated on an advisory board for Opna Bio and consulted for Sanofi. A.S.S. has consulted for Novartis and Janssen. P.G.R. serves as a consultant for Celgene/BMS, GSK, Karyopharm, Oncopeptides, Regeneron and Sanofi, and receives research grants from Oncopeptides and Karyopharm. J.R. has research funding from Kite Pharma/Gilead and Novartis, and serves on advisory boards for Astraveus, CGT Global, Smart Immune, Stratus Therapeutics, Tolerance Bio and Visterra. I.M.G. has consulted for AbbVie, Adaptive Biotechnologies, Amgen, Aptitude Health, Arcellx, AstraZeneca, BioSkrbyb Genomics, Bristol Myers Squibb, Civala, Clinical Care Options, Clinical Education Alliance, ENGAGE, Feromics, Genentech, GlaxoSmithKline, Janssen, Kite Pharma, Menarini Silicon Biosystems, ONK Therapeutics, Pfizer, Regeneron, Sanofi, Silicon Biosystems, Takeda, TG Therapeutics and Window Therapeutics; has received honoraria from Amgen, Curio Science, Janssen, MD Education, MJH Life Sciences, Physicians' Education Resource, Regeneron, Standard BioTools, Takeda, Thermo Fisher Scientific/Binding Site, Veeva and Vor Biopharma; and is also a founder and executive board member of, and holds private equity in, Predicta Biosciences. Her spouse is the chief medical officer of, and holds private equity in, Disc Medicine. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at

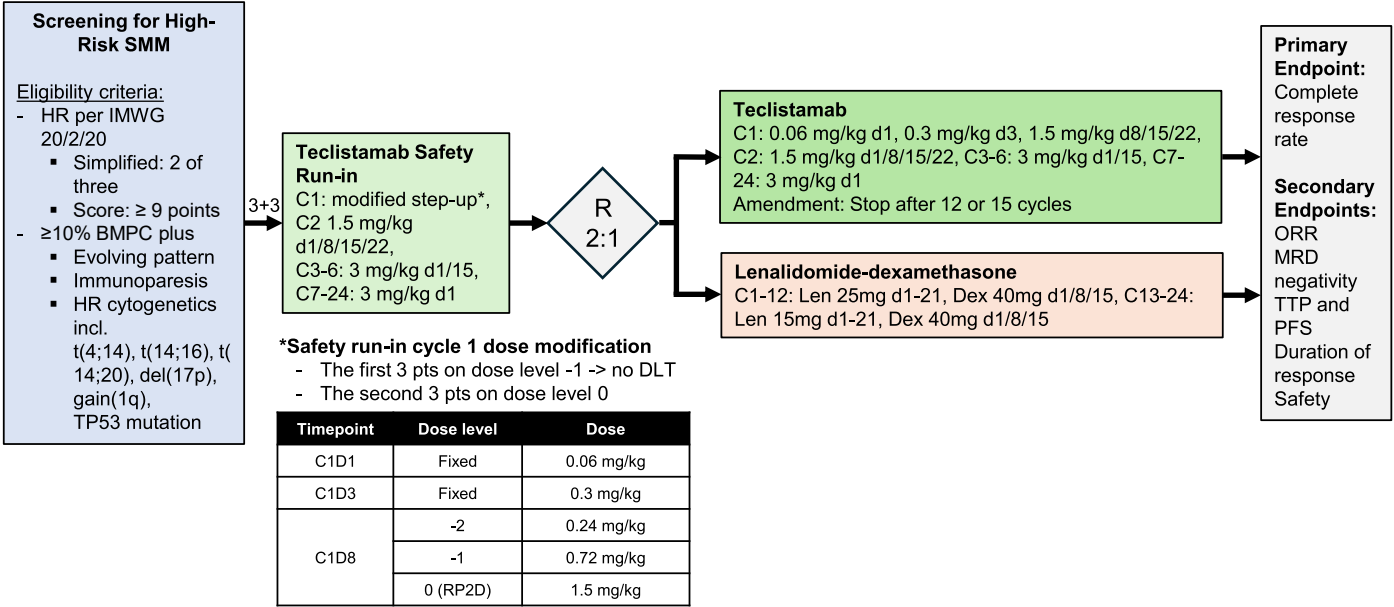
<https://doi.org/10.1038/s41591-026-04642-w>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-026-04642-w>.

Correspondence and requests for materials should be addressed to Irene M. Ghobrial.

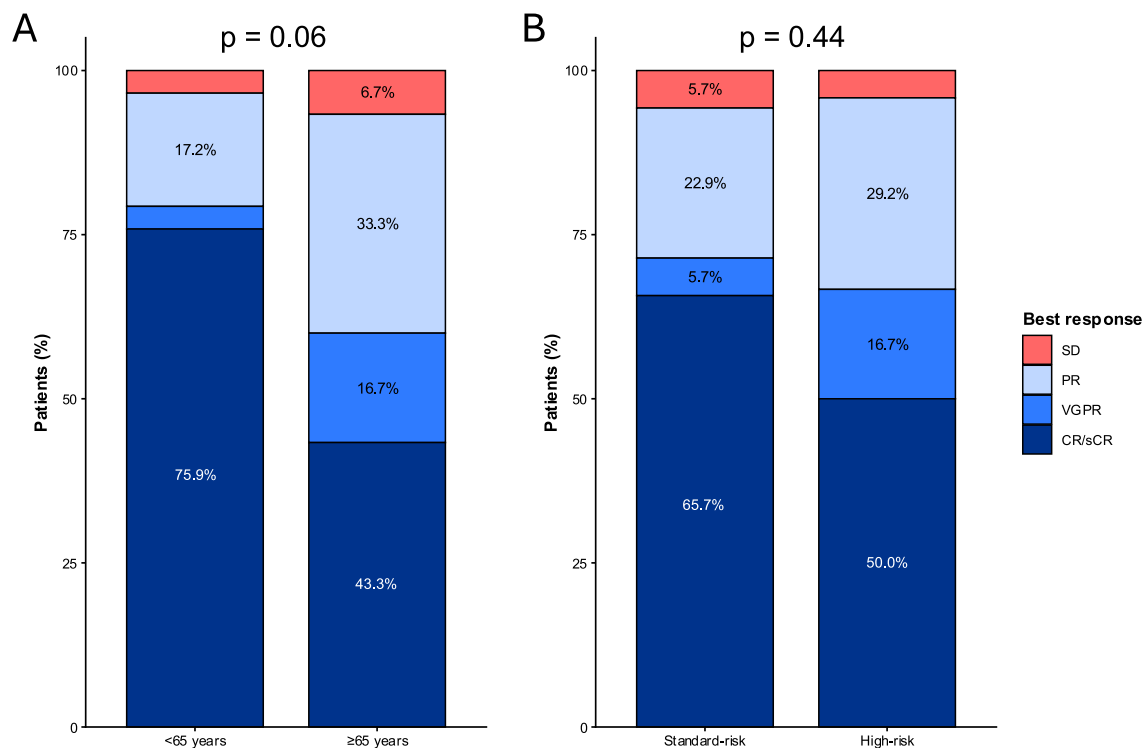
Peer review information *Nature Medicine* thanks Rahul Banerjee, Benjamin Diamond and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ulrike Harjes, in collaboration with the *Nature Medicine* team.

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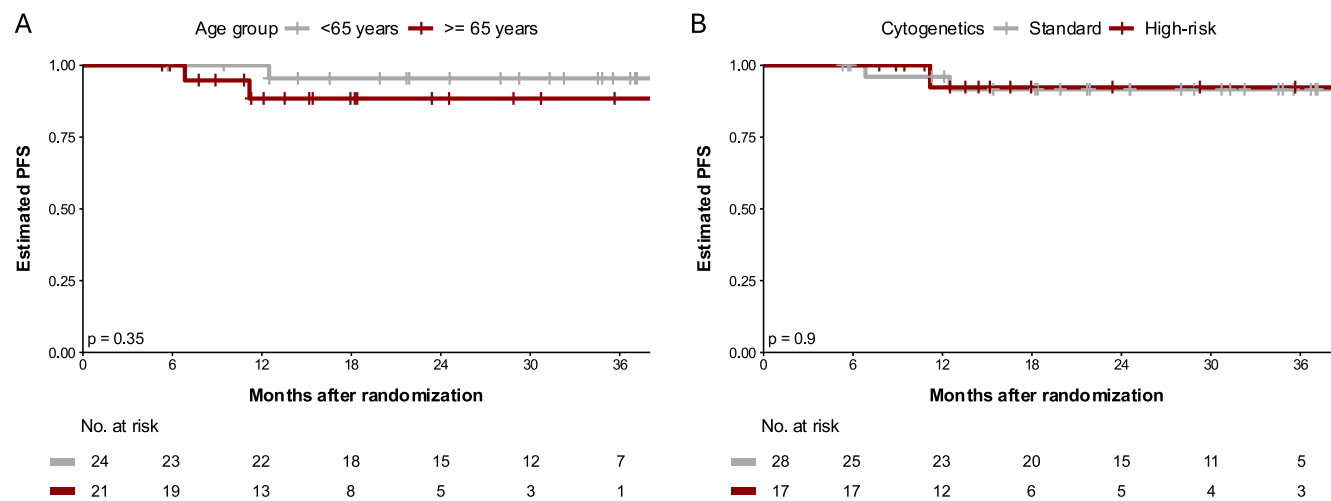
Extended Data Fig. 1 | Study schema for the randomized phase 2 trial of teclistamab versus lenalidomide–dexamethasone in high-risk smoldering multiple myeloma. Eligible patients with high-risk smoldering multiple myeloma, defined by IMWG 20/2/20 criteria and/or additional high-risk clinical or cytogenetic features, were enrolled. After an initial teclistamab safety run-in cohort treated with a modified step-up dosing schedule, patients were randomized 2:1 to teclistamab or lenalidomide–dexamethasone. Teclistamab was administered with step-up dosing followed by weekly, then every-other-week dosing, with treatment discontinuation after 12 or 15 cycles according to protocol

amendment. Lenalidomide–dexamethasone was administered in 28-day cycles according to the schedule shown. The primary endpoint was complete response rate. Secondary endpoints included overall response rate, minimal residual disease negativity, time to progression, progression-free survival, duration of response and safety. The safety run-in dose-modification schema is shown below the study diagram. IMWG, International Myeloma Working Group; BMPC, bone marrow plasma cells; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression.



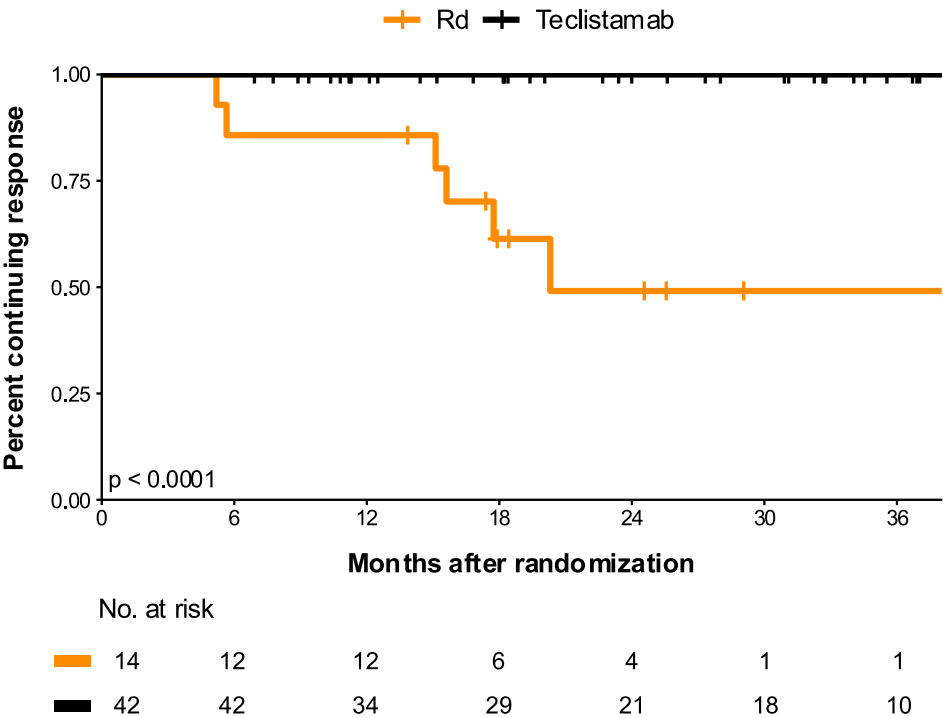
Extended Data Fig. 2 | Best IMWG response stratified by age and high-risk cytogenetic status. a,b, Stacked bar plots show best International Myeloma Working Group (IMWG) response categories among evaluable patients stratified by age group (<65 versus ≥65 years; **a**) and cytogenetic risk status (standard-risk versus high-risk; **b**). Bars indicate the proportion of patients within each

subgroup achieving sCR/CR, VGPR, PR, or SD as best response. Percentages are shown within each segment. Differences in response distribution between subgroups were assessed using Fisher's exact test; nominal *P* values are shown above each comparison.



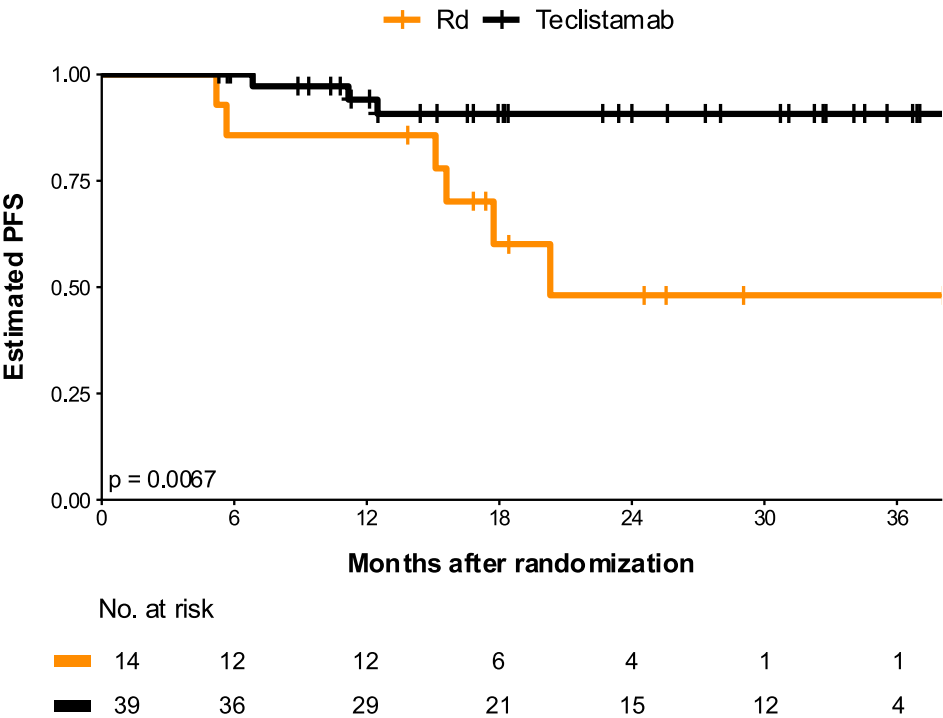
Extended Data Fig. 3 | Progression-free survival stratified by age group and cytogenetic risk status. Kaplan–Meier curves show progression-free survival (PFS) from randomization stratified by (a) age group (<65 versus ≥65 years; left)

and (b) cytogenetic risk status (standard-risk versus high-risk; right). Tick marks indicate censored observations. Numbers at risk are shown below each plot. *P* values were calculated using the log-rank test.



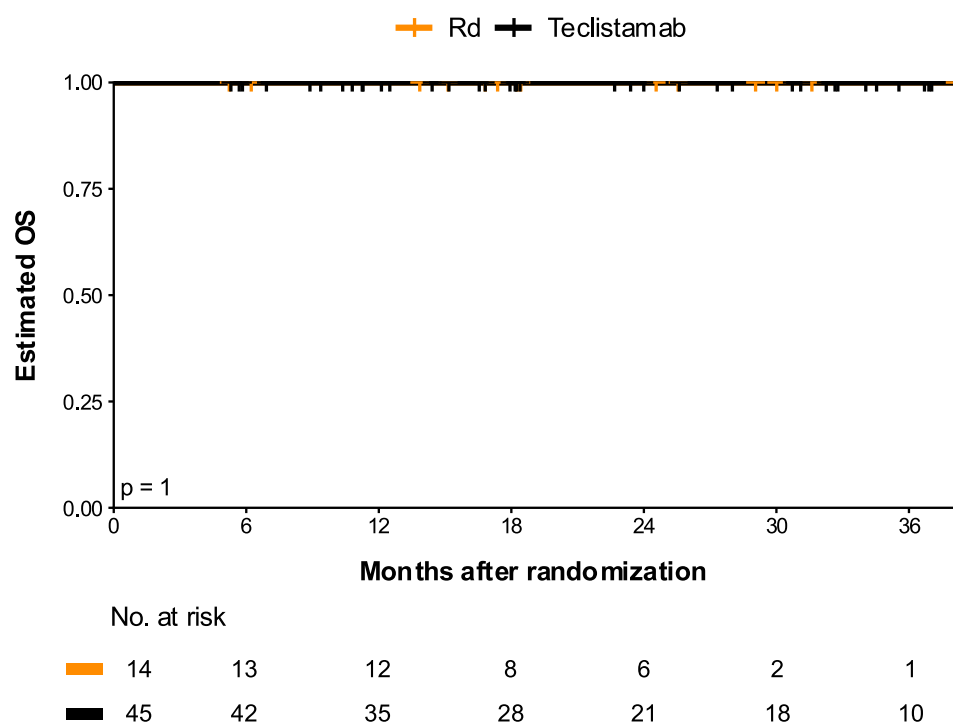
Extended Data Fig. 4 | Duration of response by treatment arm. Kaplan–Meier curves show duration of response among responders randomized to teclistamab or Rd. Duration of response was defined as the time from first documented

response to disease progression or death. Tick marks indicate censored observations. Numbers at risk are shown below the plot. The *P* value was calculated using the log-rank test.



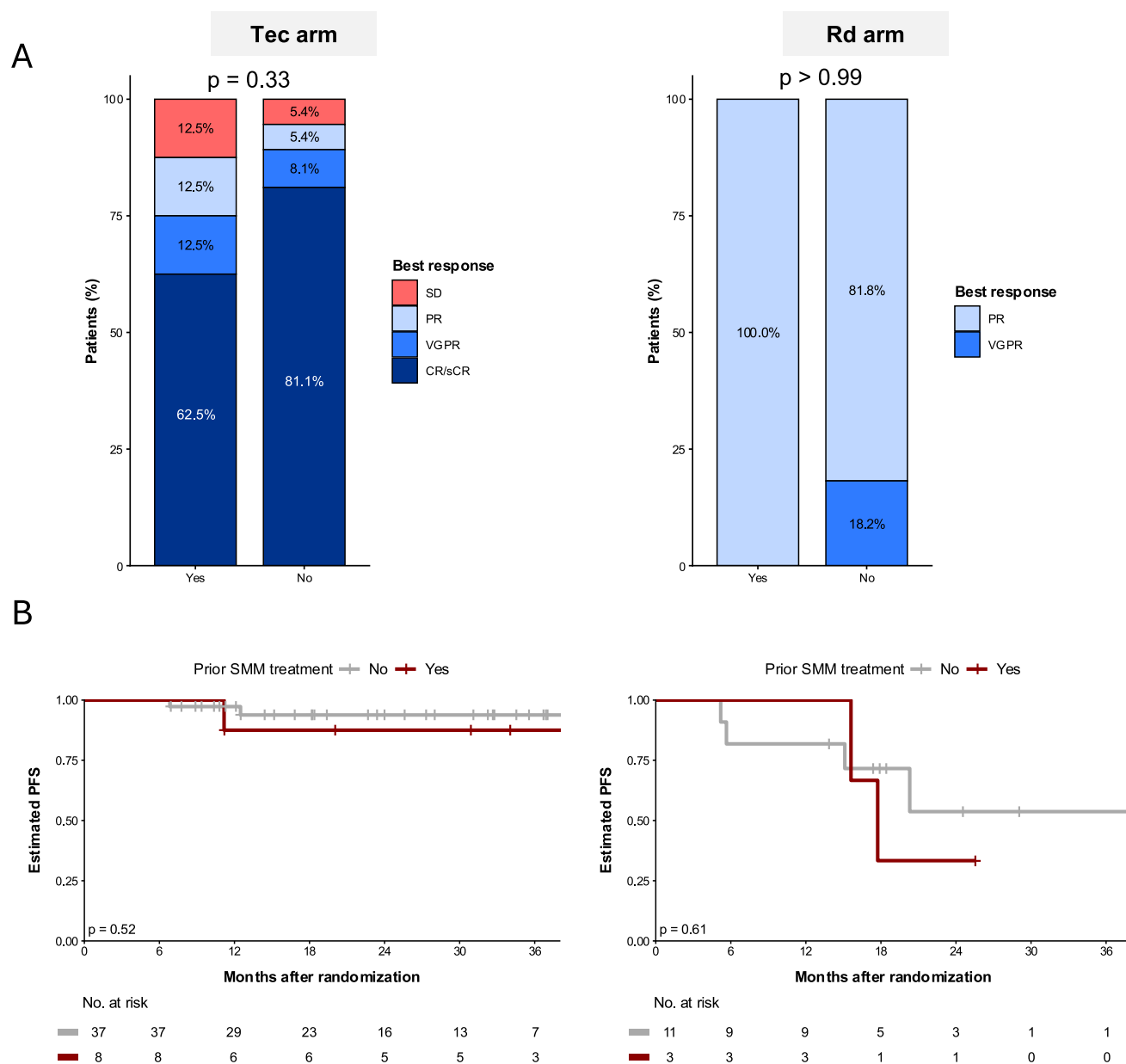
Extended Data Fig. 5 | Progression-free survival in the randomized population. Kaplan–Meier curves show progression-free survival (PFS) from randomization among patients assigned to teclistamab or Rd, excluding patients

treated in the teclistamab safety run-in. Tick marks indicate censored observations. Numbers at risk are shown below the plot. The *P* value was calculated using the log-rank test.



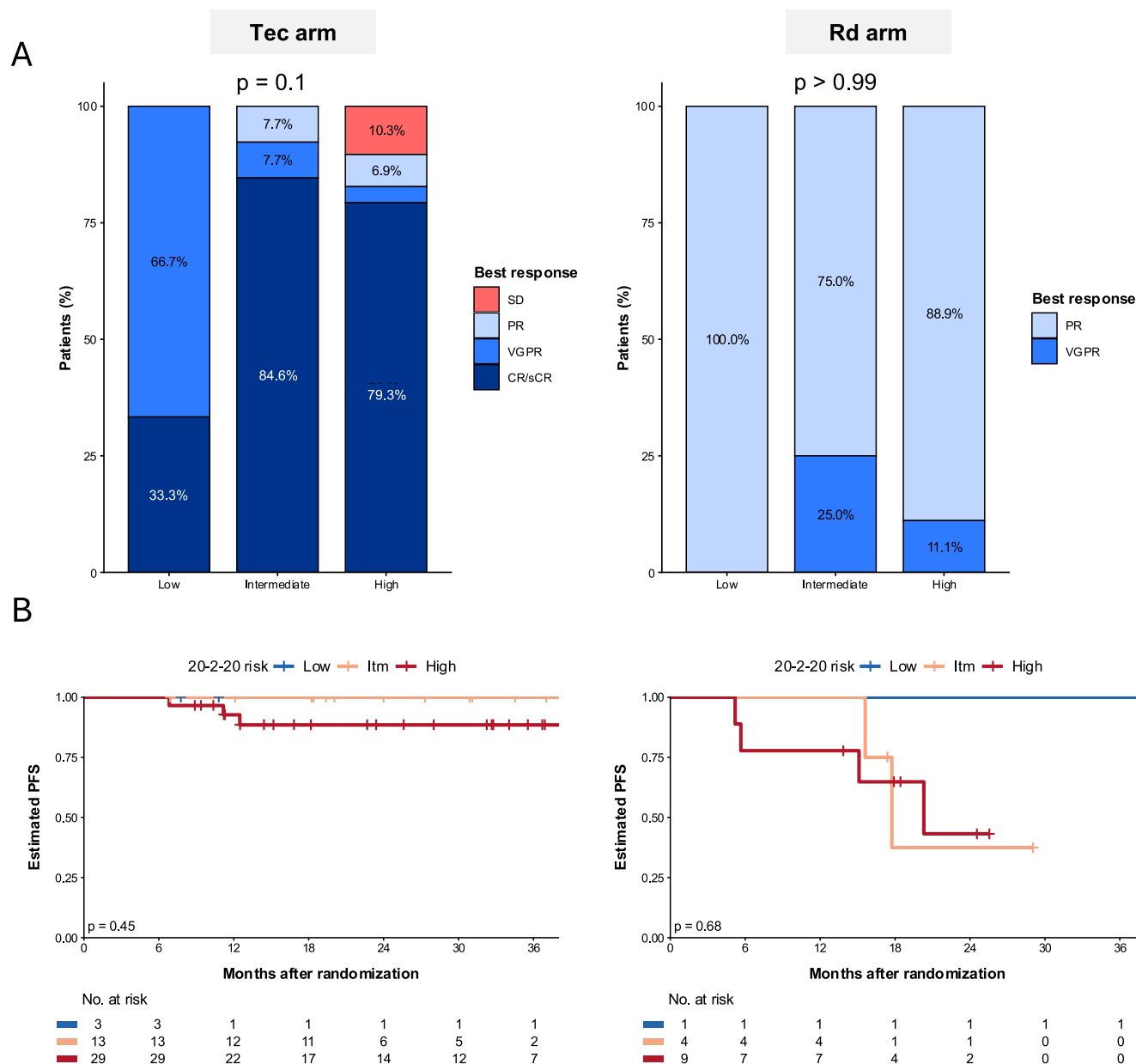
Extended Data Fig. 6 | Overall survival by treatment arm. Kaplan–Meier curves show overall survival (OS) from randomization among patients treated with teclistamab or Rd. Tick marks indicate censored observations. Numbers at risk

are shown below the plot. No deaths were observed in either treatment arm during follow-up; therefore, OS was 100% in both arms and no between-group difference was detected.



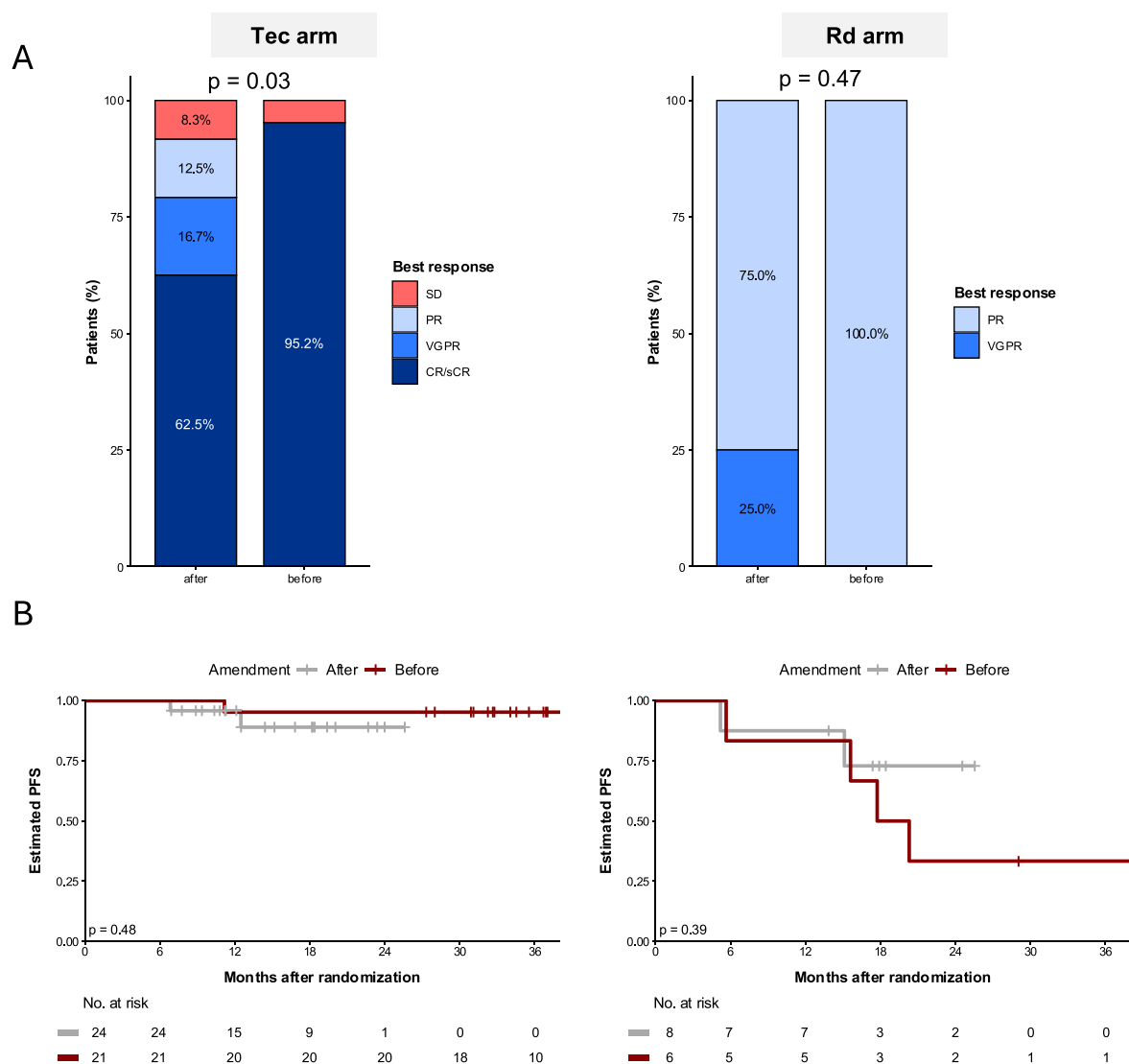
Extended Data Fig. 7 | Response and progression-free survival according to prior SMM-directed treatment. Best overall response and progression-free survival stratified by prior SMM-directed treatment status within the teclistamab and lenalidomide–dexamethasone (Rd) arms. **a**, The distribution of best overall responses according to prior SMM treatment status in the teclistamab arm and Rd arm, respectively. Response categories are shown as stacked proportions of

patients. **b**, Kaplan–Meier estimates of progression-free survival stratified by prior SMM treatment status in the teclistamab arm and Rd arm, respectively. *P* values for response comparisons were calculated using Fisher’s exact test, and *P* values for progression-free survival were calculated using the log-rank test. Tick marks indicate censored observations.



Extended Data Fig. 8 | Response and progression-free survival according to 20-2-20 risk status. Best overall response and progression-free survival stratified by 20-2-20 risk status within the teclistamab and lenalidomide–dexamethasone (Rd) arms. **a.** The distribution of best overall responses according to 20-2-20 risk status in the teclistamab arm and Rd arm, respectively. Response categories

are shown as stacked proportions of patients. **b.** Kaplan–Meier estimates of progression-free survival stratified by 20-2-20 risk status in the teclistamab arm and Rd arm, respectively. *P* values for response comparisons were calculated using Fisher's exact test, and *P* values for progression-free survival were calculated using the log-rank test. Tick marks indicate censored observations.



Extended Data Fig. 9 | Response and progression-free survival according to enrollment before or after protocol amendment. Best overall response and progression-free survival stratified by enrollment before versus after the protocol amendment within the teclistamab and lenalidomide–dexamethasone (Rd) arms. **a**, The distribution of best overall responses according to the protocol amendment status in the teclistamab arm and Rd arm, respectively. Response

categories are shown as stacked proportions of patients. **b**, Kaplan–Meier estimates of progression-free survival stratified by protocol amendment status in the teclistamab arm and Rd arm, respectively. *P* values for response comparisons were calculated using Fisher's exact test, and *P* values for progression-free survival were calculated using the log-rank test. Tick marks indicate censored observations.

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☒	☐ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
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Software and code

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Data collection	Data was collected with the OracleInForm Electronic Data Capture (v7.0). Flow-cytometry data were acquired using BD FACSDiva and analyzed using FlowJo version 10.
Data analysis	Data was analyzed using R Software (v.4.4.1). Analyses were performed in R using the packages tidyverse (v2.0.0), ggplot2 (v4.0.2), dplyr (v1.1.4), tidyr (v1.3.1), readr (v2.1.5), readxl (v1.4.3), stringr (v1.5.1), purrr (v1.0.2), forcats (v1.0.0), lubridate (v1.9.3), lme4 (v1.1-35.5), lmerTest (v3.1-3), survival (v3.7-0), survminer (v0.4.9), prodlim (v2024.06.25), ggpubr (v0.6.0), ggtext (v0.1.2) and pracma (v2.4.6), splines (v.4.4.1). No custom code or mathematical algorithm was specifically developed for this study.

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The individual-level data supporting the findings of this study are derived from an ongoing clinical trial and cannot be made publicly available because they contain potentially identifiable participant health information and are subject to participant-consent, institutional and regulatory restrictions. Qualified academic or non-commercial researchers may request access to de-identified participant-level data by contacting the corresponding author, Irene Ghobrial, at irene_ghobrial@dfci.harvard.edu, Dana-Farber Cancer Institute. Requests should include the identity and institutional affiliation of the requesting researchers, a description of the specific data requested, a scientifically justified research proposal, the proposed analyses and a dissemination plan. Requests will be evaluated by the study leadership and trial sponsor on the basis of scientific merit, compatibility with participant consent, protection of participant confidentiality and applicable institutional and regulatory requirements. Approved access will require execution of a data-use agreement and, where applicable, evidence of institutional ethics or IRB approval. Data may be used only for the approved research purpose and may not be redistributed. Initial responses to requests will generally be provided within three months. The duration and method of access will be specified in the data-use agreement. A redacted trial protocol, including the statistical analysis plan, is provided with the Supplementary Information.

Research involving human participants, their data, or biological material

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Reporting on sex and gender

This study enrolled adult human participants with high-risk smoldering multiple myeloma. Sex was recorded from the clinical record. Gender was not analyzed separately because gender-related data were not collected in a standardized manner relevant to the study objectives. Sex was considered as a baseline demographic characteristic but was not used to stratify analyses because of the small sample size and the early-phase, safety-focused design.

Reporting on race, ethnicity, or other socially relevant groupings

Race and ethnicity were recorded from the clinical record and/or self-report, where available, as part of routine clinical documentation. These variables were collected for descriptive reporting of the study population. Given the small cohort size, the single-center design, and limited statistical power, analyses stratified by race or ethnicity were not performed.

Population characteristics

The study population consisted of adult participants with high-risk smoldering multiple myeloma enrolled at a single academic center. Covariate-relevant characteristics included age, sex, race and ethnicity where available, disease-specific risk features, bone marrow plasma cell burden, laboratory parameters, cytogenetic risk features, prior disease history, and treatment-related variables relevant to study eligibility and outcome assessment. Participants met prospectively defined eligibility criteria as described in the protocol and Methods.

Recruitment

Participants were recruited from patients with high-risk smoldering multiple myeloma evaluated at Dana-Farber Cancer Institute, Oregon Health & Science University and Colorado Blood Cancer Institute. Potential participants were identified by the treating clinical teams and screened against prospectively defined protocol eligibility criteria. Eligible patients were offered participation, and all enrolled participants provided written informed consent before undergoing study-specific procedures. Potential sources of bias include referral bias from recruitment at specialized academic centers, eligibility criteria that selected patients suitable for clinical-trial participation, and self-selection among patients who agreed to enroll. Randomization reduced treatment-selection bias within the randomized cohort.

Ethics oversight

The study protocol was approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent before study participation.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Sample size

Sample size was determined by the study design rather than to power a formal hypothesis test for all endpoints. The study included an initial safety run-in followed by randomized enrollment. Per protocol, 30 participants were planned for each experimental arm and 15 concurrently randomized participants for the control arm. This design provided 73% power to detect a complete response rate of 45% in the experimental arm versus 10% in the control arm, and 82% power to detect a complete response rate of 50% versus 10%, using a one-sided Fisher's exact

test with an alpha of 0.05. Following review of preliminary efficacy and safety findings, enrollment was expanded as described in the protocol amendment and manuscript. No separate formal sample-size calculations were performed for secondary endpoints, subgroup analyses or exploratory correlative studies. These analyses used all participants, samples or evaluable measurements available for the relevant endpoint at the data cutoff. Their sample sizes were therefore determined by trial enrollment, specimen availability, longitudinal sampling and assay quality-control criteria.

Data exclusions	The primary efficacy analysis was restricted to the randomized population and excluded participants treated during the non-randomized safety run-in. Because the safety run-in cohort had comparable baseline characteristics and outcomes to the randomized teclistamab cohort, these participants were included in supportive complete response analyses and in descriptive secondary efficacy analyses of all teclistamab-treated participants, unless otherwise indicated. Secondary efficacy outcomes were compared descriptively with the Rd control arm. Safety analyses included all treated participants. Missing disease assessments, death, or loss to follow-up before the primary analysis were counted as non-response for the primary endpoint; missing data for longitudinal and correlative analyses were not imputed.
Replication	Clinical and laboratory assessments were conducted prospectively according to protocol-defined procedures and prespecified response and safety criteria. Clinical data were reviewed through standard trial data-management and source-verification procedures, and the primary efficacy analysis was performed in the prespecified randomized population. The consistency of the principal efficacy findings was assessed across related clinical endpoints, including complete response or better, overall response, MRD negativity and progression-free survival, and through supportive analyses including all teclistamab-treated participants. Exploratory correlative analyses were performed using available longitudinal specimens and, where applicable, complementary measurement approaches. The flow-cytometry assessment of residual plasma cells was performed as an orthogonal exploratory analysis in selected patients.
Randomization	After the non-randomized safety run-in, participants were randomized according to the protocol-defined allocation scheme to teclistamab or lenalidomide plus dexamethasone.
Blinding	The trial was open-label; treatment assignments were not blinded.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Cells were stained with fluorophore-conjugated antibodies against: PE/Dazzle 594 anti-human CD269 (BCMA) [19F2], BioLegend (Catalog Number: 357511), 1:100 PE/Cyanine7 anti-human CD56 (NCAM) [5.1H11], BioLegend (Catalog Number: 362509), 1:100 Brilliant Violet 510 anti-human CD19 [H1B19], BioLegend (Catalog Number: 302241), 1:100 PE anti-human CD319 (CRACC) [162.1], BioLegend (Catalog Number: 331806), 1:100 Brilliant Violet 711 anti-human CD45 [H130], BioLegend (Catalog Number: 304049), 1:100 Brilliant Violet 421 anti-human CD138 (Syndecan-1) [MI15], BioLegend (Catalog Number: 356515), 1:100 APC anti-human CD38 [HB-7], BioLegend (Catalog Number: 356605), 1:100 Viability staining was performed using LIVE/DEAD Fixable Near-IR Dead Cell Stain and Calcein AM (Life Technologies).
Validation	Each antibody was commercially validated by the manufacturer for flow-cytometric detection of the indicated human antigen. Antibody performance in this study was additionally assessed using expected positive and negative cell populations, fluorescence-minus-one controls where applicable, and patient-adapted gating based on established plasma-cell immunophenotypes.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	This study is registered at ClinicalTrials.gov under identifier NCT05469893
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Study protocol	The study protocol is provided with the Supplementary Information.
Data collection	Clinical data were collected prospectively as part of a multicenter phase 2 trial conducted at Dana-Farber Cancer Institute in Boston, Massachusetts; Oregon Health & Science University in Portland, Oregon; and Colorado Blood Cancer Institute in Denver, Colorado, United States. Participants were recruited between April 2023 and July 2025. Clinical and correlative data were collected from screening through protocol-defined treatment and longitudinal follow-up, with the current analysis including data available through the cutoff date of May 26, 2026. The trial included an initial non-randomized safety run-in followed by randomized assignment to teclistamab or lenalidomide plus dexamethasone. Clinical, laboratory, imaging, response, safety and correlative assessments were collected at protocol-defined time points. Disease assessments included serum and urine studies, bone marrow evaluations, imaging and minimal residual disease testing, as specified in the protocol.
Outcomes	The primary endpoint was complete response rate or better in the randomized population. Supportive complete response analyses included all teclistamab-treated participants, including those treated during the safety run-in. Secondary efficacy endpoints included overall response rate, MRD negativity, progression-free survival, duration of response, time to progression, PFS2 and overall survival. Safety endpoints included adverse events, serious adverse events, infections, cytopenias, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and other treatment-emergent toxicities, assessed according to protocol-defined criteria. Exploratory and correlative endpoints included longitudinal disease monitoring, MRD kinetics, serum BCMA, circulating tumor cells and other protocol-specified biomarker analyses.

Plants

Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>

Flow Cytometry

Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☒ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cryopreserved CD138-enriched bone marrow samples from two patients with mixed clonal responses by NGS were analyzed by flow cytometry as an exploratory assessment of residual plasma cells. Bone marrow mononuclear cells had been enriched for CD138-positive cells using magnetic-activated cell sorting before cryopreservation. Samples were rapidly thawed, washed in phosphate-buffered saline containing 2% fetal bovine serum, centrifuged, and resuspended in sorting buffer before staining.
Instrument	Fortessa LSR (BD Biosciences)
Software	FACSDiva and FlowJo v10
Cell population abundance	Not applicable as a quantitative abundance analysis of bulk bone marrow. Samples were CD138-enriched before analysis, and flow cytometry was performed as an exploratory orthogonal assessment of residual plasma cells in selected patients.
Gating strategy	Cells were gated to exclude debris, doublets and non-viable cells, followed by patient-adapted identification of residual plasma cells based on CD38, CD138, CD269/BCMA, CD19, CD45, CD56 and CD319 expression. Representative gating is shown in the Supplementary Information.

- ☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.