FraminGHam

on multiple myeloma

Resetting sensitivity to T cell redirection by tumor reduction and immune modulation

Clinical Lymphoma, Myeloma & Leukemia, 2026 April; 26(4):244–8

Teclistamab in multiple myeloma with one to three previous lines of therapy

The New England Journal of Medicine, 2026 July 30; 395(5):440–53

Concurrent administration of BCMA and GPRC5D chimeric antigen receptor (CAR) T cells in advanced multiple myeloma

Blood, 2026 July 7; Epub ahead of print

Talquetamab–daratumumab in relapsed or refractory myeloma

The New England Journal of Medicine, 2026 August 13; 395(7):671–83

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RESETTING SENSITIVITY TO T CELL REDIRECTION BY TUMOR REDUCTION AND IMMUNE MODULATION

Clinical Lymphoma, Myeloma & Leukemia, 2026 April; 26(4):244–8

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BACKGROUND & AIM: Bispecific antibodies (BsAbs) such as teclistamab can be effective in treating patients with relapsed or refractory multiple myeloma (RRMM). However, response rates are lower in patients with a high tumour burden and/or extramedullary disease. There is some evidence to suggest that tumour debulking using chemotherapy and/or radiotherapy, and immune modulation involving T-cell stimulation, can restore responsiveness to BsAbs. This paper presents the case of a patient with teclistamab-refractory multiple myeloma who regained responsiveness following tumour reduction and immune modulation.

TYPE OF ARTICLE: Case history.

FINDINGS: A woman with RRMM had disease progression after five lines of therapy, presenting with soft tissue plasmacytomas of increasing size, new paramedullary bone plasmacytomas and increasing levels of M protein IgG kappa (IgGκ) and free light chain kappa (FLCκ). Teclistamab was initiated but was stopped early in cycle 2 because of disease progression. The lack of response was considered likely to be due to a high tumour burden and extramedullary disease. Therefore, the patient received debulking therapy with daratumumab plus chemotherapy comprising vincristine, etoposide, doxorubicin, cyclophosphamide and dexamethasone (DaraEPOCH), as well as radiotherapy targeting some of the soft tissue plasmacytomas. An initial response was seen but was short-lived.

As no additional treatment options were available, it was decided to reintroduce teclistamab, this time in combination with pomalidomide to improve T-cell activation. The patient experienced grade 2 cytokine release syndrome during step-up dosing, which resolved. After one cycle of teclistamab plus pomalidomide she showed a partial biochemical response, indicated by a reduced IgGκ level and suppressed FLCκ, After seven cycles, a complete biochemical response was seen, with M protein no longer present and continued suppression of FLCκ, and this was maintained at the time of reporting after 10 cycles. A CT scan during cycle 3 showed a significant reduction in the irradiated soft tissue plasmacytomas, as well as a reduction in plasmacytomas located outside of the irradiated area, findings that were consistent with a partial response based on IMWG criteria.

CONCLUSIONS: In a patient with teclistamab-refractory multiple myeloma, chemo/radiotherapy-based tumour debulking plus immune modulation restored responsiveness to teclistamab, resulting in sustained remission. This case suggests this may be a feasible approach to mitigate resistance to BsAb therapy in patients with RRMM who have a high tumour burden and/or extramedullary disease.

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TECLISTAMAB IN MULTIPLE MYELOMA WITH ONE TO THREE PREVIOUS LINES OF THERAPY

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AUTHORS: Touzeau C, Mina R, Quach H, et al., on behalf of the MajesTEC-9 Trial Investigators
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BACKGROUND & AIM: Teclistamab is a fully immune-based bispecific antibody monotherapy targeting CD3 and B-cell maturation antigen. It is approved for the treatment of adults with relapsed or refractory multiple myeloma (RRMM) who have already undergone multiple prior treatment regimens. The aim of this study was to evaluate the efficacy and safety of teclistamab as early-line monotherapy in patients with RRMM.

STUDY DESIGN: Open-label, multicentre, randomized phase 3 trial.

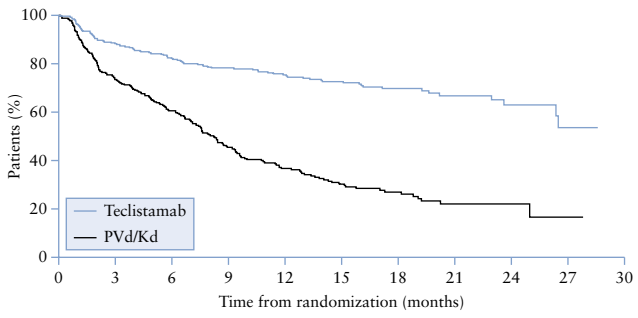
ENDPOINTS: Primary: progression-free survival (PFS). Secondary endpoints included the proportion of participants with a complete response or better and overall survival (OS).

METHOD: Patients with RRMM who had previously received one to three lines of therapy (including an anti-CD38 monoclonal antibody and lenalidomide) were randomized to receive teclistamab (*n*=296) or investigator's choice of either pomalidomide, bortezomib and dexamethasone (PVd) or carfilzomib and dexamethasone (Kd) (*n*=297).

RESULTS: At the interim analysis (median follow-up 17.3 months) the estimated 18-month PFS rate was significantly higher in the teclistamab group, at 69.8% versus 26.9% in the PVd/Kd group (hazard ratio 0.29, 95% confidence interval 0.23–0.38; $p<0.001$; Figure). Moreover, 65.9% of teclistamab recipients had a complete response or better versus 16.8% of participants treated with PVd/Kd ($p<0.001$). The estimated 18-month OS rate was also significantly higher in the teclistamab arm (79.2% versus 68.6%; HR 0.60, 95% CI 0.43–0.83; $p=0.002$). There were more grade 3/4 adverse events with teclistamab versus PVd/Kd (84.9% versus 76.3% of recipients), including grade 3/4 infection in 41.6% versus 29.0%. Overall, 66.0% of teclistamab recipients experienced cytokine release syndrome (mostly grade 1/2) and 4.1% developed immune effector cell-associated neurotoxicity syndrome.

CONCLUSION: Among patients with RRMM with one to three prior lines of therapy, teclistamab was associated with significant improvements in PFS and OS compared with PVd/Kd, with a higher proportion of patients achieving a complete response or better.

Kaplan–Meier estimates of PFS



https://doi.org/10.1056/NEJMoa2603870

CONCURRENT ADMINISTRATION OF BCMA AND GPRC5D CHIMERIC ANTIGEN RECEPTOR (CAR) T CELLS IN ADVANCED MULTIPLE MYELOMA

Blood, 2026 July 7; Epub ahead of print

AUTHORS: Mailankody S, Mitra S, Herrera K, Zicchedu B, Cadzin B, Eren OC, Farzana T, Ullah T, Landa J, Derkach A, Chaudhari J, McAvoy D, Hosszu K, Shah GL, Landau HJ, Maura F, Dogan A, Giralt SA, Wang X, Sadelain M, Smith EL, Brentjens RJ, Leslie CS, Usmani SZ, Perica K
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BACKGROUND & AIM: Despite major advances in chimeric antigen receptor T-cell (CAR-T) therapies for treating multiple myeloma, such as those targeting B-cell maturation antigen (BCMA) and GPRC5D (G-protein-coupled receptor, class C, group 5, member D) antigen, most patients eventually relapse. There is evidence that concurrent administration of MCARH125 (a BCMA-targeted CAR-T) and MCARH109 (a GPRC5D-targeted CAR-T) leads to deeper and more durable responses. The aim of this study was to evaluate the efficacy and safety of this approach in patients with relapsed or refractory multiple myeloma.

STUDY DESIGN: Phase 1 dose-escalation trial.

ENDPOINTS: Primary: safety. Secondary endpoints included clinical response, BCMA and GPRC5D expression, and MCARH109 and MCARH125 expansion.

METHOD: The study enrolled 15 adults with multiple myeloma with at least three prior lines of therapy and Eastern Cooperative Oncology Group performance status 0–1. All patients completed T-cell apheresis followed by lymphodepleting chemotherapy. CAR-T dose assignment used a 3+3 dose-escalation design: dose level 0 (safety lead-in, MCARH125 at 150×10^6 cells and no MCARH109; n=6); dose level 1 (MCARH125 at 150×10^6 cells and MCARH109 at 50×10^6 cells; n=3); and dose level 2 (both MCARH125 and MCARH109 at 150×10^6 cells; n=6).

RESULTS: An objective response was seen in all six patients at dose level 0 and in seven of nine patients (78%) at dose levels 1 and 2. Median progression-free survival was 20.1 months at dose level 0 and 18.2 months at dose levels 1 and 2. Reduction and loss of GPRC5D and BCMA expression were seen in two patients who were primary refractory to dual-antigen targeting and three patients who relapsed after an initial response. Higher peak CAR-T expansion (p=0.041) and area under the curve (p=0.0087) were seen with MCARH125 alone compared with concurrent MCARH125 and MCARH109, despite equivalent MCARH125 dosing. All patients developed cytokine release syndrome (all grade 1/2). Immune effector cell-associated haemophagocytic syndrome occurred in one patient each at dose levels 0 and 2, and was considered a dose-limiting toxicity. One patient at dose level 0 developed grade 1 immune effector cell-associated neurologic syndrome; no other neurological toxicities were observed.

CONCLUSIONS: The administration of concurrent MCARH125 and MCARH109 therapy was found to be feasible, with strong safety and efficacy outcomes. However, the occurrence of primary refractoriness and relapse suggests ongoing treatment challenges.

https://doi.org/10.1182/blood.2025032122

TALQUETAMAB–DARATUMUMAB IN RELAPSED OR REFRACTORY MYELOMA

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AUTHORS: Mina R, Beksac M, Rodríguez-Otero P, et al., on behalf of the MonumenTAL-3 Investigators
CENTRE FOR CORRESPONDENCE: Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, North Carolina, USA

BACKGROUND & AIM: Talquetamab is a bispecific antibody that targets GPRC5D (G-protein-coupled receptor, class C, group 5, member D) on myeloma cells and CD3 on T cells. It is licensed for use in relapsed or refractory multiple myeloma (RRMM) after four or more prior lines of therapy. The aim of this study was to evaluate the efficacy of two talquetamab-containing regimens – talquetamab plus daratumumab (Tal-D) and talquetamab plus daratumumab and pomalidomide (Tal-DP) – as earlier-line therapy in RRMM.

STUDY DESIGN: Interim analysis of a multicentre, open-label, phase 3 trial.

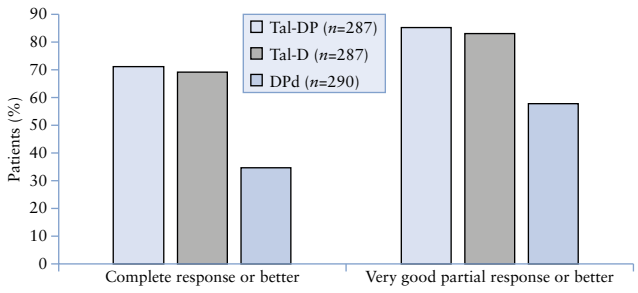
ENDPOINTS: Primary: progression-free survival (PFS). Key secondary: overall response; complete or stringent complete response; measurable residual disease-negative complete response; overall survival.

METHOD: Adults with RRMM with one or more prior lines of therapy were randomized to receive Tal-DP (*n*=287) or Tal-D (*n*=287) in 28-day cycles, or daratumumab plus pomalidomide and dexamethasone (DPd; *n*=290). Treatment was continued until disease progression, death or unacceptable toxicity.

RESULTS: At a median follow-up of 24.6 months (range 0.03–35.4 months), the estimated 24-month PFS rate was 51.2% with DPd, versus 81.3% with Tal-DP (hazard ratio 0.28, 95% confidence interval 0.20–0.40; $p<0.001$) and 77.6% with Tal-D (HR 0.33, 95% CI 0.24–0.46; $p<0.001$). The overall response rate was 77.6% with DPd versus 88.2% with Tal-DP and 88.5% with Tal-D (Figure); the rate of complete or stringent complete response was 34.5% versus 71.1% and 69.0%; and the measurable residual disease-negative complete response rate was 15.9% versus 52.3% and 46.3%, respectively (all $p<0.001$). The estimated 24-month overall survival rate was 79.1% with DPd, versus 89.2% with Tal-DP (HR 0.47, 95% CI 0.30–0.73) and 87.9% with Tal-D (HR 0.51, 95% CI 0.33–0.78). The safety profiles of the talquetamab-containing arms were consistent with previous reports for each agent in the combinations.

CONCLUSION: Among patients with RRMM and one or more prior line of therapy, those who received Tal-DP or TAL-D had significantly higher PFS rates than those who received DPd.

Treatment response rates



https://doi.org/10.1056/NEJMoa2604657