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# Teclistamab in multiple myeloma with coexisting myelodysplastic syndrome or acute myeloid leukemia

Short Running Title: Bispecific therapy in MM with concurrent MDS/AML

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**Authors' Contributions:**

RF: data collection, data analysis, manuscript writing. XJB: myeloid disease assessment, manuscript review. SPSA, ALG, ADC, SK, CEL, SML, EAS, DTV, AW: clinical care of patients, manuscript review. SPSA: study conception, supervision, manuscript review.

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Longer survival and cumulative treatment exposure in multiple myeloma (MM) have increased the clinical relevance of coexisting myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), including therapy-related myeloid neoplasms. Prior cytotoxic therapy and selection of susceptible clones during lenalidomide exposure contribute to this risk.[1,2] These dual diagnoses create intersecting treatment constraints: impaired hematopoiesis can limit MM therapy, myeloid-directed treatment can compound cytopenias and infection risk, and persistent cytopenias may reflect either malignancy or treatment toxicity.

B-cell maturation antigen (BCMA)-targeted therapies, like teclistamab, have shown high efficacy in RRMM across pivotal clinical trials, including MajesTec-1, -3, and -9.[3,4,5] However, these clinical trials excluded patients with MDS and other active malignancies, leaving limited evidence for this population. We describe six selected teclistamab recipients with MM and MDS/AML diagnosed before or after treatment initiation, focusing on treatment delivery, MM response, and myeloid disease course.

We retrospectively reviewed patients treated at the University of Pennsylvania, between January 1, 2023, and December 31, 2025, who had: (1) RRMM requiring therapy, (2) a diagnosis of MDS or AML, and (3) receipt of at least one dose of teclistamab. Clinical data were abstracted from the electronic medical record, including demographics, prior MM therapies, cytogenetic and molecular features of MM and MDS/AML, laboratory parameters at teclistamab initiation, infectious complications, transfusion requirements, and treatment responses. Myeloma responses were assessed per IMWG criteria. Myeloid disease risk was categorized according to IPSS-M when applicable.[6] This study was deemed exempt and patient consent was waived by the University of Pennsylvania Institutional Review.

Six male patients (aged 70-86 years) met criteria. Median prior lines of therapy was 6.5. Four were penta-class exposed and two were triple-class exposed. Patients 1 and 2 had previously received idecabtagene vicleucel.

Three patients were diagnosed with MDS/AML before initiating teclistamab, while the remaining were diagnosed after therapy initiation. The interval from MM diagnosis to MDS/AML diagnosis varied, with a median of 46.8 months (range 0–132.8 months). Four patients had very low or low IPSS-M risk disease, and one had moderately high-risk features. Patient 3, who was treated as AML, was classified as adverse risk per European LeukemiaNet (ELN) 2022/2024 less-intensive criteria.[7,8] Median follow-up from teclistamab initiation was 24.0 months (range 10.8–38.8 months).

Cytopenias were common, and patients 1–3 required temporary teclistamab holds for worsening counts. Management of MDS/AML included observation or supportive care, azacitidine for patient 1, azacitidine plus venetoclax for patient 3, and luspatercept for patient 6 (Table 1). All patients received antiviral, Pneumocystis prophylaxis, and intravenous immunoglobulin (IVIG) to maintain IgG levels > 400 mg/dL. Documented infections included recurrent pneumonia, rhinovirus/enterovirus, COVID-19 and chronic norovirus-associated diarrhea (Table 2). All patients achieved at least a very good partial response (VGPR) or better during initial teclistamab course; patient 3 also received palliative radiation. Five stopped treatment after a median of 9.6 months (range 6.5-18.1 months): two enrolled in a limited-duration teclistamab trial (NCT05932680)[9], two due to cytopenias requiring transfusions, and one because of recurrent infections. Patient 6 continued teclistamab with a complete response (CR). Patients 1, 3 and 4 restarted teclistamab after MM progression. CR was reported after retreatment in patients 1 and

3, whereas patient 4 progressed three months after restarting. Patient 2 died from progressive MM after switching therapy.

Five of six patients demonstrated stable MDS throughout the period of teclistamab exposure. Patient 1 developed high-risk MDS approximately 11 months after teclistamab initiation and progressed to AML approximately 15 months later. No other myeloid progression was reported.

In this single-center series, teclistamab produced deep MM responses in six selected patients with MDS or AML diagnosed before or after treatment initiation. These dual diagnoses create competing therapeutic demands: controlling MM while preserving limited hematopoietic reserve and managing a second marrow malignancy. Cytopenias and infections constrained treatment delivery despite MM responses, illustrating that disease control and treatment tolerance must be assessed separately.

Selection bias is the principal limitation of these observations. Patients with rapidly progressive MDS/AML, those requiring urgent induction chemotherapy or allogeneic transplantation, and those dying before a subsequent MM relapse would be unlikely to receive teclistamab. This series therefore preferentially captures patients who survived and remained suitable for MM-directed therapy; four of the five patients with MDS had very low or low IPSS-M risk. Moreover, three myeloid diagnoses were established after teclistamab initiation. Their earlier exposure cannot demonstrate feasibility in patients with known active MDS/AML at treatment initiation. The findings should therefore be interpreted as a descriptive experience in selected patients rather than evidence of safety across the broader population with dual diagnoses.

The mechanisms underlying cytopenias in this setting are likely multifactorial, including impaired hematopoiesis from either malignancy, cumulative treatment exposure, concurrent myeloid-directed therapy, and treatment-associated inflammation. Clonal hematopoiesis and inflammatory signaling have been associated with hematologic toxicity and secondary myeloid neoplasms after BCMA-directed CAR T-cell therapy,[10,11] but their contribution during bispecific-antibody treatment remains uncertain. Without systematic pretreatment marrow assessment and myeloid sequencing, we cannot determine whether diagnoses made after teclistamab reflected previously unrecognized disease or subsequent clonal evolution. Although uniform myeloid progression was not observed, the heterogeneous trajectories do not establish that teclistamab leaves myeloid disease biology unaffected. Similarly, patient 1's progression from MDS to AML cannot be compared with the natural history of MDS without an appropriate comparator. Myeloid-associated immune dysregulation provides an additional rationale for studying this population because it could affect the efficacy of both CAR T cells and bispecific antibodies. The observed MM responses demonstrate that teclistamab activity can occur despite coexisting myeloid disease, but do not establish preserved T-cell function or resistance to immune dysfunction. A practical distinction is that teclistamab does not require lymphodepleting chemotherapy, which may be difficult to deliver in patients with substantial marrow failure. Its ongoing administration also permits treatment holds for cytopenias or infections. These considerations do not establish superiority over CAR T-cell therapy. Reports of secondary myeloid neoplasms after BCMA-directed CAR T-cell treatment are complicated by prior cytotoxic exposure and pre-existing clones,[10,11] and this series cannot determine whether the corresponding risk differs with bispecific antibodies.

Management requires close collaboration between myeloma and leukemia teams to identify the cause of cytopenias, prioritize treatment, coordinate therapies, and individualize transfusion and infection support, consistent with the experience reported by Hochman et al.[12] Persistent or worsening cytopenias warrant reassessment for myeloid disease rather than automatic attribution to teclistamab. Antimicrobial prophylaxis, immunoglobulin replacement, and careful monitoring remain central to treatment delivery. Limited-duration teclistamab is under prospective investigation,[9] but these cases cannot establish whether treatment discontinuation reduces infections or preserves durable MM control in patients with concurrent MDS/AML.

In addition to selection bias, the small sample size, retrospective design, incomplete molecular profiling, and heterogeneous myeloid-directed treatment limit interpretation. The absence of a comparator precludes conclusions about relative efficacy, toxicity, or myeloid progression. Teclistamab achieved MM responses in these selected patients, while cytopenias and infections remained important treatment constraints. Prospective studies should distinguish pre-existing from subsequently diagnosed MDS/AML, characterize baseline myeloid risk and clonal evolution, and capture outcomes among patients unable to receive MM-directed therapy.

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Table 1:

| Patient | Age/ Sex | Status | MM History | | | | | | | MDS/AML History | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | MM Isotype | MM Cytogenetics/ FISH/ Molecular | Lines of Therapy (incl. Tec) | Triple/Penta Class Exposed | MDS-Linked Therapy Exposure | Autologous HSCT | CAR-T | MDS/AML Diagnosis | BM Blast % at Dx | IPSS-M Risk | MDS/AML Cytogenetics/ FISH/Molecular | Time MM dx to MDS/AML dx | MDS Management & Transfusion History |
| 1 | 86/M | Alive | Kappa light chain | Normal karyotype and sequencing studies | 13 | Penta-class | Melphalan, cyclophosphamide, fludarabine, lenalidomide, pomalidomide, radiation | No | Yes - ide-cel | MDS | 6% | 0.82 (High) | -7; SETBP1 (VAF 46%); FISH not done | ~10 yrs, 10 months | Azacytidine (6 cycles); active surveillance Platelets: 1 unit/wk; pRBC: every 2 weeks |
| 2 | 77/M | Deceased-MM progression | IgG Kappa | Complex chromosomal abnormalities; t(11;14) | 9 | Penta-class | Melphalan, cyclophosphamide, fludarabine, lenalidomide, pomalidomide, etoposide, doxorubicin, cisplatin, radiation | Yes (MEL200 ASCT) | Yes - ide-cel | MDS | 1% | -0.91 (Low) | 45,XY,-7[3]; Monosomy 7; DNMT3A (VAF 23%) | 2 yrs, 2 months, 14 days | Active surveillance pRBC: 2-3 units/wk; Platelets: 1-3 units/wk |
| 3 | 75/M | Alive | IgA Kappa | -1p, -IgH, t(14;16) | 6 | Penta-class | Melphalan, cyclophosphamide, lenalidomide, pomalidomide, doxorubicin, radiation | Yes (MEL200 ASCT) | No | t-AML | 13% (aspirate), 20% (core) | N/A —AML; ELN 2022 Intermediate risk) | 46,XY,del(13)(q12q22)[11]/46,XY[9]; DNMT3A (VAF 49%); IKZF1 (VAF 49%); XPO1 (VAF 43%) | ~7 yrs, 8 months | Azacitidine + Venetoclax (10 cycles) pRBC: 1 unit/2 wks; Platelets: twice weekly |
| 4 | 80/M | Alive | IgG Lambda | Normal karyotype; +1q21, trisomy 7, monosomy 13 with extra IGH copy | 7 | Penta-class | Cyclophosphamide, lenalidomide, pomalidomide, etoposide | No | No | MDS | 3% | -1.70 (Very Low) | 47,XY,+Y[3]/46,XY[17]; ASXL1 (2 mutations, VAF 14% each); PLCG2 (VAF 44%) | ~4 yrs, 6 months | Active surveillance; no transfusions |
| 5 | 70/M | Alive | IgG Lambda | +1q21, del13q | 3 | Triple-class | Melphalan, lenalidomide, radiation | Yes (MEL200 ASCT) | No | MDS | 1% | -1.07 (Low) | ASXL1, NF1, SRSF2 (VAF unavailable) | ~3 yrs, 3 months | Active surveillance; iron supplementation for mild anemia |
| 6 | 80/M | Alive | Lambda light chain | Normal karyotype | 3 | Triple-class | Cyclophosphamide, lenalidomide | No | No | MDS | 3% | -0.98 (Low) | CUX1 (VAF 53%); SF3B1 (VAF 45%); TET2 (VAF 46% & 45%); DNMT3A (VAF 47%); TCF3 (VAF 52%) | 0 | Luspatercept; pRBC: 1-2 units/wk |

Table 2:

| Patient | Timing of MDS/AML Dx Relative to Teclistamab | Duration of 1st Tec Regimen | Reason for Stopping Tec | Best Response on Tec | Complications/CRS with Tec | Infections During Tec | Infection Prophylaxis | Tec Re-initiation | Complications/CRS with Tec Re-initiation |
|---|---|---|---|---|---|---|---|---|---|
| 1 | After Teclistamab | 6.5 months | Limited-duration Teclistamab study | VGPR | CRS grade 2; Acute transaminitis | None | Valacyclovir, Bactrim, IVIG | Yes | CRS grade 2 |
| 2 | Before Teclistamab | 9.6 months | Worsening thrombocytopenia requiring transfusions | VGPR | CRS grade 2 causing AFib with RVR | None | Acyclovir, Bactrim, IVIG | No | None |
| 3 | After Teclistamab | 18.1 months | Pancytopenia requiring transfusions | VGPR* | Prophylactic Tocilizumab given (no CRS) | Norovirus (chronic diarrhea); Rhinovirus/Enterovirus | Valacyclovir, Bactrim, IVIG | Yes | CRS grade 2 |
| 4 | After Teclistamab | 6.8 months | Limited-duration Teclistamab study | sCR | CRS grade 2 | Several PNA events (including Rhinovirus hospitalization); COVID-19 | Acyclovir, Atovaquone, IVIG | Yes | None |
| 5 | Before Teclistamab | 17.9 months | Recurrent infections | VGPR | CRS grade 1; Unintentional weight loss (related to recurrent infections) | Pseudomonas PNA; Recurrent bronchitis/PNA | Acyclovir, Bactrim, IVIG | No | None |
| 6 | Before Teclistamab | 9.3 months** | Ongoing** | CR | CRS grade 2; ICANS grade 2 | None | Acyclovir, Bactrim, IVIG | No | None |

**Table Legends:**

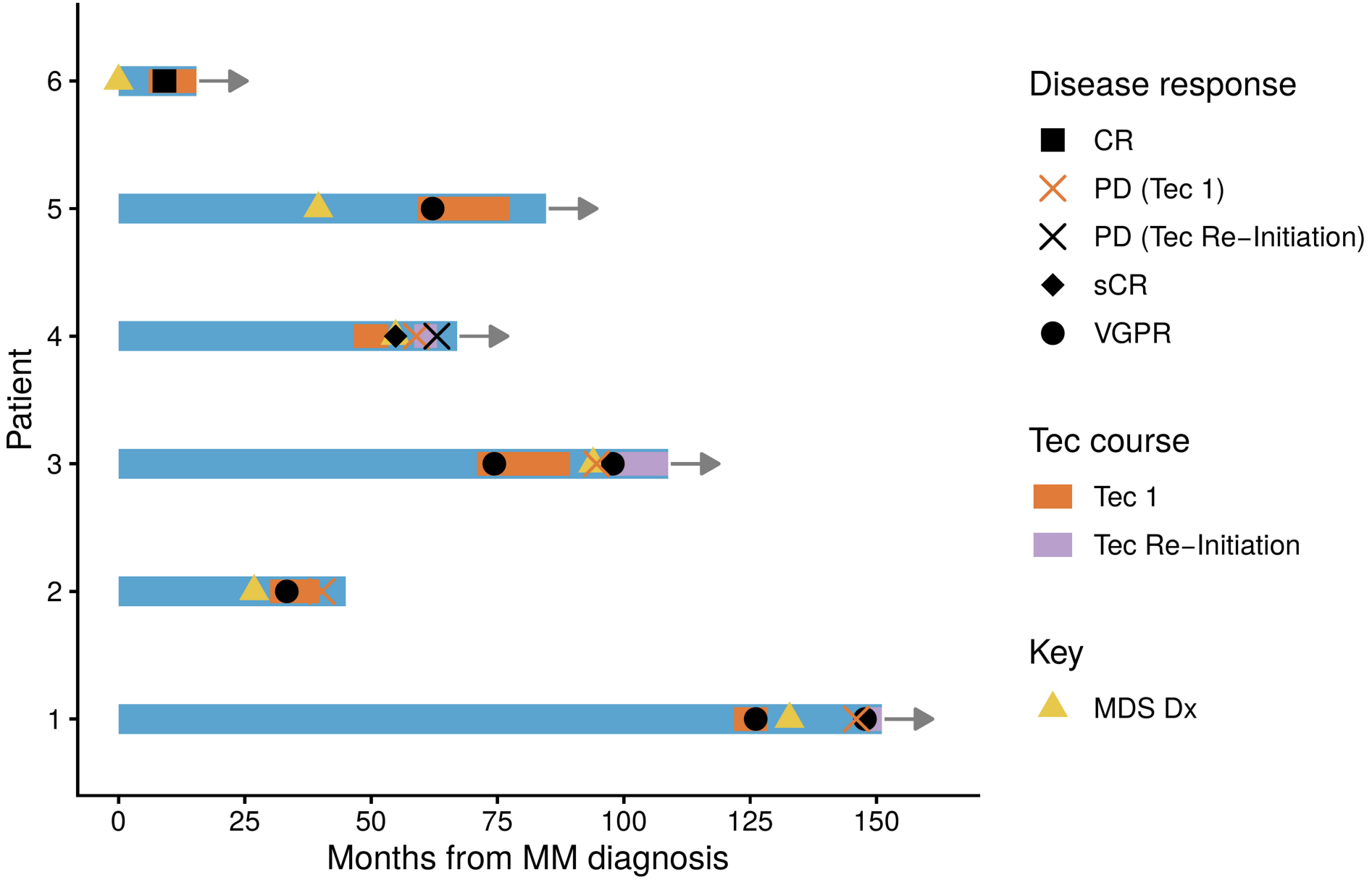
Table 1: Patient demographics, baseline multiple myeloma and MDS/AML characteristics. Multiple myeloma (MM); fluorescence in situ hybridization (FISH); teclistamab (Tec); myelodysplastic syndrome (MDS); acute myeloid leukemia (AML); hematopoietic stem cell transplantation (HSCT); Molecular International Prognostic Scoring System (IPSS-M); bone marrow (BM); diagnosis (Dx); packed red blood cells (pRBC); variant allele fraction (VAF); high-dose melphalan 200mg/m2 (MEL200); week (wk); weeks (wks); European LeukemiaNet (ELN); idecabtagene vicleucel (ide-cel)

Table 2: Teclistamab course, including duration, best response, infection events, and complications while on treatment. *Response after concurrent radiation therapy. **Data as of January 2026. Patient 6 continues teclistamab therapy. Cytokine release syndrome (CRS); complete response (CR); Teclistamab (Tec); stringent complete response (sCR); very good partial response (VGPR); pneumonia (PNA); atrial fibrillation (AFib); rapid ventricular response (RVR); intravenous immunoglobulin (IVIG).

**FIGURE 1**

[High-quality JPG/TIFF figure at 600 dpi, 10×13 inches to be uploaded separately]

Figure 1: Swimmer plot of MM disease course and teclistamab treatment in patients with concurrent MDS/AML. Blue bars represent MM disease course; orange and purple bars show initial teclistamab treatment and re-initiation, respectively. Yellow triangles mark MDS/AML diagnosis, while arrowheads denote ongoing survival. Patient 3 was diagnosed with treatment-related AML. Complete response (CR); progressive disease (PD); teclistamab (Tec); stringent complete response (sCR); very good partial response (VGPR); diagnosis (Dx).


Patient
6
5
4
3
2
1
0
25
50
75
100
125
150
Months from MM diagnosis
Disease response
CR
PD (Tec 1)
PD (Tec Re−Initiation)
sCR
VGPR
Tec course
Tec 1
Tec Re−Initiation
Key
MDS Dx