Supplementary Appendix

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Supplemental Methods

Study Designs and Patients

The primary objectives of the phase 1 portion of MajesTEC-1 (NCT03145181) and MonumenTAL-1 (NCT03399799) were to identify the recommended phase 2 dose(s) of teclistamab and talquetamab, respectively, in the dose escalation portion (part 1) and to characterize the safety of each agent at the recommended phase 2 dose in the dose expansion portion (part 2). Key secondary objectives were to characterize anti-tumor activity, pharmacokinetics (PK), and pharmacodynamics. Exploratory objectives included evaluation of soluble B cell maturation antigen (sBCMA) and investigation of predictive biomarkers of response to teclistamab or talquetamab.

Dosing Schedule

In MajesTEC-1, teclistamab was administered intravenously every two weeks (doses of 0.0003-0.0192 mg/kg on days 1 and 15 of every 28-day cycle), intravenously every week (doses of 0.0192-0.72 mg/kg on days 1, 8, and 15 of every 21-day cycle), or subcutaneously every week (doses of 0.08-3.0 mg/kg on days 1, 8, and 15 of every 21-day cycle). Details on MajesTEC-1 methods have been previously described.[13] In MonumenTAL-1, talquetamab was dosed intravenously every two weeks (doses of 0.5-3.38 μg/kg on days 1 and 15 of every 28-day cycle), intravenously every week (doses of 1.5-180 μg/kg on days 1, 8, and 15 of every 21-day cycle), or subcutaneously every week (doses of 1.5-800 μg/kg days 1, 8, and 15 of every 21-day cycle).[14] To mitigate the risk of severe cytokine release syndrome, a step-up dosing strategy was used for full doses of ≥0.0384 mg/kg for teclistamab and ≥3.38 μg/kg for talquetamab.

Patients were considered responders if their response at the assessed timepoint was a partial response, very good partial response, complete response, or stringent complete response. Patients were categorized as nonresponders if their response at the assessed timepoint was minimal response, stable disease, or progressive disease. Tumor burden in patients was

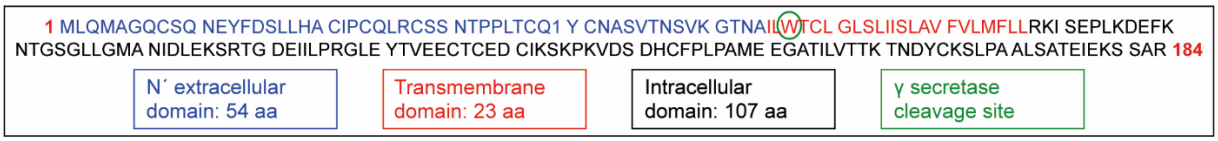
evaluated through the measurement of bone marrow plasma cell (BMPC) levels and the presence of extramedullary plasmacytomas. BMPC levels were locally assessed by bone marrow aspirate or biopsy samples at screening. Extramedullary plasmacytomas were assessed by physical exam or radiologic imaging at screening. Cytogenetic risk was determined using full karyotyping or fluorescence in situ hybridization and defined as the presence of one or more of the following cytogenetic markers: del(17p), t(4;14), or t(14;16).

P values between patients with high versus standard cytogenetic risk were calculated using an unpaired 2-sample Wilcoxon test. The effect of baseline sBCMA as a potential covariate on teclistamab PK was assessed in a preliminary population PK analysis using nonlinear mixed effect modeling with limited data from 93 patients in MajesTEC-1 (nominal *P* value of 0.001 was used to determine the significance of the covariate effect).

Serum Sample Collection and Analysis

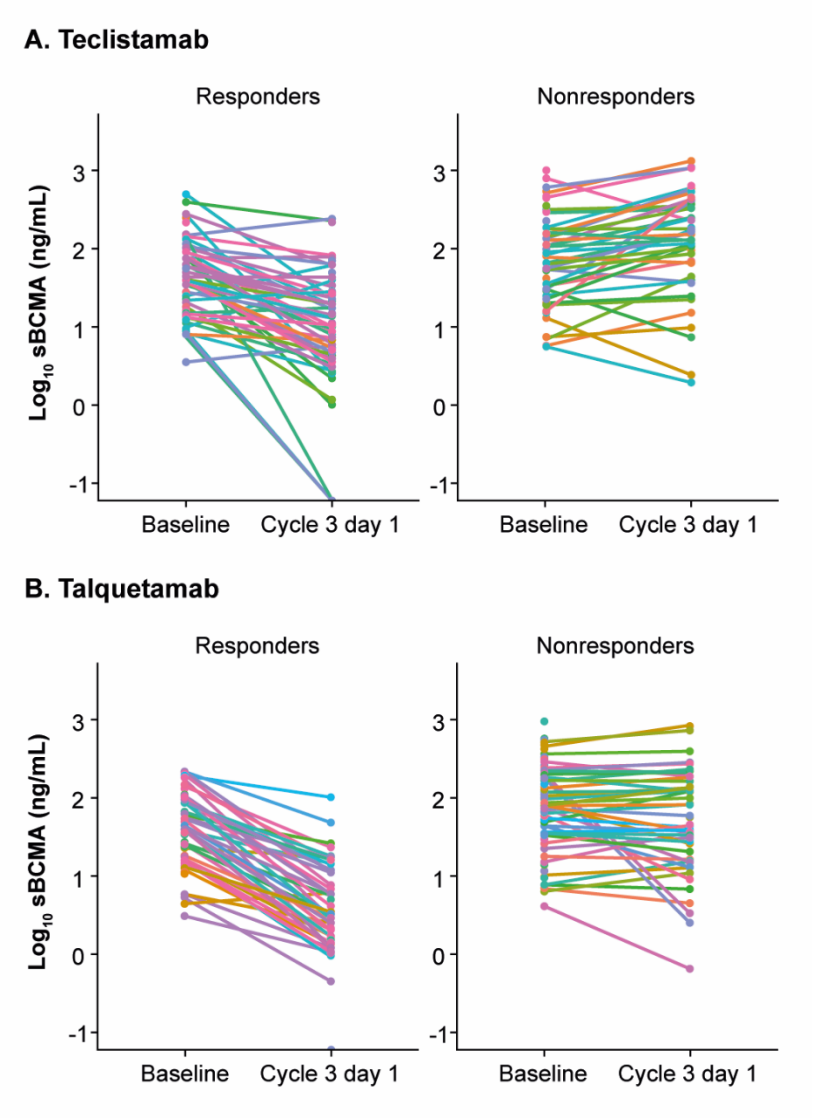
Blood samples were collected for PK analysis on days 1, 2, 3, 8, and 15 of cycles 1 and 3, on days 1 and 15 of cycle 2, and on day 1 of cycle 4 in biweekly intravenous dosing cohorts and weekly intravenous and subcutaneous dosing cohorts; in the subcutaneous dosing cohorts, additional samples were collected on days 4 and 6 of cycles 1 and 3 in MajesTEC-1 and on day 4 of cycles 1 and 3 in MonumenTAL-1. Serum samples were analyzed for teclistamab or talquetamab concentrations using a validated electrochemiluminescence-based immunoassay format on the Meso Scale Discovery (MSD®) platform, with the lowest quantifiable concentration of 1.00000 ng/mL. In both MajesTEC-1 and MonumenTAL-1, an aliquot was taken from the PK samples for analysis of sBCMA. The predose sample (collected on cycle 1 day 1 prior to dosing with teclistamab or talquetamab) was used for estimation of baseline sBCMA values.

Supplemental Figure 1. BCMA sequence and domains.



aa, amino acid; BCMA, B-cell maturation antigen.

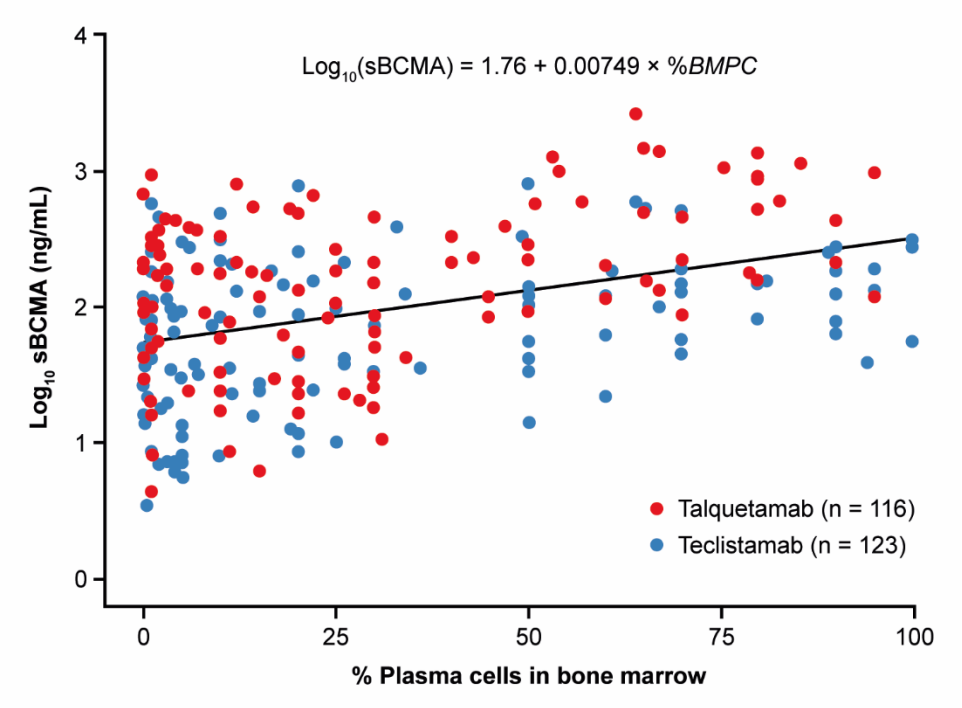
Supplemental Figure 2. sBCMA levels at baseline and on cycle 3 day 1 in responders and nonresponders to teclistamab and talquetamab



Analyses in Panel A include all patients who received doses of teclistamab (IV doses 0.0003–0.72 mg/kg and SC doses 0.08–3.0 mg/kg). Analyses in Panel B include all patients who received doses of talquetamab (IV doses 1–180 µg/kg and SC doses 5–800 µg/kg). Data cutoff date, November 13, 2020, for MajesTEC-1 and November 16, 2020, for MonumenTAL-1. Data are for individual patients; colors were used to distinguish patients. Patients were categorized as responders or nonresponders based on their responses at the cycle 3 day 1 timepoint. Cycle 3 day 8 data were used for 3 patients treated with teclistamab and 2 patients treated with talquetamab who had missing cycle 3 day 1 data.

IV, intravenous; sBCMA, soluble B-cell maturation antigen; SC, subcutaneous.

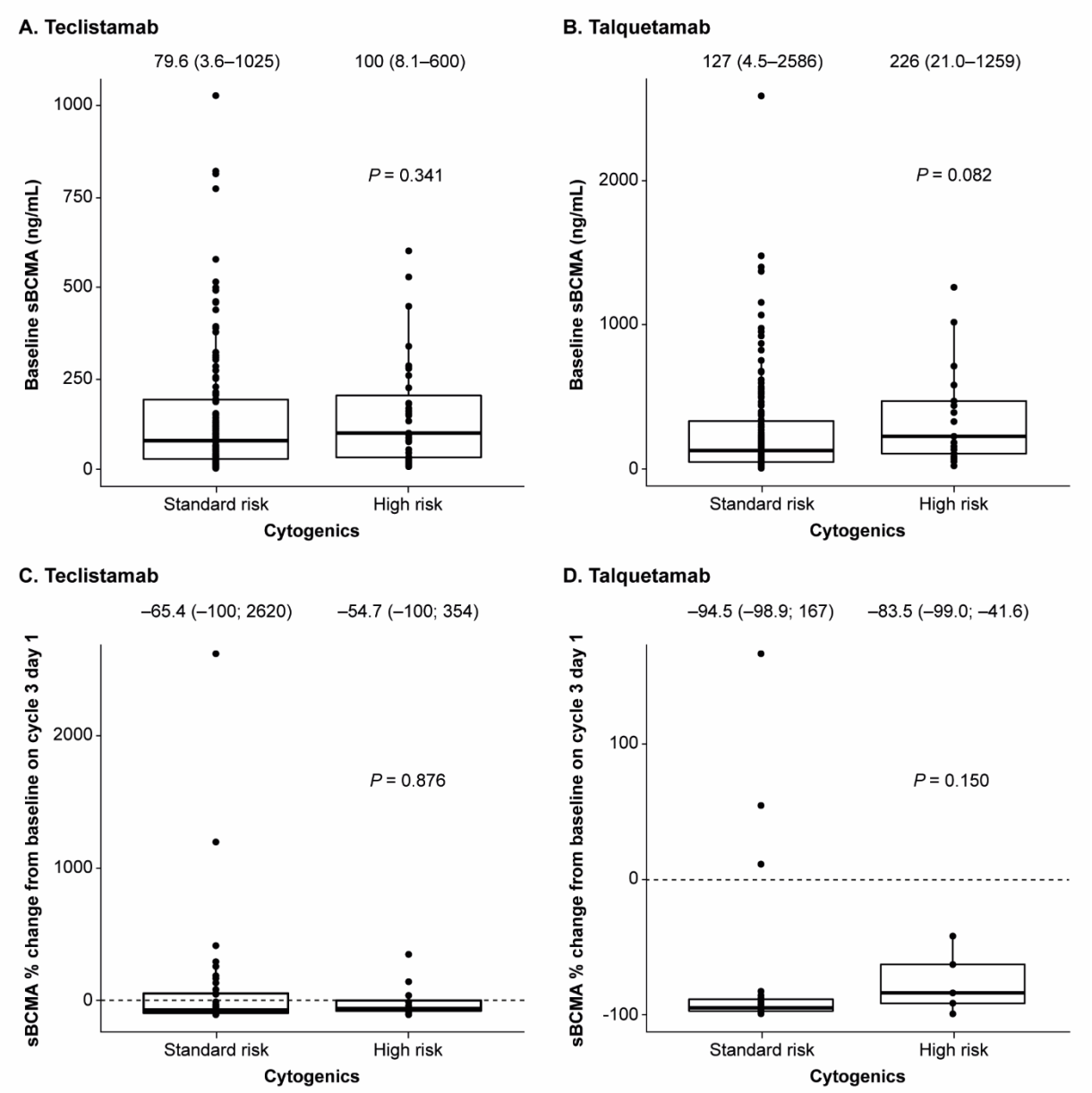
Supplemental Figure 3. Correlation between baseline sBCMA and percentage of plasma cells in bone marrow.



Includes patients with data for both baseline sBCMA and baseline percent BMPC. Data were excluded for patients with extramedullary plasmacytomas

BMPC, bone marrow plasma cells; sBCMA, soluble B-cell maturation antigen; N/A not applicable

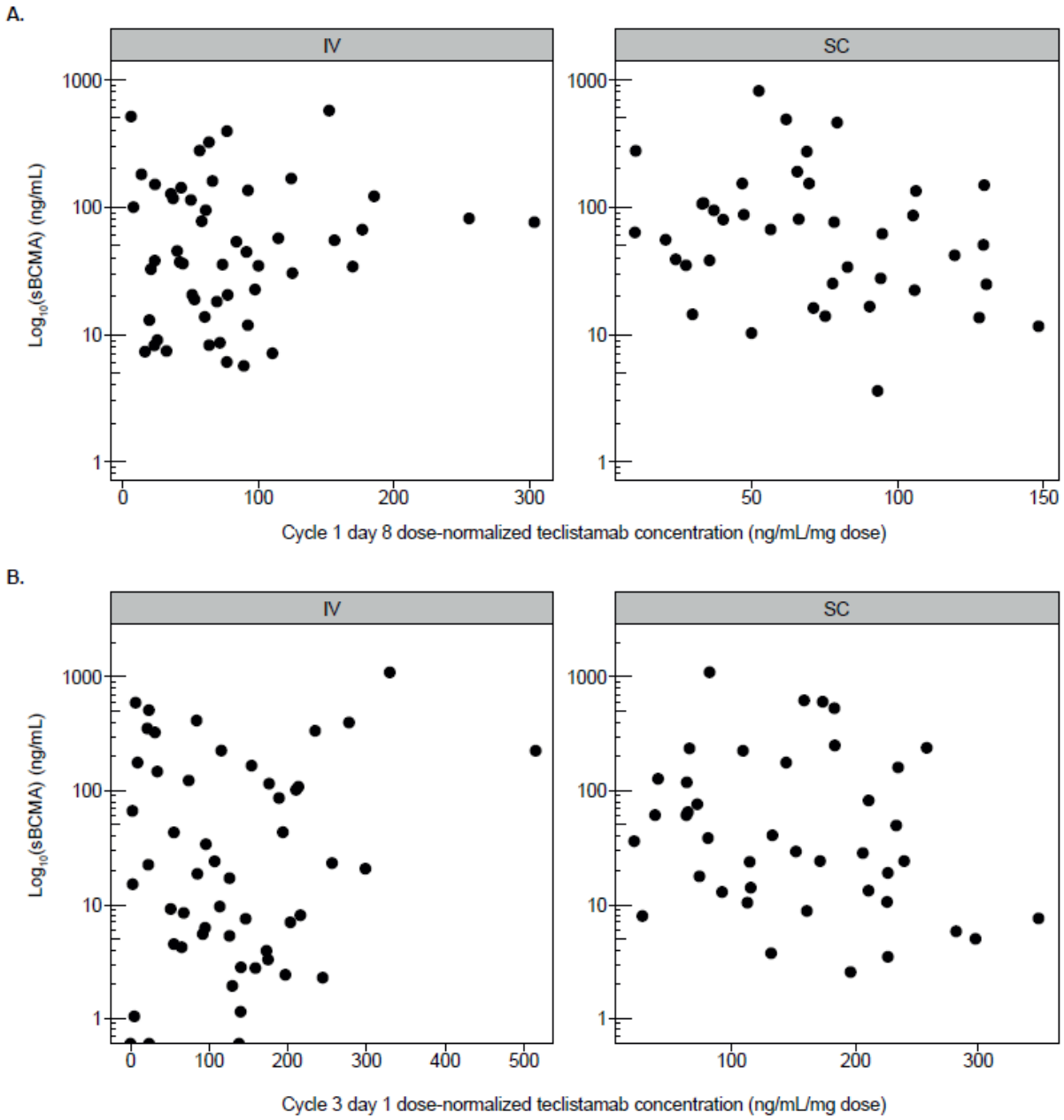
Supplemental Figure 4. sBCMA and cytogenetic risk. Baseline sBCMA in (A) MajesTEC-1 and (B) MonumenTAL-1 and change in sBCMA from baseline on cycle 3 day 1 in patients treated with (C) teclistamab or (D) talquetamab.



Results in panels A and C are shown for patients treated with active doses of teclistamab IV (0.270–0.72mg/kg) and teclistamab SC (0.72–3.0mg/kg). Results in panels B and D are shown for patients treated with active doses of talquetamab IV (60–180 µg/kg) and talquetamab SC (405–800 µg/kg). Median (range) shown for baseline sBCMA levels and Median (Min; Max) shown for % sBCMA change from baseline.

IV, intravenous; sBCMA, soluble B-cell maturation antigen; SC, subcutaneous.

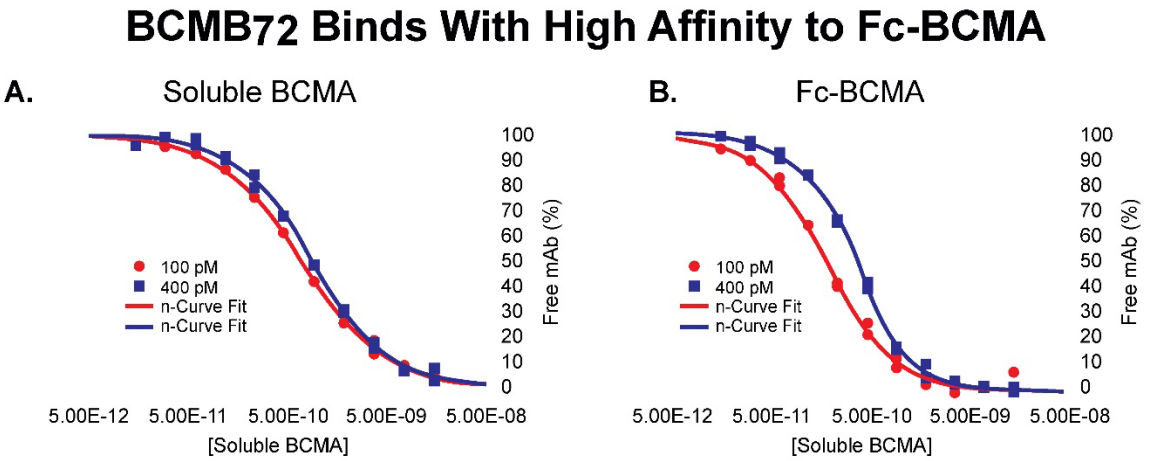
Supplemental Figure 5. sBCMA baseline (A) and C3D1 (B) levels and dose-normalized teclistamab exposure.



Analyses were done on patients who received all dose levels of teclistamab (IV doses 0.0003–0.72 mg/kg and SC doses 0.080–3.0 mg/kg)

C, cycle, D, day; IV, intravenous; sBCMA, soluble B-cell maturation antigen; SC, subcutaneous.

Supplemental Figure 6. Teclistamab binding to full length BCMA (Fc-BCMA) and sBCMA



Duobody	Antigen	SPR K_D (pM)	KinExA K_D (pM)
	Fc-BCMA	150 – 200*	-
BCMB72.001	Soluble BCMA (Rosa)	930	-
	Soluble BCMA (AB Biosciences)	1350	-

sBCMA, soluble BCMA; Fc-BCMA, full length BCMA; Kd, disassociation constant; mAb, monoclonal antibody; SPR, surface plasmon resonance