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Pharmacodynamic Profiles of Patients With Newly Diagnosed vs Relapsed/Refractory Multiple Myeloma Who Received Teclistamab or Talquetamab Plus Daratumumab and Lenalidomide in the Phase 1b MajesTEC-2 and MonumenTAL-2 Studies

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Key Takeaway

Patients with NDMM demonstrate more favorable baseline and longitudinal immune profiles when treated with Tec-Dara-Len or Tal-Dara-Len, which may result in improved outcomes vs RRMM

Conclusions

Lower expression of co-inhibitory receptors such as LAG-3 in effector memory T cells, which are typically observed in RRMM vs NDMM, is associated with response in Tec-Dara-Len and Tal-Dara-Len cohorts

Greater T-cell recovery and clonal expansion potential in patients with NDMM is suggestive of a favorable immune profile and may contribute to improved outcomes with bispecific combinations, such as Tec-Dara-Len and Tal-Dara-Len

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Poster

Supplementary material

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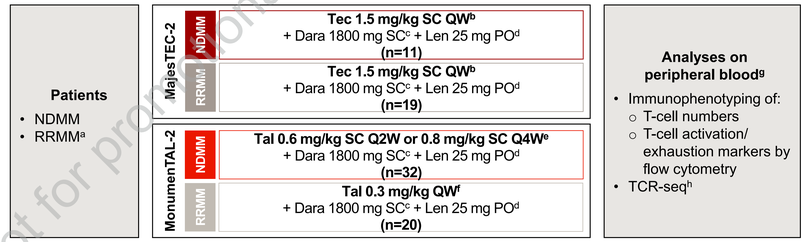
Introduction

- Analysis of immune profiles may reveal patient populations that could benefit from novel therapies and combination therapies in multiple myeloma
- The first-in-class bispecific antibodies teclistamab (Tec; targeting B-cell maturation antigen) and talquetamab (Tal; targeting G protein–coupled receptor class C group 5 member D) have demonstrated deep, durable responses as monotherapies in patients with relapsed/refractory multiple myeloma (RRMM)[1-4]
- Tec or Tal in combination with daratumumab (Dara; anti-CD38 monoclonal antibody) and lenalidomide (Len; immunomodulatory drug), may further augment T-cell cytotoxic activity, enhance efficacy, and improve patient outcomes, through complementary mechanisms of action (**Supplemental Figure 1**)[5-9]
- Here, we report differential immune signatures between patients with newly diagnosed multiple myeloma (NDMM) vs RRMM treated with Tec-Dara-Len in MajesTEC-2 or Tal-Dara-Len in MonumenTAL-2

Methods

- MajesTEC-2 (NCT04722146) and MonumenTAL-2 (NCT05050097) enrolled patients with NDMM and RRMM (**Figure 1**)
- Biomarker data cut-offs were April 15, 2024 (MajesTEC-2), and September 23, 2024 (MonumenTAL-2)

Figure 1: MajesTEC-2 and MonumenTAL-2 treatment regimens



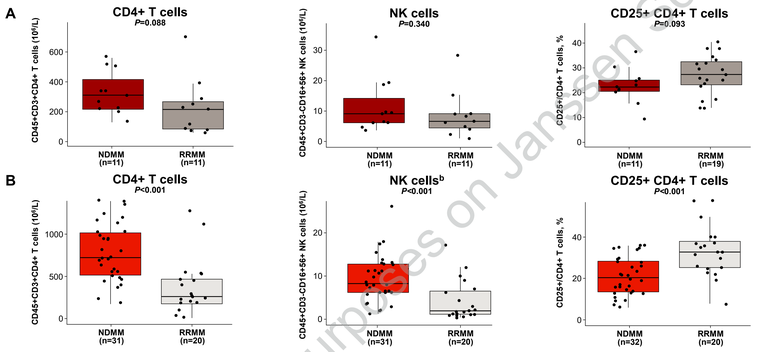
[a]In MajesTEC-2, patients with RRMM had 1–3 prior LOT, including a PI and an immunomodulatory drug. In MonumenTAL-2, patients with RRMM had 1–3 or ≥3 prior LOT, including a PI and an immunomodulatory drug. [b]After step-up doses (0.06 and 0.3 mg/kg). [c]Administered QW during cycles 1 and 2, Q2W during cycles 3–6, and once (on day 1) during each subsequent 28-day cycle. [d]Administered daily for 21 days of a 28-day cycle from cycle 2 onwards. Dexamethasone was given concurrent with the first 3 full Len-containing cycles. [e]After step-up doses (0.01, 0.06, and 0.4 mg/kg). [f]After step-up doses (0.01 and 0.06 mg/kg). [g]Samples were collected for analyses at baseline and post treatment at cycle 2 and/or cycle 3. Statistical significance was determined by the Wilcoxon test. [h]Only available for MonumenTAL-2. LOT, line of therapy; PI, proteasome inhibitor; PO, orally; Q2W, every other week; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCR-seq, T-cell receptor sequencing.

Results

Baseline immune fitness in patients with NDMM vs RRMM

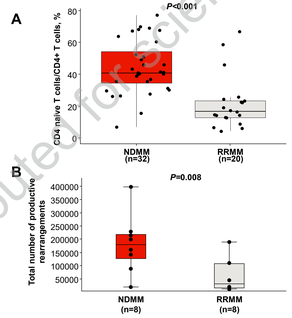
- The immune fitness profile (**Figures 2** and **3A** [Tal-Dara-Len]), T-cell repertoire (**Figure 3B** [Tal-Dara-Len]), and T-cell memory phenotypes (**Supplemental Figures 2** [Tec-Dara-Len] and **3** [both]) were investigated in NDMM vs RRMM; the proportion of LAG-3+ effector memory T cells in association with clinical response was also assessed (**Figure 4**)
  - At baseline, patients with NDMM exhibited a higher number of CD4+ T cells and NK cells, a higher proportion of naive T cells, and a more diverse T-cell repertoire, suggestive of a fitter immune status[10]

Figure 2: More favorable baseline immune fitness[a] in patients with NDMM vs RRMM enrolled in the (A) Tec-Dara-Len and (B) Tal-Dara-Len cohorts



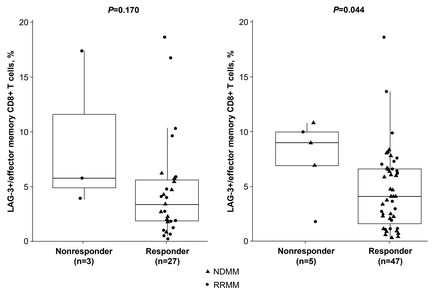
[a]Indicated by higher peripheral T-cell and NK-cell counts and lower proportions of T cells expressing activation markers (CD25). [b]1 outlier in the NDMM group (y=45.581) is not shown. NK, natural killer.

Figure 3: Higher baseline proportion of naive CD4+ T cells (A)[a] and more diverse T-cell repertoire (B)[b] in patients with NDMM vs RRMM enrolled in the Tal-Dara-Len cohort



[a]Assessed by flow cytometry. Corresponding Tec-Dara-Len data with similar results shown in **Supplemental Figure 2** and a less differentiated (more naive) immune profile, with lower proportions of effector memory T cells observed in NDMM vs RRMM, is shown for both cohorts in **Supplemental Figure 3**. [b]Assessed by TCR-seq. Similar results were observed during assessment of down-sampled rearrangements.

Figure 4: Lower baseline proportion of effector memory CD8+ T cells expressing LAG-3[a] associates with response in patients with NDMM and RRMM enrolled in the (A) Tec-Dara-Len and (B) Tal-Dara-Len cohorts

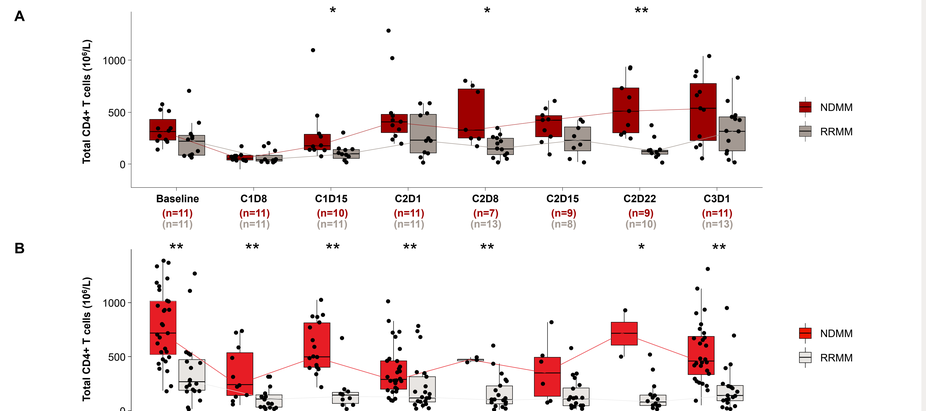


[a]LAG-3 is expressed on differentiated T cells and can be a marker of T-cell exhaustion or immune suppression. Sample collection and analysis determined by sample availability. Similar trends were observed in PD-1+LAG-3+ central memory CD8+ T cells.
LAG-3, lymphocyte activation gene-3; PD-1, programmed cell death protein-1.

Longitudinal correlatives in patients with NDMM vs RRMM

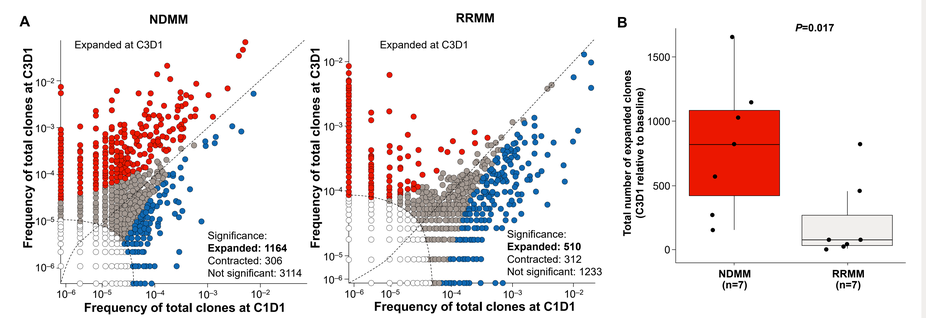
- T-cell recovery (**Figure 5** and **Supplemental Figure 4**) and T-cell clonal expansion (**Figure 6** [Tal-Dara-Len]) were investigated in NDMM vs RRMM
  - After Tec-Dara-Len or Tal-Dara-Len, greater T-cell recovery after C1D15 and greater T-cell clonal expansion in patients with NDMM vs RRMM suggest a more beneficial and functional immune profile, as well as therapy-induced T-cell expansion

Figure 5: Greater recovery of CD4+ T cells[a] with (A) Tec-Dara-Len and (B) Tal-Dara-Len in patients with NDMM vs RRMM



[a]Corresponding data for total CD3+ T cells with similar results as CD4+ T cells shown in **Supplemental Figure 4**. *Indicates *P*<0.05. **Indicates *P*<0.01. C, cycle; D, day.

Figure 6: Greater T-cell clonal expansion[a] in (A) a representative patient with NDMM (left) or RRMM (right) and (B) all patients with NDMM vs RRMM[b] treated with Tal-Dara-Len



[a]Greater T-cell clonal expansion shown here, together with greater T-cell recovery (**Figure 5**), may contribute to enhanced efficacy of Tec-Dara-Len or Tal-Dara-Len and improved patient outcomes (see **MajesTEC-5 Oral #493** of outcomes with Tec combination regimens in NDMM). [b]Shows all unique, expanded (higher in C3D1) clones that were detected in the other sample. C, cycle; D, day.

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Multiple Myeloma

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